C–H Arylation

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Remote C–H Functionalization by a Palladium-Catalyzed Transannular Approach

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Over the past two decades, transition-metal-catalyzed direct C–H functionalization[1] has emerged as a powerful strategy for the construction of C–C and C–heteroatom bonds and often proved to be more atom- and step-economical than the traditional cross-coupling methods.[2] Despite significant progress, regioselectivity in the C–H functionalization reactions, especially at a remote position from the reactive functional group or the directing group, still remains a daunting challenge.[3]

Alicyclic amines are an important class of organic compounds as copious substituted saturated nitrogen heterocycles possess diverse biological activities.[4] Thus, developing methods for the efficient functionalization of such core structures has become a highly investigated field of research over the past few decades.[5] To this end, functionalization by direct C–H activation has been explored by different research groups (Figure 1).[6] However, these methods mainly deal

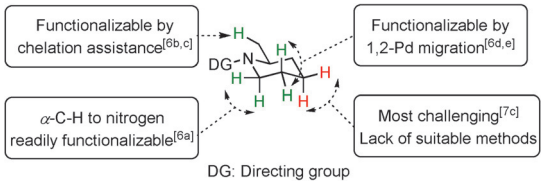
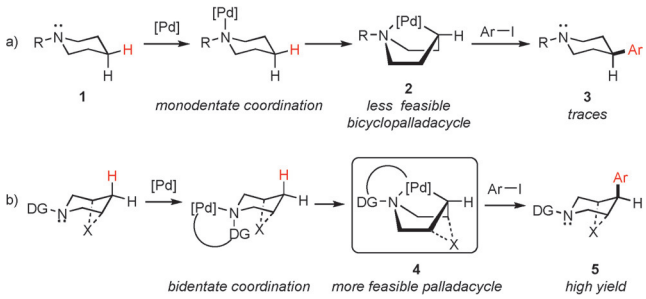


Figure 1. Synthetic approaches for the regioselective C–H functionalization of alicyclic amines.

with the transition-metal-catalyzed functionalization of C–H bonds at the activated α-position of the nitrogen atom.[6a] Gaunt et al. nicely demonstrated the utility of Pd^{II}-catalyzed C–H activation on exocyclic alkyl groups of alicyclic amines in the synthesis of strained nitrogen heterocycles[6b] and in arylation reactions.[6c] Functionalization of the β-C–H bonds of the alicyclic ring is also feasible via α-C–H activation followed by a 1,2-palladium migration process.[6d,e] Regioselective substitution at further remote positions of open-chain or cycloalkyl amines was achieved by Daugulis et al.[7a] and He and Chen[7b] using a bidentate directing group. In contrast, similar remote C_{sp^3}–H activation of alicyclic amines is challenging[7c] and until recently no efficient method was available. This Highlight describes an important contribution by Sanford and co-workers on a novel palladium-catalyzed transannular C–H arylation of alicyclic amines.[8]

The authors hypothesized that the coordination of the nitrogen atom of an alicyclic amine to the palladium catalyst could facilitate selective transannular C–H activation to generate a bicyclo[2.2.1]palladacycle **2** (Scheme 1a). However, the low equilibrium population of the high-energy boat conformer **2** and the high barrier towards activation of an inert secondary C_{sp^3}–H bond resulted in traces of the desired arylated product **3**. To address this, the authors engineered the protected alicyclic amine **6** for the desired transannular C–H arylation; in **6** a cyclopropane ring containing C–H bonds having high s character is fused to the alicyclic amine (Scheme 2). The authors further introduced an additional directing group on the nitrogen atom. The bicyclic core, in combination with bidentate coordination[9] resulting from the formation of the more stable palladacycle **4**, was anticipated to enhance the equilibrium population of the boat conformation (Scheme 1b).



Scheme 1. Envisioned approaches for transannular C–H arylation.

During the initial optimization studies under typical reaction conditions for C–H activation using $Pd(OAc)_2$ as the catalyst and AgOPiv as an additive, the desired arylated product **7** was obtained only in 18% yield (Scheme 2). The major byproduct was the aminal **8**, which was formed by α-oxidation of **6** to the corresponding iminium ion followed by intramolecular trapping with the amide nitrogen atom. To avoid this undesired oxidation, AgOPiv was replaced by

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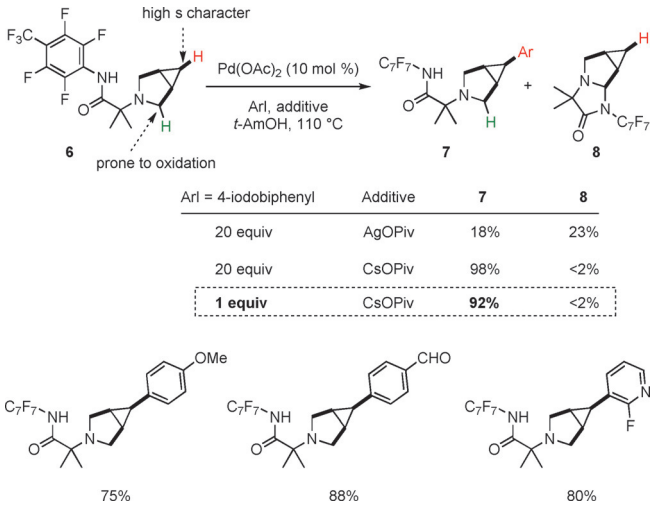
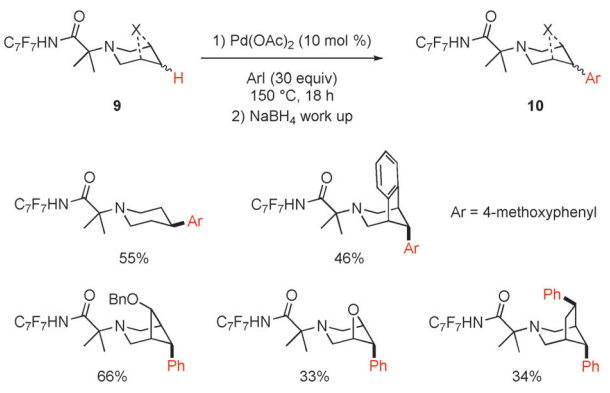


Scheme 2. Reaction optimization and scope using the model substrate **6**. OPiv = pivalate.

CsOPiv, which resulted in a sharp improvement in the yield to 98%. Importantly, under these conditions the arylation proceeded with high efficiency even with an equimolar amount of aryl iodide (92% yield).

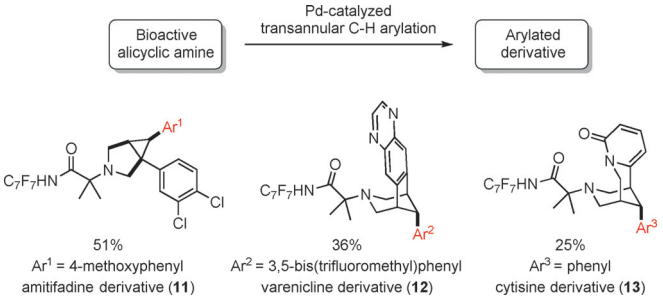
The scope of the transannular C–H arylation reaction of **6** is broad and aryl groups bearing electron-donating, electron-neutral, and electron-withdrawing substituents as well as heteroarenes were installed in high yields (Scheme 2). However, the authors faced a major challenge when the simple piperidine derivative **9** was tested (Scheme 3). Rather forcing conditions, elevated temperatures and a high excess of aryl iodide, were needed to overcome the constraint associated with the required, but thermodynamically unfavorable boat conformation for the cyclometalation step. Good to moderate yields were obtained under the modified reaction conditions with the unsubstituted piperidine derivatives as well as with different bicyclic analogues (Scheme 3). It is noteworthy that for bicyclic piperidine derivatives the aryl group was installed at the axial position with high selectivity, which is extremely difficult to achieve using other synthetic methods.

An important aspect of this intriguing transannular C–H activation is the application for the late-stage functionalization of bioactive molecules.[10] This would facilitate the



Scheme 3. Substrate scope of transannular C–H arylation with piperidine derivatives.

efficient synthesis of a series of analogues that might be beneficial for structure–activity relationship studies. For example, the bicyclic triple re-uptake inhibitor amitifadine was arylated to form derivative **11** in moderate yield (Scheme 4). Similar functionalization was performed in other



Scheme 4. Late-stage functionalization of bioactive molecules.

bioactive molecules like varenicline and cytisine to deliver **12** and **13**, respectively. In both cases the aryl group was selectively placed at the axial position, which was unambiguously ascertained by X-ray crystallographic studies.

Although the new synthetic method of Sanford and co-workers is highly attractive, its scope with monocyclic amines is limited, and it is only viable with aryl iodides as the coupling partner as much diminished yields were reported with other aryl halides and trifluoromethanesulfonates. Thus, further improvement of this elegant method with regard to the scope of simple piperidine derivatives and other electrophilic coupling partners is highly anticipated, as it will further unfold the potential of such transannular C–H activation methods as an effective and reliable synthetic strategy.

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