Article

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ACS Catal., **Just Accepted Manuscript** • DOI: 10.1021/acscatal.8b04927 • Publication Date (Web): 15 Apr 2019

Native Directed Site-Selective δ-C(sp³)-H and δ-C(sp²)-H Arylation of Primary Amines

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ABSTRACT: A Pd(II)-catalyzed, selective δ-C(sp³)–H and δ-C(sp²)–H arylation method for free primary aliphatic amines using NH_2 as a native directing group has been developed. A variety of free primary amines with adjacent quaternary centers and/or with alpha esters react with a diverse range of aryl and heteroaryl iodides to provide δ-aryl and δ-heteroaryl amines.

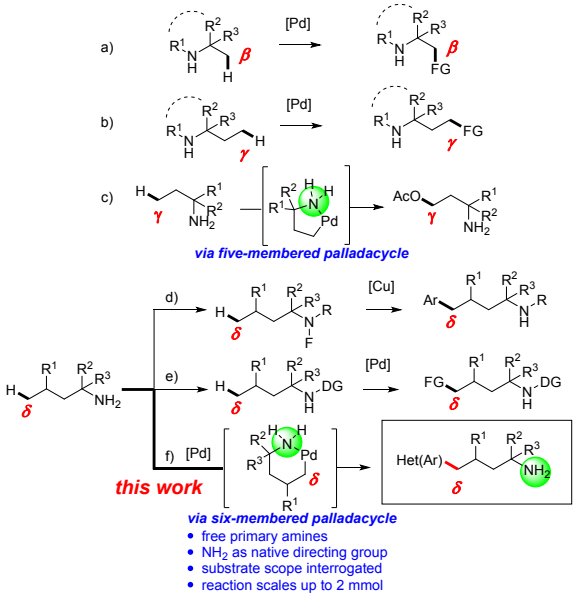
KEYWORDS free primary amine • native directing • δ-C–H arylation • Pd-catalysis • six-membered palladacycle

Most marketed small molecule drugs contain one or more amine groups, either aromatic heterocyclic or aliphatic.[1] "Escaping from flatland" with high sp³ vs. sp² character (aliphatic amines) enhances clinical success.[2] The percentage of sp³-hybridized carbon atoms in a potential lead guides candidate selection, presumably by improving drug-likeness while imparting a defined 3D shape to better fit into the binding pocket of a biological target.[2]

Substantial effort has been directed toward developing efficient methods for the synthesis and selective derivatization of aliphatic amines.[3] Prominent among these are reactions using transition-metal-catalyzed site-selective C–H functionalization[4] mediated through directing groups (DGs).[5] A limitation of DG-based strategies has been the stepwise attachment and later removal of the DG from the amine, often over multiple steps or requiring harsh conditions. A preferred alternative developed by many groups uses transient directing groups[6] (TDGs) that are both installed and removed *in situ*. Even more preferred would be a method using the unmodified amine itself is a native directing group. Secondary amines have previously been used in this way (Scheme 1a and 1b),[7] however, only one example of an unmodified primary amine as a native directing group for C(sp³)–H activation had appeared, Shi's amine-directed γ-C(sp³)–H acetoxylation (Scheme 1c).[8]

Pd-catalyzed δ-selective C–H functionalization of aliphatic amines has been less well-developed in comparison to γ-selective C–H activation, presumably due to the requirement for a kinetically less favorable six-membered palladacycle intermediate.[9] However, copper-catalyzed arylation of δ-C(sp³)−H of amides via radical relay has been reported recently (Scheme 1d).[10] Also, DG-assisted-δ-C(sp³)−H functionalization of amines has also been realized by many groups (Scheme 1e). Examples are the Chen group's study of the intramolecular amination of alkyl picolinamides;[9a] Daugulis and co-worker's δ-C(sp³)−H oxidation of alkyl picolinamides;[9b] The Shi laboratory's δ-C(sp³)−H alkenylation and alkylation of picolinamide-protected amino acids and peptides;[9c,d] and the δ-C(sp³)−H arylation of picolinamide by Wang and co-workers, using 3-pinanamine as a substrate.[9e]

Herein we report efforts towards a Pd-catalyzed site-selective δ-C(sp³)−H and δ-C(sp²)−H arylation of primary aliphatic amines, with the NH_2 group as the directing group (Scheme 1f), to give δ-aryl or heteroaryl amines.



Scheme 1. Aliphatic Amine C(sp³)-H Functionalization

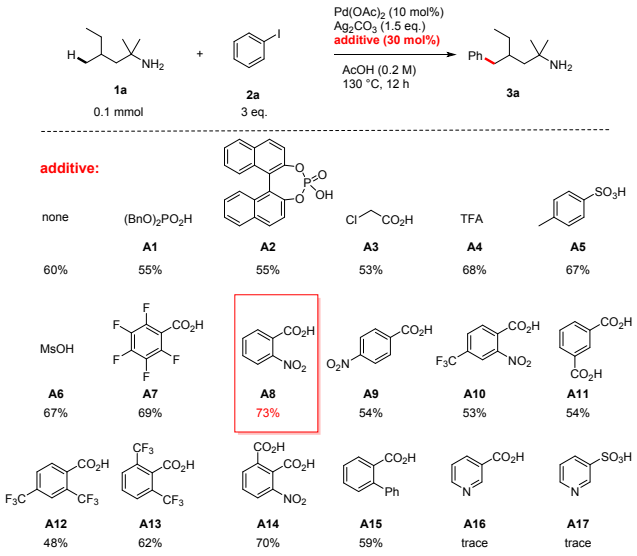
Free amines are not typically good substrates for palladium catalyzed C−H bond activation reactions because they form stable bis-amine palladium complexes. A sterically hindered secondary amine can facilitate dissociation of this complex to enable C−H bond activation.[7b] For primary amines, weak acid additives such as acetic acid can aid dissociation of the

complex,[8] while not halting coordination to palladium through complete conversion to ammonium salts. Accordingly, we investigated δ-C(sp^3)−H arylation in the presence of AcOH with 2,4-dimethylhexan-2-amine (**1a**) and iodobenzene (**2a**). To our delight, using $Pd(OAc)_2$ and Ag_2CO_3 in AcOH at 130 ºC for 12 hours provided 60% yield of the desired product (yields reported herein are NMR yields, based upon NMR integration vs. an internal standard, unless otherwise noted).

Solvents that were used in other CH arylation processes thought to proceed by ion-pairing mechanisms[11] were less well-suited for this conversion, including THF,[11a] toluene,[11b] and 1,4-dioxane (see supporting information P12; TFA and formic acid were also ineffective as solvents).

Given the importance of acetic acid as the reaction solvent, we explored the possibility of using a small amount (30 mol%) of another acidic additive. (Table 1). The additive had only a modest effect. The highest yield (73%) was obtained using 2-nitrobenzoic acid (**A8**). Acids with a metal-coordinating heterocycle impeded conversion (**A16**, **A17**).

Table 1. Screening of Additives[a,b]

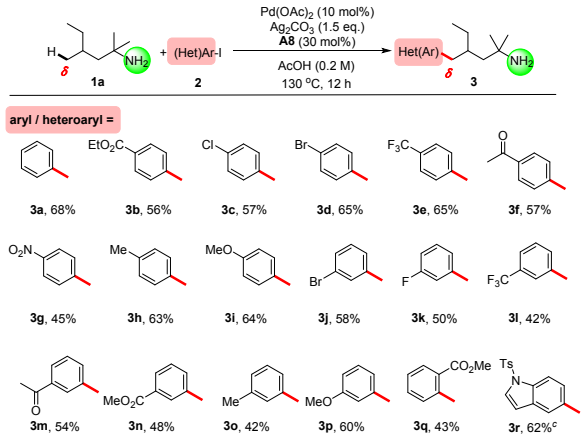


[a]The reactions were run with **1a** (0.1 mmol), **2a** (0.3 mmol), $Pd(OAc)_2$ (10 mol%), Ag_2CO_3 (0.15 mmol, 1.5 eq.), additive (30 mol%), AcOH (0.5 mL), 130 ºC, 12 hr; [b]NMR yield, 1,3,5-trimethoxybenzene was used as internal standard.

Other silver salts were somewhat suitable, for example Ag_2O gave only slightly reduced yields (see supporting information P12). Variations of reaction temperature gave no additional improvement. To study the potential importance of CO_2 in this process,[6j] we studied the Ag_2O-mediated reaction under an argon atmosphere using degassed solvent and also under a CO_2 atmosphere. Neither modification had a significant effect (see supporting information P12). These control experiments strongly suggest that neither dissolved nor *in situ* generated CO_2 is involved in this directed C-H activation process.

We then used these preferred reaction conditions to explore the scope of the reaction with respect to the aryl iodide reagent (Table 2). Aryl iodides with most para functional groups, either electron-withdrawing (CO_2Et, Cl, Br, CF_3, Ac) or electron-donating (Me, OMe) gave similar conversion to products (yield 56-65%, **3a-3f**, **3h**, **3i**). Using p-nitrophenyl iodide (**3g**) gave a diminished yield (45%). We found that meta-substituted phenyl iodides were often slightly less suitable (yields 42−60%, **3j−3p**), while ortho-substituted phenyl iodides (2-F, 2-Me and 2-OMe) gave the poorest results (<20% NMR yield, and the products were not separated). Only methyl 2-iodobenzoate provided the product in acceptable yield (43%, **3q**). A heteroaryl iodide, 5-iodo-1-tosyl-1H-indole, notably gave **3r** in reasonable yield (62%) after acetylation (see supporting information for all experimental details). [12]

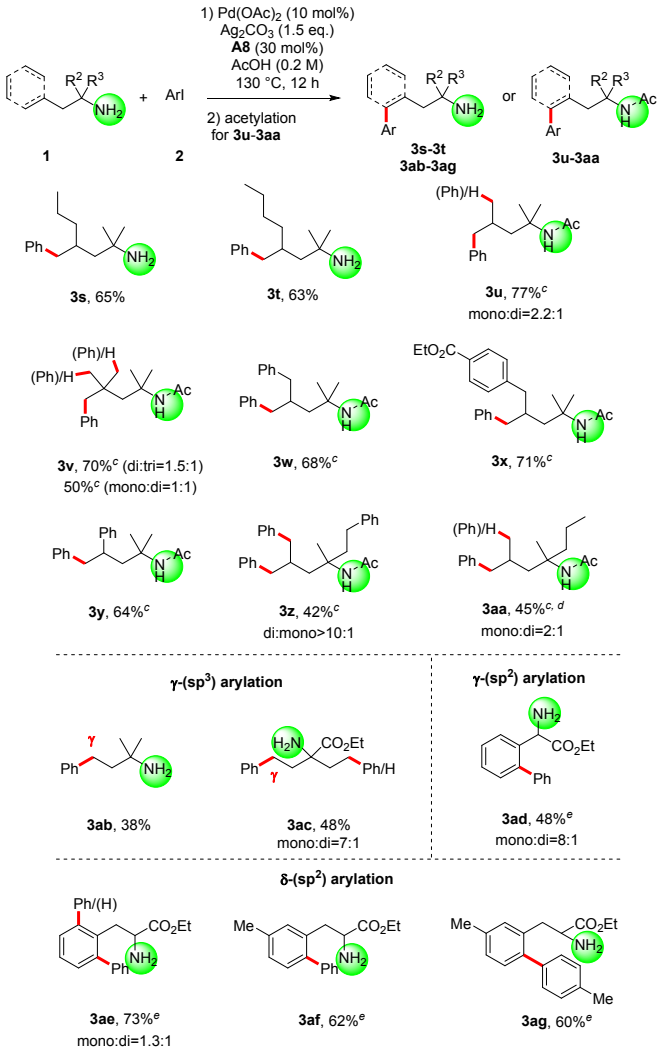
Table 2. Screening of Aryl Iodides[a,b]



[a]The reactions used **1a** (0.2 mmol), **2** (0.6 mmol), $Pd(OAc)_2$ (10 mol%), Ag_2CO_3 (0.3 mmol, 1.5 eq.), **A8** (30 mol%), AcOH (1 mL), 130 ºC, 12 hr; [b]Isolated yield; [c]Isolated yield of product following N-acetylation.

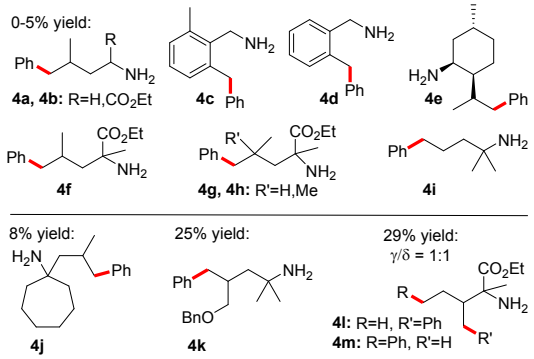
The amine substrate scope of the δ-C(sp^3)−H arylation with iodobenzene was then explored (Table 3).[12] δ-C(sp^3)−H arylation of amines with α,α-dimethyl group substitution proceeded well with yields between 63% to 77% (**3s-3y**). With two equivalent methyl groups containing C(sp^3)−H bonds, 2,4-dimethylpentan-2-amine was more reactive, and gave both mono and diarylation products in 77% combined yield (**3u**, mono:di=2.2:1). A triarylation product formed when three equivalent methyl groups containing C(sp^3)−H bonds were present, and 2,4,4-trimethylpentan-2-amine provided **3v** in 70% combined yield (di:tri=1.5:1) at 130 ºC and 50% combined yield (mono:di=1:1) at 110 ºC. Furthermore, amines with larger α-substituents gave products only in low yield (**3z** and **3aa**). ɤ-C(sp^3)−H arylation also proceeded, with the appropriate starting material. **3ab** and **3ac** were produced in 38% and 48% yields respectively, under the same reaction conditions. It is noteworthy that in certain instances an alpha ester was tolerated (see **3ac**, **3ad**, **3af**, and **3ag**) and in the latter three examples a quaternary primary amine was not required for conversion. [6k, 13] The ɤ-C(sp^2)−H arylation process may be generally more favorable due to the presence of a C(sp^2)−H bond, which is more reactive toward insertion.

Table 3. Screening of Primary Alkyl amines[a,b]



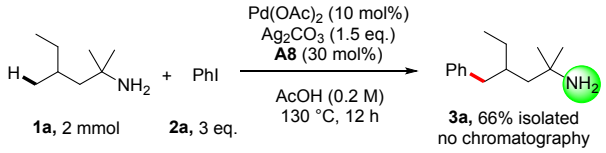
[a]The reactions were run with 1 (0.2 mmol), 2 (0.6 mmol), $Pd(OAc)_2$ (10 mol%), Ag_2CO_3 (0.3 mmol, 1.5 eq.), **A8** (30 mol%), AcOH (1 mL), 130 ºC, 12 hr; [b]Isolated yield; [c] Isolated yield of product following acetylation; [d]d.r. = 1:1 for mono-product; [e]$AgSbF_6$ (0.6 mmol, 3 eq.) was used instead of Ag_2CO_3, HFIP:AcOH=9:1 (1 mL) was used instead of AcOH.

Scheme 2 shows products obtained in low yields under these conditions. From **4a-4e** we see that the steric environment of the amines should be crowded for catalyst turnover and suggests that perhaps placing more bulky ligands on the metal may compensate in the case of less sterically-demanding amine substrates. Subtle electronic effects are also apparent (**4f-4h**, **4k**) and δ/γ selectivity may be problematic (**4l-4m**). The supporting information (P13) describes these and other challenging reactions.



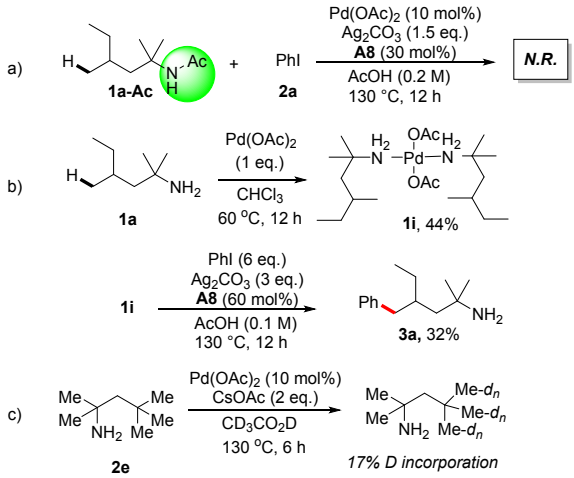
Scheme 2. Less successful attempts

To test the efficiency of our δ-C(sp^3)–H arylation methodology on a more preparative scale, 2 mmol of substrate gave 66% isolated yield of product without chromatography, not significantly altered from the 68% NMR yield obtained on a 0.2 mmol scale (Scheme 2).



Scheme 3. Scale-up Reaction

Scheme 4 shows other reactions investigated to define the reaction scope. N-acylated substrate **1a-Ac** gave no desired product under standard conditions (4a), confirming that the free amino group plays a vital role as a native directing group. The bis-palladium intermediate **1i** was obtained using amine **1a** and $Pd(OAc)_2$ in chloroform. Treatment of complex **1i** with iodobenzene under standard conditions gave product **3a** in modest yield, suggesting that acetic acid can aid in the dissociation of the stable bis-amine palladium complex (4b). Treatment of **2e** with $Pd(OAc)_2$ (10 mol%) in CD_3CO_2D at 130 °C for 6 hours gave 17% deuterium incorporation at the δ-methyl groups (4c).[9b]



Scheme 4. Additional control experiments

As the review and revision of this manuscript was underway, related work on the δ-C(sp^3)–H arylation of free primary amines mediated by transient directing groups (which are absent in the

methodology discussed here) was reported by Yu and colleagues.[14]

In summary, we have developed a Pd(II)-catalyzed, selective δ-C(sp^3)−H and δ-C(sp^2)−H arylation of free primary aliphatic amines using the unmodified NH_2 group as a directing group. Acetic acid as the solvent is essential for successful conversion. Using 2-nitrobenzoic acid as an additive also modestly improves yields in the process. Reactions are likely amenable to scale-up without loss of efficiency. While the substrate scope is somewhat limited with respect to the amine substrate, certain non-quaternary amines are suitable. The scope is quite broad with respect to the aryl/heteroaryl iodide component. Synthetic applications, particularly to improve yields and to broaden substrate scope are under investigation, as are mechanistic studies. Improvements to these procedures will be communicated rapidly upon their discovery.

ASSOCIATED CONTENT

*Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

General information and procedures, experimental details and data (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. ‡These authors contributed equally.

ACKNOWLEDGMENT

We thank Scott J. Novick for HRMS analysis.

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12. Free amine products of **3r** and **3u-3aa** could be isolated by simple acid/base work-up or by reverse-phase preparative HPLC in lower yields than the isolated yields of Ac-protected products shown in Table 2 and Table 3. It's worth poiting out under our experimental conditions, there were no Ac-protected products detected by crude LCMS or NMR analysis. This is in contrast to Shi's work (ref. 8), wherein mixtures of free amines and Ac-protected amines were obtained under their reaction conditions.

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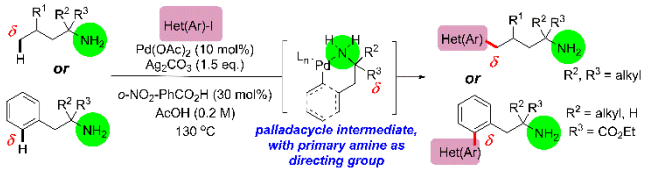
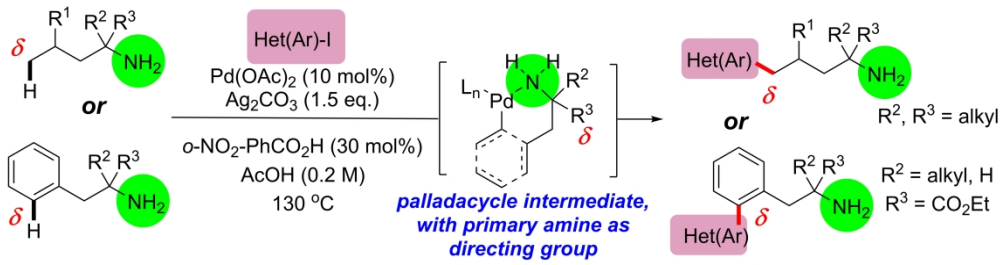
Graphic for Table of Contents Only





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