A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition GDCh Chemie

www.angewandte.org

Accepted Article

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To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.202105204

Link to VoR: https://doi.org/10.1002/anie.202105204

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10.1002/anie.202105204

RESEARCH ARTICLE

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Ligand Enabled δ-C(sp^3)–H Borylation of Aliphatic Amines

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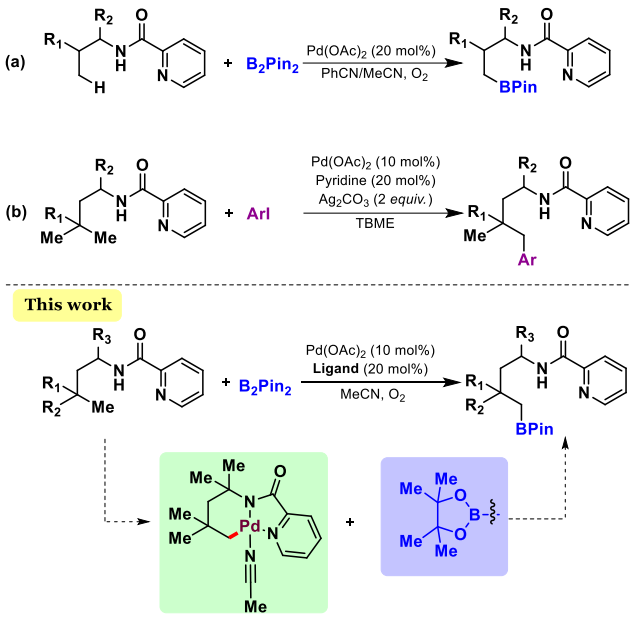
Abstract: Directed C–H functionalization has been realized as a complimentary technique to achieve borylation at a distal position of aliphatic amines. Here, we demonstrated the oxidative borylation at the distal delta position of aliphatic amines using various borylating agents, a palladium catalyst and a rightly tuned ligand in the presence of a cheap oxidant. Moreover, an organopalladium δ-C(sp^3)–H activated intermediate has been isolated and crystallographically characterized to get mechanistic insight.

Introduction

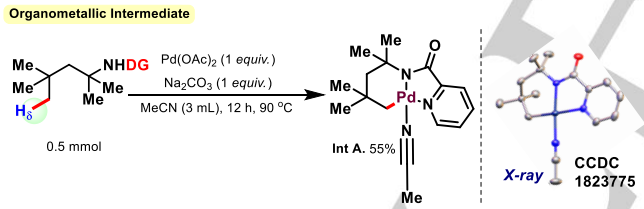
Boronic acids and their esters are of great importance in synthetic organic chemistry, transition metal catalysis, material science and medicinal chemistry.[1-2] Alkyl boronic acids in particular, have attracted considerable attention as potent protease inhibitors.[3] However, obstacles associated with the preparation of alkyl boronic acids and corresponding esters limit their utility.[4-5] Thus, the development of a method which is complementary to the existing hurdles is highly desirable. Moreover, most of the natural products and pharmaceutical agents consist of aliphatic amines as their structural units in the bioactive sites.[6-7] Due to their ubiquity and importance, the late-stage derivatization of amine-containing substrates have widespread utility in organic chemistry and medicinal chemistry. Initial efforts on C–H bond functionalization of aliphatic amines was mainly attentive to the transformations initiated by α-C–H cleavage of amines with the strategy of a hydrogen transfer or oxidation process.[8-9] However, the direct transformations of the remote aliphatic C–H bonds of amines have rarely been witnessed due to the reactivity difference of the inert C–H bonds.[10-11] Such C–H bond functionalization reactions were reported in the presence of stoichiometric or catalytic amounts of transition metals; however, with the limitation in terms of catalyst loading and selectivity.[12] Thus, a site selective C–H borylation would not only provide an easier synthetic route to some complex molecules but also possibly give a direct access to interesting newer molecules.

In the past decade, efforts made on C–H borylation reactions mostly utilized Ir- and Rh-catalysts, in which the regioselectivity is controlled by either a steric factor [13] or a directing group (DG).[14] In contrast, very limited success has been obtained in palladium catalysis.[15] These approaches were dedicated towards achieving direct borylation selectively and precisely at a specific position in a complex molecule. Although numerous reports are available in the literature about the directed ortho C–H borylation reactions of arenes with Pd catalysis,[16] methodologies for direct borylation of inert C(sp^3)–H bonds in an aliphatic chain is scarce. Among those, only a few palladium catalyzed distal C(sp^3)–H borylation strategies can be found. In this regard, Shi group in 2014 reported the borylation at the γ-position, which is the farthest accessible position so far, albeit with poor site selectivity (Scheme 1a) and with high palladium loading.[17] Moreover, excess amounts of a borylating agent was used which limits the utility of the protocol. We aimed to search for a protocol to reach one step further, the delta (δ) position. However, formation of a thermodynamically less favoured six-membered palladacycle over the more stable five-membered palladacycle is the bottleneck for such a transformation. In 2018 our group has demonstrated highly efficient distal δ-arylation of aliphatic amino acids using the picolyl moiety as the directing group in the presence of low palladium loading and simple pyridine as a ligand (Scheme 1b).[18]



Scheme 1. δ-Borylation of aliphatic amines

We believed a similar approach could be attempted for the borylation reaction as well. On the other hand, cross coupling reactions and C–H borylation reactions commonly involve Pd(II)/Pd(0) or Pd(II)/Pd(IV) catalytic cycles.[19] Therefore, a highly tuned condition is essential so that only the anticipated reaction proceeds efficiently avoiding the deborylation or undesired coupling. Herein, we report a highly selective oxidative borylation of aliphatic distal primary C(sp^3)–H bonds of amines with bis(pinacolato)diboron and its derivatives.



Scheme 2. δ-Crystallographic structure of intermediate **A**

Results and Discussion

Initially, we have chosen tert-octylamine as the standard substrate and tethered with the picolyl directing group. When we subjected the DG attached amine with bis(pinacolato)diboron (B_2pin_2) as the reagent in the presence of catalytic palladium acetate under oxygen (O_2) atmosphere, we observed a small amount of the desired borylation product. As a proof of concept we also obtained the delta C–H bond activated crystal structure (Scheme 2), which is a clear indication that the distal C–H bond is being activated under the reaction conditions. Subsequently, we began optimizing various parameters of the reaction. It has been observed that quinoline and pyridine based ligands are quite effective in such transformations. Therefore, we started to test various quinolines (**L1-L9**, Table 1) and found that simple quinoline (**L1**) resulted in 38% yield. Substituted quinoline (**L2**) resulted in improved yield of 44%. Changing the substitution to hydroxy at 2-position (**L3**) and methoxy at 6-position (**L5**) yielded 53% and 63% products, respectively. Interestingly, 2-hydroxy pyridine (**L19**) resulted in 65%, while the 2,4-dihydroxy quinoline (**L8**) drastically decreased the yield to 15%. We next thought to fine tune around multi-substituted pyridine in order to find an optimum yielding ligand. Subsequently, studying different 2-hydroxy pyridine based ligands (**L10-L17**), we found that 2-hydroxy-6-methyl substituted pyridine (**L20**) is best for this transformation with improved yield (71%).Subsequently, we pursued the optimization process with variety of N-protected amino acids (**L21-L38**) ligands. However, these were found to be less effective for this transformation.

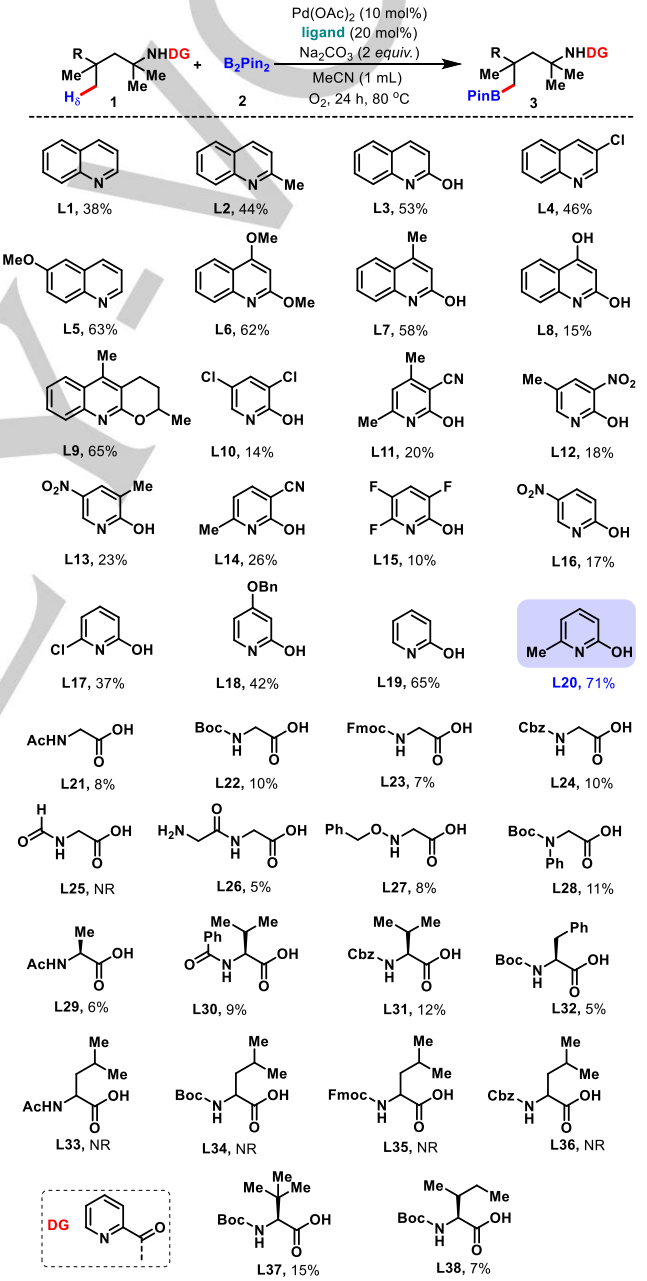
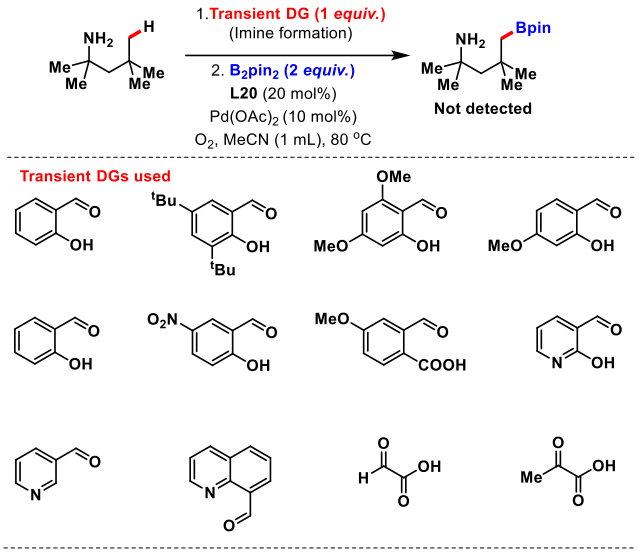


Table 1. Effect of ligand on δ-C(sp^3)–H borylation of aliphatic amine

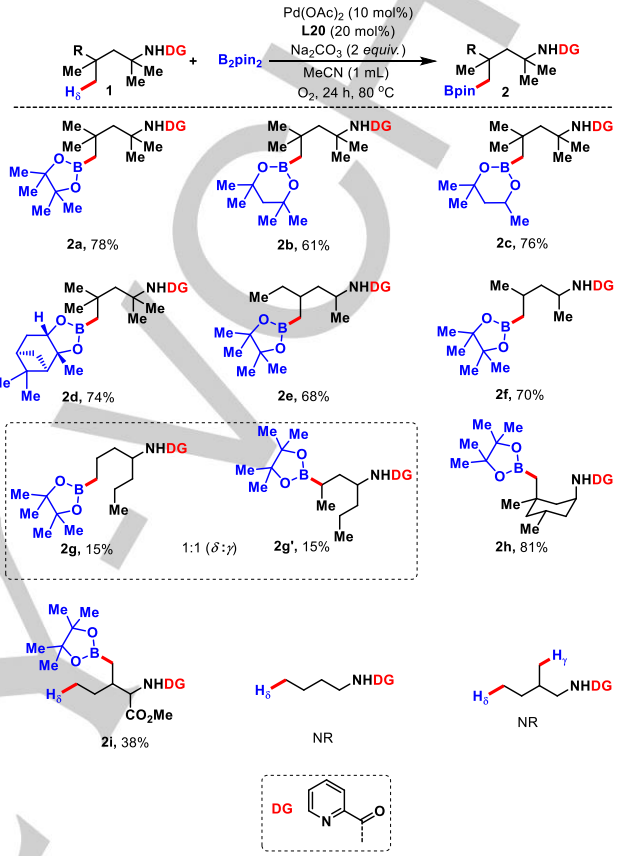
Finally, the influence of a transient directing group was also examined for borylation of aliphatic amines. However, such transient directing group was found to be completely ineffective for the present transformation (Scheme 3). A similar result was observed using directing ability of aliphatic free amines.



Scheme 3. Transient directing group approach for δ-Borylation of aliphatic amines

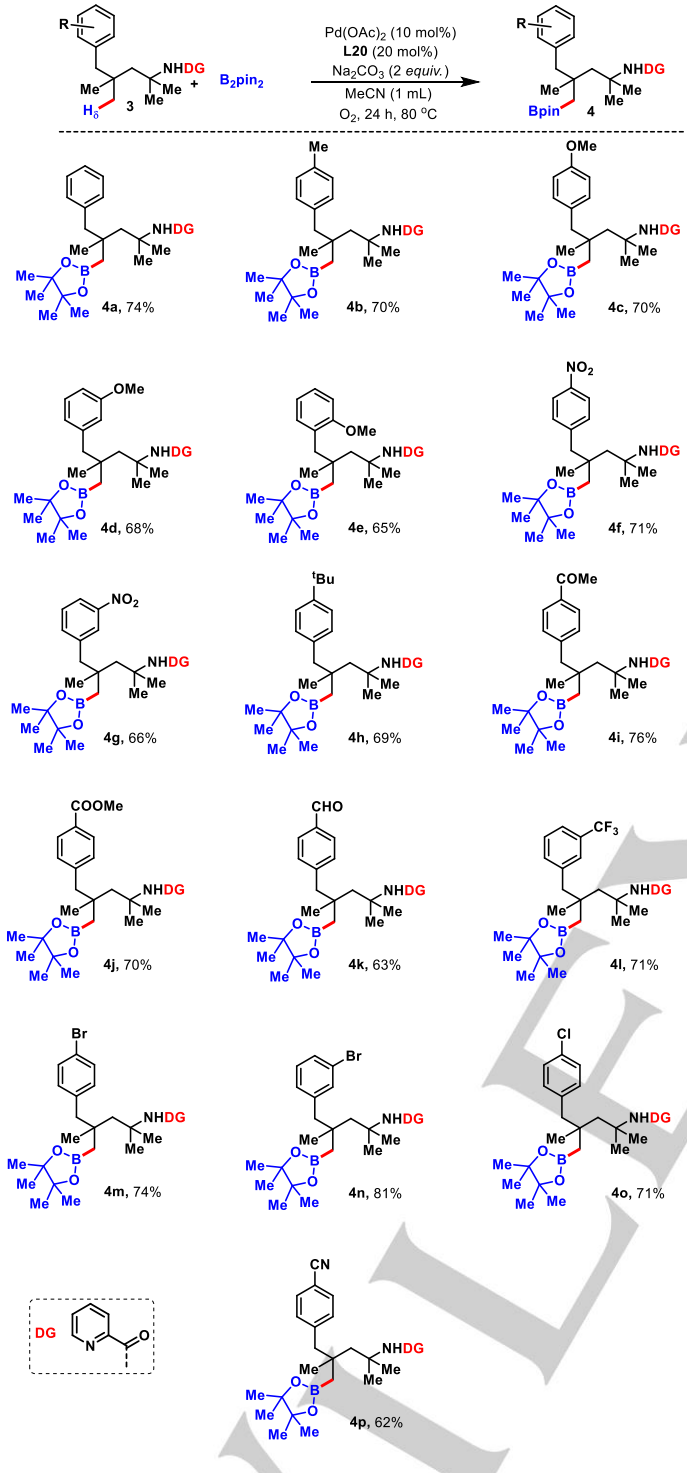
To further increase the yield of the reaction, we tested a series of bases with varied strength. It was found that alkali carbonates play a pivotal role in the reaction, specifically Na_2CO_3, addition of which in 2 equivalents provided the best yield. Oxidants which are customary in palladium catalyzed C–H activation reactions were also essential for the reaction (see supporting information). However, a mild oxidant was required to be used to prevent over oxidation of palladium and subsequent side reactions. To our delight, we found cheap and environment friendly O_2 works best for the δ-borylation reaction. Notably, the reaction was very sensitive to acidic additives (see supporting information). Various other parameters were also optimized using **L20** as the ligand. A combination of $Pd(OAc)_2$ (10 mol%), O_2 (balloon) and Na_2CO_3 (2 equiv.) in acetonitrile (MeCN) solvent provided 78% yield of the desired δ-borylated product. Different borylating reagents such as bis(2,4-dimethylpentane, 2,4-glycolato)diboron, bis(hexylene glycolato)diboron and bis(pinanediolato)diboron, all produced δ-borylated products in preparatively useful yields (**2b-2d**) under this optimized reaction condition (Scheme 4). We next proceeded to examine alicyclic amines that have multiple competitive sites for the reaction (Scheme 4).

In case of 3,5,5-trimethylcyclohexanamine (**2i**), there are three distinguishable methyl groups present, one at the secondary γ-position while the other two comprises of axial and equatorial at the γ-position. However, the δ-borylation reaction occurred specifically at one of the methyl centers present in the quaternary γ-position keeping other two methyl groups intact. Less strained amines possessing multiple reacting sites such as β, γ, δ and ε-positions also underwent borylation selectively at the δ-position (**2e**, and **2f**). However, for the substrate which possesses primary δ-C(sp^3)–H and secondary γ-C(sp^3)–H bonds, both γ- and δ-borylated products were obtained in equal ratio (**2g** and **2g'**). For the isoleucine derivative, borylation occurred at the proximal γ-position over distal δ-position (**2h**). Despite our best efforts completely unbiased aliphatic amines failed to give borylated products under the standard conditions.

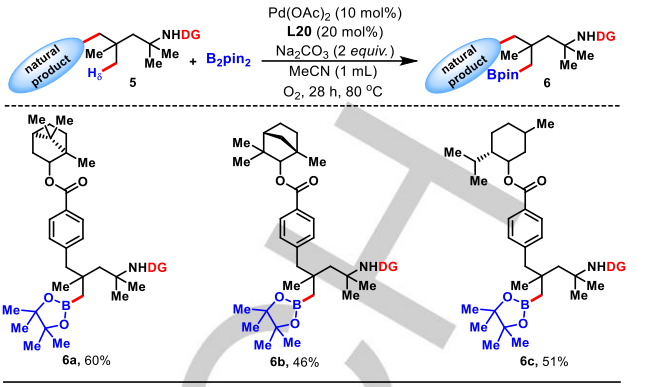


Scheme 4. δ-Borylation of aliphatic amines

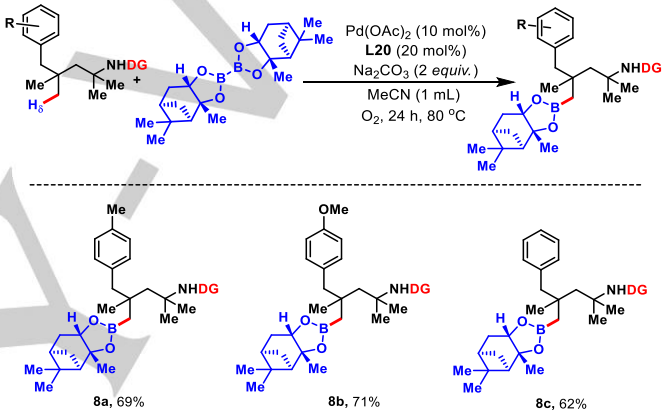
We next explored scope of the reaction with arene substituted aliphatic amines (Scheme 5). Simple phenyl substituted amine was found to give the desired product with a synthetically useful yield (**4a**). Amines containing substituents of different electronic nature on the arene ring viz 4-methyl (**4b**), 4-methoxy (**4c**),3-methoxy (**4d**), 2-methoxy (**4e**), 4-tert butyl (**4h**), nitro (**4f** and **4g**), keto (**4i**), ester (**4j**), aldehyde (**4k**), trifluromethyl (**4l**) and cyano (**4p**) were also compatible as substrates under the standard reaction conditions providing good to excellent yields of the δ-borylated products. Moreover, substrates containing halogen substituents such as bromo and chloro gave reasonably high yield of the desired products (**4m**, **4n** and **4o**). We were also able to achieve borylation of natural products containing substrates such as isopinocampheol (**6a**), fenchyl alcohol (**6b**) and menthol (**6c**) selectively at δ-position in synthetically useful yields (Scheme 6). Importantly, the chiral boryalting agent bis [pinanediolato]diborane can also be introduced regioselectively at the distal delta position (entries **8a-8c**, Scheme 7).



Scheme 5. δ-Borylation of aliphatic amines containing natural products

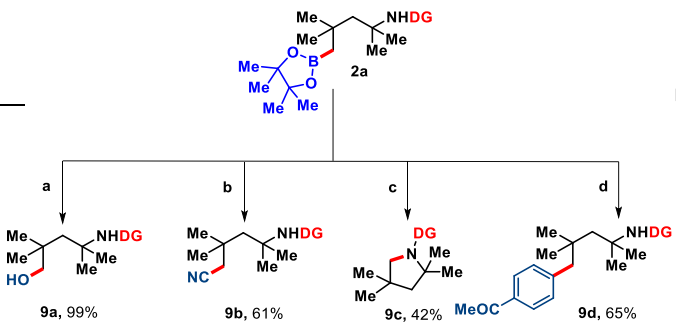


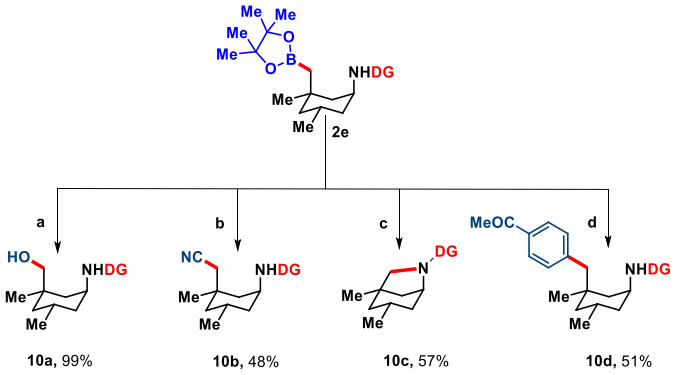
Scheme 6. δ-Borylation of aliphatic amines containing natural products



Scheme 7. δ-Borylation of aliphatic of amines with chiral boronating agents

To illustrate the synthetic utility of the δ-borylated amine, **2a** and **2e** were subjected to various transformations (Scheme 8) such as hydroxylation (**9a** and **10a**), cyanation (**9b** and **10b**), direct synthesis of heterocycle (**9c** and **10c**), and Suzuki-Miyaura cross-coupling reaction with aryl iodide (**9d** and **10d**). In particular, challenges associated with direct cyanation and synthesis of heterocycle from C–H bonds make the protocol very interesting.

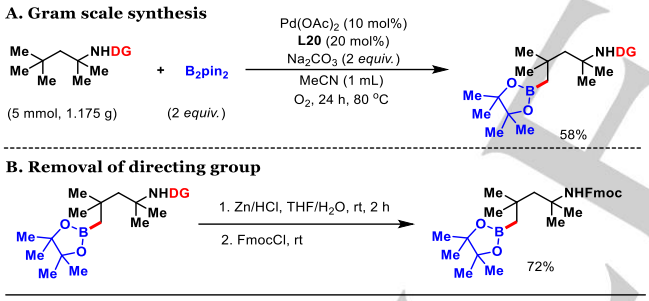




Scheme 8. Synthetic transformations of the δ-borylated amine

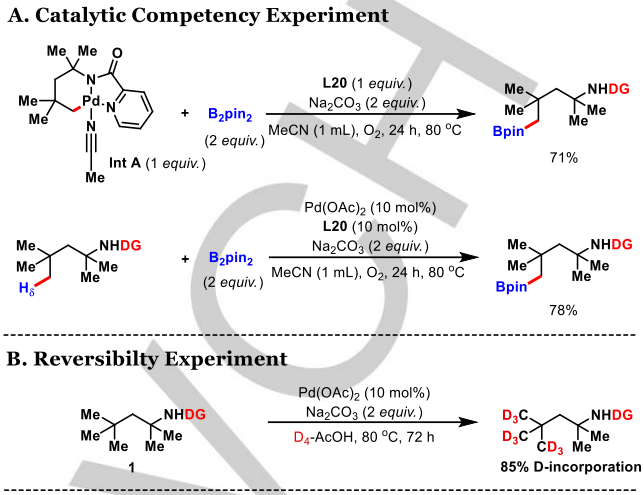
a) *Oxidation*- H_2O_2,aqueous buffer (*pH* 7), THF, RT, 2h, b) *Cyanation*-**2a/2e** (0.1mmol), CuCN (0.1 mmol), K_2CO_3 (0.30 mmol), DMF (2 mL), 60 °C, 4 h, c) *N-Heterocylization* -**2a/2e** (0.1mmol), O_2 (ballon), $Cu(OAc)_2$ (10 mol %), CH_2Cl_2 (1 mL), 40 °C, 12 h, d) *Suzuki reaction* - **2a/2e** (0.1 mmol), $Pd(OAc)_2$ (10 mol%), X-Phos (40 mol%), 1-(4-iodophenyl)ethan-1-one (0.2 mmol), K_3PO_4 (2 *equiv.*), toluene (2 mL), N_2,120 °C, 30 h.

Synthetic usefulness of the protocol was further established by performing the gram scale reaction with 58% yield (Scheme 9A). The directing group (DG) removal was achievable under mild conditions by treating the δ-borylated product with Zn/HCl in THF at room temperature. Free amine thus formed was subsequently protected as Fmoc derivative using FmocCl (72% yield, Scheme 9B).[8b]



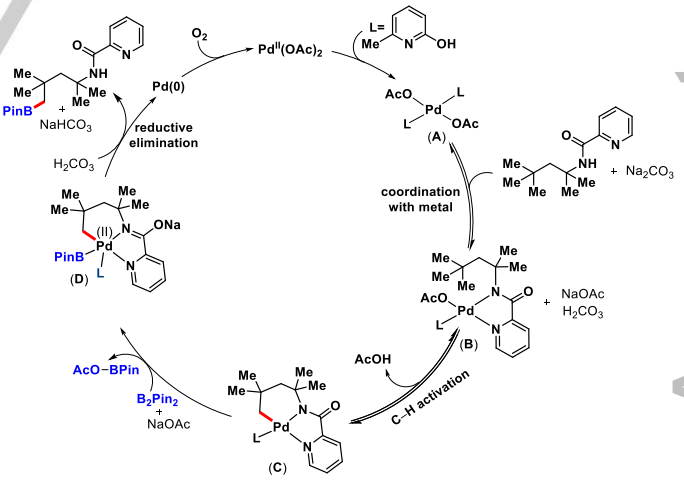
Scheme 9. Gram scale synthesis and directing group removal of the δ-borylated amine

To obtain mechanistic insight, we embarked on the synthesis of the organopalladium complex that might be involved in this transformation. The acetonitrile co-ordinated [5,6]-fused cyclopalladated intermediate (Int **A**) was successfully isolated by reacting **1** with $Pd(OAc)_2$ (Scheme 2) and characterized by different spectroscopic methods including X-ray crystallography. The formation of the δ-borylated product upon stoichiometric reaction of intermediate **A** with bis(pinacolato) borane under otherwise similar conditions implicates the intermediacy of the complex. Furthermore, the borylation was carried out using catalytic quantity of Int A indicates it as a viable precatalyst complying with the present transformation (Scheme 10A). Reversibility of the δ-C–H activation step with protodepalladation was validated by deuterium incorporation (85%) into the methyl groups (Scheme 10B). This suggests C–H activation is less likely to be the r.d.s. of the reaction. In fact, kinetic isotopic effect value close to unity (k_H/k_D = 1.06) is in agreement with the hypothesis that C–H activation is not the r.d.s of the reaction.



Scheme 10. Synthesis and catalytic competency of the organopalladium intermediate

Based on the above studies, a plausible mechanism (Scheme 11) is outlined as,[20] the reaction initiates via metal-ligand complex formation to generate the pre-catalyst (**A**) followed by the coordination with the substrate forming the metal-substrate chelate complex (**B**). The selective distal δ-C–H activation leads to the formation of the six-membered palladacycle intermediate (**C**). Subsequently, borylation takes place to give the desired δ-borylated product. Presence of oxygen regenerates the active catalyst to continue the cycle.



Scheme 11. Plausible reaction mechanism

Conclusion

In summary, we have developed a palladium catalyzed ligand enabled δ-borylation of aliphatic amines with diverse borylating agents. The protocol provides access to a variety of selectively boronated acyclic and cyclic aliphatic amines. The 2-hydroxy-6-methyl-pyridine was identified as the effective ligand for enabling the facile δ-borylation of amines. A six-membered palladacycle intermediate was isolated and characterized. Control experiments with the isolated organopalladium complex and kinetic studies shed light into the mechanism for this transformation.

Acknowledgements

We thank SERB India (CRG/2018/003915) for financial support. Fellowship support for H.B.C. and P.D (UGC) and for A.M (CSIR) are humbly acknowledged. We would also like to acknowledge NSF (CHE-2029932), Robert A. Welch Foundation (D2034-20200401), and Texas Tech University for financial support.

Conflict of interest

The authors declare no conflict of interest

Keywords: δ-Borylation • Pd-catalysis • C–H activation • mechanistic studies

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10.1002/anie.202105204

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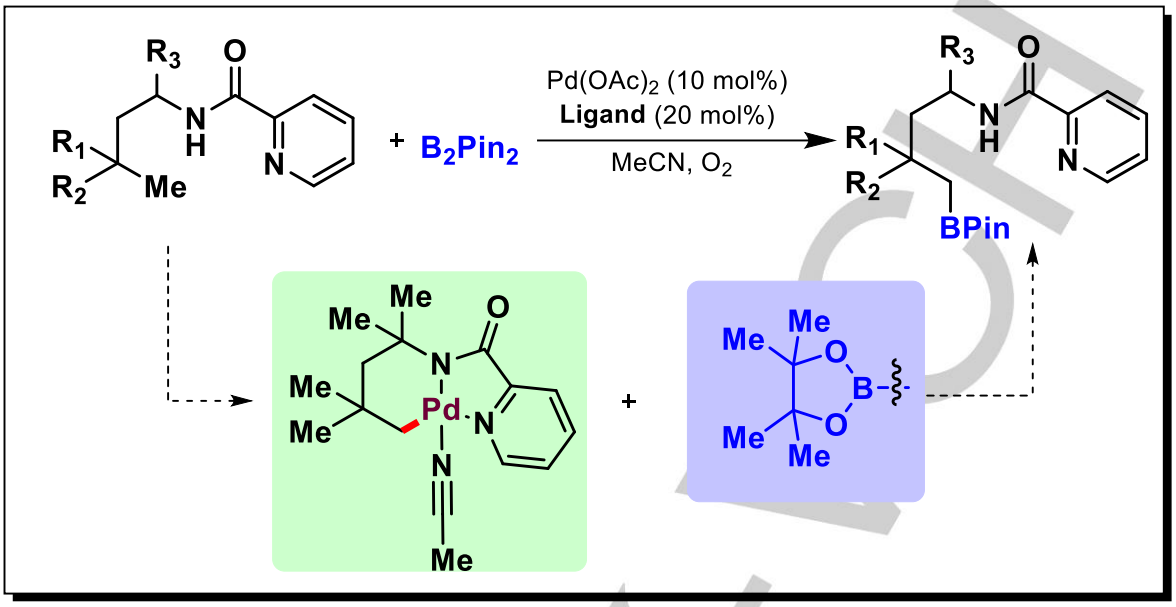

Directed C–H functionalization has been realized as a complimentary technique to achieve borylation at a distal position of aliphatic amines. Here, we demonstrated the oxidative borylation at the distal delta position of aliphatic amines using various borylating agents, a palladium catalyst and a rightly tuned ligand in the presence of a cheap oxidant. Moreover, an organopalladium δ-C(sp^3)–H activated intermediate has been isolated and crystallographically characterized to get mechanistic insight.