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COMMUNICATION

Palladium-Mediated C_γ–H Functionalization of Alicyclic Amines

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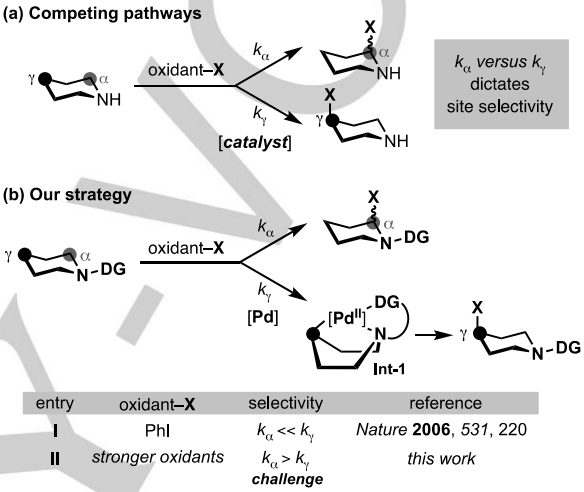
Abstract: This paper describes a new method for the transannular functionalization of the γ-C-H bonds in alicyclic amines to install C(sp^3)–halogen, oxygen, nitrogen, boron, and sulfur bonds. The key challenge for this transformation is controlling the relative rate of C_γ–H versus C_α–H functionalization. We demonstrate that this selectivity can be achieved by pre-complexation of the substrate with Pd prior to the addition of oxidant. This approach enables the use of diverse oxidants that ultimately install various heteroatom functional groups at the γ–position with high site- and diastereoselectivity.

Alicyclic amines bearing various substitution patterns are common structural motifs in bioactive molecules.[1] Conventional synthetic routes to these structures require multi-step sequences to assemble the appropriately functionalized alicyclic amine cores.[2] Approaches involving the late-stage C–H functionalization of pre-assembled alicyclic amines would complement existing synthetic routes and thus streamline the diversification of these motifs. Over the past several decades, numerous methods have been developed for functionalization at the activated C_α–H position of alicyclic amines (Scheme 1a, k_α).[3] These studies have shown that the proximity of the C_α–H bond to nitrogen greatly enhances its reactivity towards oxidative functionalization.[4] For example, C(sp^3)–H bonds α to nitrogen have relatively low bond dissociation energies (~90 kcal/mol).[5] Furthermore, oxidation of nitrogen to a radical cation renders the C_α–H site highly acidic (pK_a ~ 16) relative to unactivated C(sp^3)–H bonds.[6] In contrast, the C(sp^3)–H bonds that are remote from nitrogen (for example, C_γ–H) are typically much less reactive than C_α–H, making it significantly more challenging to selectively target these sites.

Conceptually, the selective γ-functionalization of alicyclic amines requires controlling the relative reactivity of the C_α–H (Scheme 1a, k_α) versus C_γ–H sites (Scheme 1a, k_γ). To date, most successful efforts have achieved selectivity through modification of the substrate. Common strategies involve (a) blocking the C_α–H sites with other substituents (thus decreasing k_α),[7] (b) protonating the amine nitrogen to electronically deactivate C_α–H (thus decreasing k_α),[8] or (c) employing a directing group to accelerate C_γ–H functionalization (increasing k_γ).[9] In an example of the latter, our group recently demonstrated that installing a directing group on the amine nitrogen can enable transannular C_γ–H activation via a boat-like intermediate (**Int-1**, Scheme 1b).[10] When the Pd catalyst for this transformation is paired with a mild aryl iodide (ArI) oxidant, k_γ is significantly greater than k_α. As such, directed transannular C–H arylation outcompetes background α-functionalization (Scheme 1b, entry **I**).

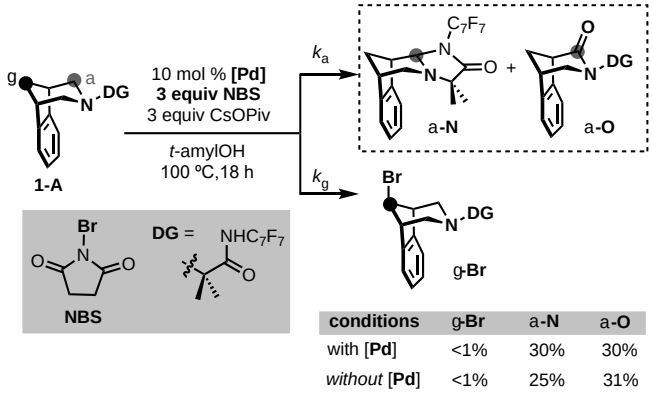


entry	oxidant–X	selectivity	reference
I	PhI	$k_\alpha << k_\gamma$	*Nature* **2006**, *531*, 220
II	*stronger oxidants*	$k_\alpha > k_\gamma$ ***challenge***	*this work*

Scheme 1. (a) Competing C_α–H versus C_γ–H (b) Our strategy.

An important goal for enhancing the utility of this transformation is to broaden the scope of functional groups that can be introduced at C_γ. In principle, this can be achieved by replacing the aryl iodide with an alternative oxidant (oxidant–X) that is designed to transfer the functional group of interest (X). However, in practice, changing to alternative, more kinetically reactive oxidants (for example, *N*-halosuccinimides, hypervalent iodine reagents, electrophilic fluorinating reagents) results in a dramatic increase in k_α, such that the background α-functionalization pathway predominates (Scheme 1b, entry **II**; *vide infra* for examples). In this report, we present a strategy to address this challenge that leverages the *in situ* formation of Pd(II) amine complexes to enable selective transannular C_γ–H functionalization with a wide range of oxidants.

Initial studies targeted the Pd-catalyzed transannular C_γ–H bromination of **1-A** with *N*-bromosuccinimide (NBS). Notably, NBS has been successfully employed in related Pd-catalyzed ligand-directed C(sp^3)–H bromination reactions (of non-amine containing substrates),[11] while **1-A** was shown to be an effective substrate for transannular C_γ–H arylation with PhI. At 100 °C in *tert*-amyl alcohol, **1-A** reacts with PhI to afford the C_γ–H phenylation product in 30% yield, with *no detectable background α-functionalization products* ($k_\alpha << k_\gamma$). However, when NBS was used in place of PhI under otherwise analogous catalytic conditions, none of the C_γ–H bromination product **γ-Br** was detected (Scheme 2). Instead, α-oxidation products **α-N** and **α-O** were formed in 30% and 30% yield, respectively (Scheme 2).[12] When this reaction was conducted in the absence of Pd catalyst, **α-N** and **α-O** were obtained in nearly identical yields of 25% and 31%. These results demonstrate that with NBS, the rate of background α-oxidation (k_α) is significantly greater than that of Pd-catalyzed γ-oxidation (k_γ).

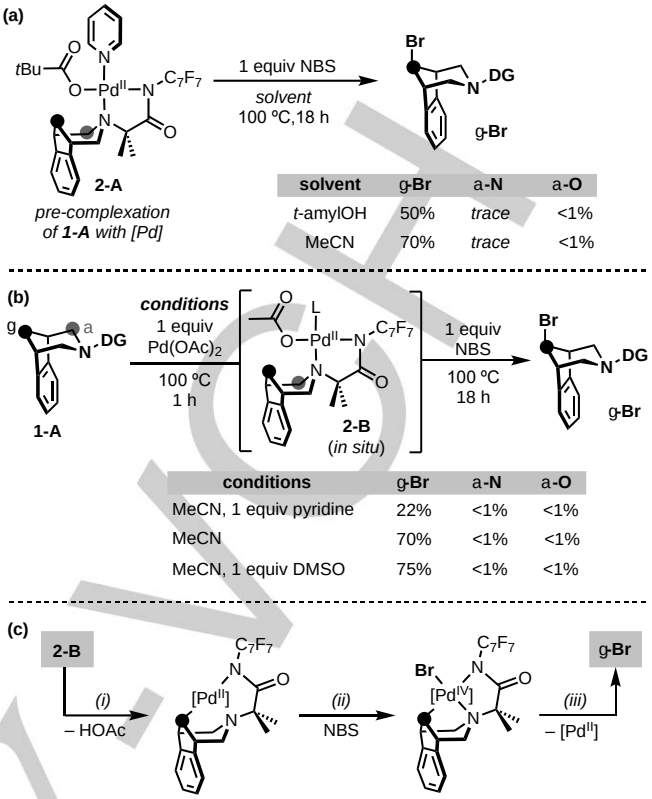


conditions	g-Br	a-N	a-O
with [**Pd**]	<1%	30%	30%
without [**Pd**]	<1%	25%	31%

Scheme 2. Pd-catalyzed C–H bromination with NBS.

We hypothesized that these relative rates might be reversed by pre-assembling a complex between substrate **1-A** and Pd (Scheme 3a).[13] This proposal was predicated on our previous report showing that γ-H/D exchange is fast at the isolable Pd-complex **2-A** (occurring at temperatures as low as 40 ºC).[13] This suggests that pre-complexation to Pd could enhance k_γ versus k_α in the NBS reactions. Indeed, the treatment of 1 equiv of complex **2-A** with 1 equiv of NBS in *t*-amylOH at 100 ºC for 18 h led to the selective formation of **γ-Br** in 50% yield (Scheme 3a). Only traces (<1%) of **α-N**/**α-O** were detected in this reaction. **γ-Br** was formed as a single regio- and stereoisomer, as determined by NMR spectroscopy. As discussed below, this stereochemistry suggests that C_γ–Br bond formation occurs via an inner sphere process with retention of configuration. Changing the solvent to MeCN led to a higher (70%) yield of **γ-Br**, again with <1% of **α-N**/**α-O**.

To render this approach more practical, we next pursued a 2-step 1-pot approach to the *in situ* assembly/γ-functionalization of a **1-A**/Pd complex. First, 1 equiv of **1-A**, 1 equiv of $Pd(OAc)_2$, and 1 equiv of pyridine were stirred at 100 ºC for 1 h in MeCN. NBS (1 equiv) was then added, and the mixture was heated at 100 ºC for an additional 18 h. This afforded a modest 22% yield of **γ-Br** with <1% of **α-N**/**α-O** (Scheme 3b). Conducting the analogous reaction in the absence of pyridine gave 70% yield of **γ-Br**, and the addition of 1 equiv of DMSO further improved the yield to 75% while maintaining high selectivity (<1% of **α-N**/**α-O**).[14]



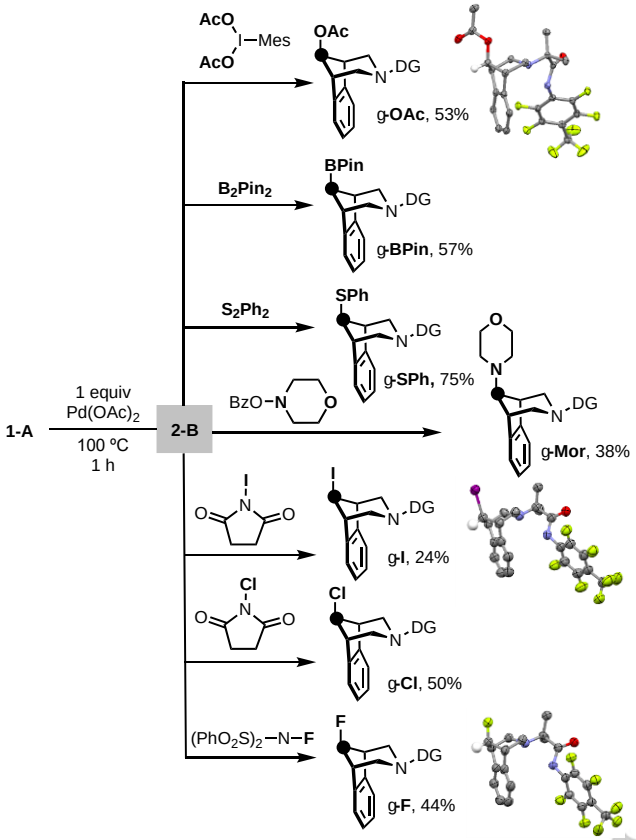
solvent	g-Br	a-N	a-O
t-amylOH	50%	*trace*	<1%
MeCN	70%	*trace*	<1%

conditions	g-Br	a-N	a-O
MeCN, 1 equiv pyridine	22%	<1%	<1%
MeCN	70%	<1%	<1%
MeCN, 1 equiv DMSO	75%	<1%	<1%

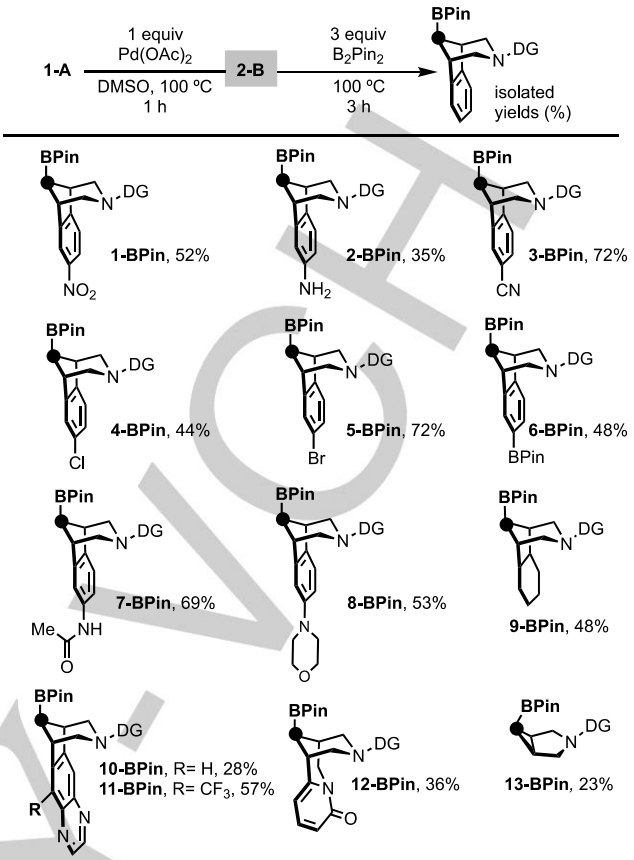
Scheme 3. (a) **γ-Br** with complex **2-A** (b) *In situ* method for **γ-Br**. (c) Proposed pathway.

A proposed pathway for this sequence based on literature precedent for the individual steps is shown in Scheme 3c. Initial coordination of **1-A** to $Pd(OAc)_2$ affords **2-B**, where L is likely MeCN or DMSO.[13],[15] Acetate-assisted transannular C_γ–H activation[10c], [16] (Scheme 3c, *i*) is followed by oxidation of this alkyl Pd^{II} intermediate to Pd^{IV} with NBS (Scheme 3c, *ii*).[17] $C(sp^3)$–Br bond-forming reductive elimination from this highly reactive Pd^{IV} center[18] then proceeds via an inner sphere mechanism with retention of configuration at carbon[19] to afford the product **γ-Br** (Scheme 3c, *iii*).

We next explored the use of a series of different oxidants in this 2-step, 1-pot protocol in order to install diverse functional groups at the γ-position. As shown in Scheme 4, this approach enabled the formation of C–O, C–S, C–N, C–F, C–Cl, C–I, and C–B bonds in high γ-selectivity and modest to good isolated yields. The site- and stereoselectivity of each functionalization was established via ^{1}H NMR spectroscopy (all products) as well as X-ray crystallography (for **γ-I, γ-F, γ-OAc**). In all cases, the major product derived from C_γ–H functionalization with retention of configuration during the C–X bond-forming step.[20]



Scheme 4. γ-functionalizations with *in situ* method.



Scheme 5. Scope of C_γ-BPin functionalization.

Finally, we evaluated the scope of C_γ–H functionalization with respect to alicyclic amine substrates. The borylation reaction with B_2Pin_2 was selected for this study based on the versatility of the boronate ester products (which can be readily transformed into amines, alcohols, or C–C bonds).[21] As shown in Scheme 5, nitro, amino, cyano, chloro, bromo, boronate ester, and amide substituents were all well tolerated. Other bicyclic amines, including those derived from the bioactive molecules varenicline (**10-BPin**) and cytisine (**12-BPin**) also reacted to afford C_γ–H borylated products with high selectivity.[22]

In summary, this report describes a strategy for the selective C_γ–H oxidation of alicyclic amines via pre-formation of amine-Pd complexes. This pre-complexation increases the relative rate of the desired C_γ–H activation versus competing background C_α–H oxidation. This work adds to a growing suite of methods in which the use of stoichiometric Pd enables selective late-stage diversification of complex organic molecules.[23] While catalytic processes are often favored by the organic chemistry community, this stoichiometric approach provides rapid and selective access to numerous challenging-to-synthesize alicyclic amine derivatives. In the context of, for example, medicinal chemistry, the speed, selectivity, and diversity of products generated via this approach counterbalance the cost of the Pd. Ultimately, we anticipate that pre-complexation could prove valuable for tuning selectivity in other reactions of alicyclic amines as well as in metal-mediated C–H functionalizations of more diverse substrates.

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Keywords: C–H activation • Palladium • Alicyclic amines • Relative rates

[1] a) E. Vitaku, D. T. Smith, J.T. Njardarson, *J. Med. Chem.* **2014**, *57*, 10257-10274; b) R. D. Taylor, M. MacCoss, A.D. G. Lawson, *J. Med. Chem.* **2014**, *57,* 5845−5859.

[2] S. Källström, R. Leino, *Bioorg. Med. Chem.* **2008**, *16*, 601-635.

[3] For examples of C_α–H of alicyclic amines, see: a) S. J. Pastine, D. Gribkov, D. Sames, *J. Am. Chem. Soc*. **2006**, *128*, 14220−14221; b) K. R. Campos, *Chem. Soc. Rev*. **2007**, *36*, 1069−1084; c) E. A. Mitchell, A. Peschiulli, N. Lefevre, L. Meerpoel, B. U. W. Maes, *Chem. - Eur. J.* **2012**, *18*, 10092−10142; d) L. Shi, W. Xia, *Chem. Soc. Rev*. **2012**, *41*, 7687−7697; e) J. He, L. G. Hamann, H. M. L. Davies, R. E. J. Beckwith, *Nat. Commun.* **2015**, *6*, 5943; f) J. E. Spangler, Y. Kobayashi, P. Verma, D.-H. Wang, J.-Q. Yu, *J. Am. Chem. Soc*. **2015**, *137*, 11876−11879; g) W. Chen, L. Ma, A. Paul, D. Seidel, *Nat. Chem.* **2017**, *10*, 165−169.

[4] For examples of amines undergoing side reactions in presence of metal catalysts and oxidants, see: a) S. Murahashi, T. Naota, K. Yonemura, *J. Am. Chem. Soc.* **1988**, *110*, 8256-8258; b) N. S. Venkataramanan, G. Kuppuraj, S. Rajagopal, *Coord. Chem. Rev*. **2005**, *249*, 1249-1268; c) J. Park, Y. Morimoto,

Y.-M. Lee, Y. You, W. Nam, S. Fukuzumi, *Inorg. Chem*. **2011**, *50*, 11612-11622; d) P. Liu, Y. Liu, E L.-M. Wong, S. Xiang, C.-M. Che, *Chem. Sci*. **2011**, *2*, 2187-2195; e) X. W. Cai, M. Sha, C. P. Guo, R. M. Pan, *Asian J. Chem.* **2012**, *24*, 3781-3784; f) J. Genovino, S. Lütz, D. Sames, B. B. Touré, *J. Am. Chem. Soc.* **2013**, *135*, 12346-12352; g) Z. Ling, L. Yun, L. Liu, X. Fu, *Chem. Commun.* **2013**, *49*, 4214-4216; h) H. A. Malik, B. L. H. Taylor, J. R. Kerrigan, J. E. Grob, K. N. Houk, J. Du Bois, L. G. Hamann, A. W. Patterson, *Chem. Sci.* **2014**, *5*, 2352-2361; i) S. Kim, J. W. Ginsbach, J. Y. Lee, R. L. Peterson, J. J. Liu, M. A. Siegler, A. A. Sarjeant, E. I. Solomon, K. D. Karlin, *J. Am. Chem. Soc*. **2015**, *137*, 2867-2874.

[5] D. D. M. Wayner, K. B. Clark, A. Rauk, D. Yu, D. A. Armstrong, *J. Am. Chem. Soc.* **1997**, *119*, 8925-8932.

[6] J. C. K. Chu, T. Rovis, *Angew. Chem. Int. Ed*. **2018**, *57*, 62-101.

[7] For remote C–H functionalization blocking C_α–H sites on alicylic amines, see: a) A. McNally, B. Haffemayer, B. S. Collins, M. J. Gaunt, *Nature* **2014**, *510*, 129-133; b) J. Calleja, D. Pla, T. W. Gorman, V. Domingo, B. Haffemayer, M. J. Gaunt, *Nature Chemistry* **2015**, *7*, 1009-1016.

[8] For remote C−H functionalization protonating nitrogen on alicylic amines, see: a) C. Annese, L. D'Accolti, M. De Zotti, C. Fusco, C. Toniolo, P. G. Williard, R. Curcu, *J. Org. Chem*. **2010**, *75*, 4812-4816; b) C. T. Mbofana, E. Chong, J. Lawniczak, M. S. Sanford, *Org. Lett*. **2016**, *18*, 4258-4261; c) D. M. Schultz, F. Lévesque, D. A. DiRocco, M. Reibarkh, Y. Ji, L. A. Joyce, J. F. Dropinski, H. Sheng, B. D. Sherry, I. W. Davies, *Angew. Chem. Int. Ed.* **2017**, *56*, 15274-15278; d) M. Lee, M. S. Sanford, *Org. Lett.* **2017**, *19*, 572-575; e) C. M. White, J. Zhao, *J. Am. Chem. Soc*. **2018**, *140*, 13988-14009.

[9] For remote C−H functionalization using directing groups, see: a) D. Antermite, J. A. Bull, *Synthesis* **2019**, *51*, 3171-3204; b) C. He, W. G. Whitehurst, M. J. Gaunt, *Chem* **2019**, *5*, 1031-1058; c) Z. Li, M. Dechantsreiter, S. Dandapani, *J. Org. Chem*. **2020**, *85*, 6747-6760.

[10] a) J. J. Topczewski, P. J. Cabrera, N. I. Saper, M. S. Sanford, *Nature* **2016**, *531*, 220−224; b) P. J. Cabrera, M. Lee, M. S. Sanford, *J. Am. Chem. Soc*. **2018**, *140*, 5599-5606; c) A. L. Dewyer, P. M. Zimmerman, *ACS Catal*. **2017**, *7*, 5466-5477.

[11] R.-Y. Zhu, T. G. Saint-Denis, Y. Shao, J. He, J. D. Sieber, C. H. Senanayake, J.-Q. Yu, *J. Am. Chem. Soc.* **2017**, *16*, 5724-5727.

[12] Even at 50 °C (under otherwise analogous conditions to Scheme 2), the yields of **γ-Br**, **α-N**, and **α-O** were 0, 12, and 15%, respectively.

[13] E. Y. Aguilera, M. S. Sanford, *Organometallics* **2019**, *38*, 138-142.

[14] Other L-type ligands were also evaluated (e.g. bipyridine, PPh_3) and all gave poor yields of **γ-Br**.

[15] In our hands, complex **2-B** with L = DMSO proved challenging to isolate, providing further impetus for generating this putative intermediate *in situ*.

[16] a) D. Lapointe, K. Fagnou, *Chem. Lett.* **2010**, *39*, 1118-1126; b) J. B. Gary, M. S. Sanford, *Organometallics* **2011**, *30*, 6143-6149; c) L. Ackermann, *Chem. Rev.* **2011**, *111*, 1315-1345; d) S. L. Gorelsky, D. Lapointe, K. Fagnou, *J. Org. Chem*. **2012**, *77*, 658-668; e) S. I. Gorelsky, *Coord. Chem. Rev*. **2013**, *257*, 153-164.

[17] S. R. Whitfield, M. S. Sanford, *J. Am. Chem. Soc*. **2007**, *129*, 15142-15143.

[18] J. Racowski, M. S. Sanford in *Topics in Organometallic Chemistry*, *Vol. 53*, (Eds.: A. Canty), Springer, **2011**, pp. 61-84.

[19] a) J. M. Racowski, B. J. Gary, M. S. Sanford, *Angew. Chem. Int. Ed.* **2012**, *51*, 3414-3417; b) Y.-Q. Chen, S. Singh, Y. Wu, Z. Wang, W. Hao, P. Verma, J. X. Qiao, R. B. Sunoj, J.-Q. Yu, *J. Am. Chem. Soc.* **2020**, *142*, 9966-9974.

[20] Compound **α-N** was formed as a minor product (15% yield) with *N*-iodosuccinimide. With *N*-chlorosuccinimide, *N*-fluorobenzenesulfonimide, iodomesitylene diacetate, morpholino benzoate, B_2Pin_2, and S_2Ph_2, compound **α-N** was also detected but in <10% yield.

[21] a) M. A. Larsen, J. F. Hartwig, *J. Am. Chem. Soc.* **2014**, *136*, 4287-4299; b) J. W. B. Fyfe, A. J. B. Watson, *Chem* **2017**, *3*, 31-55; c) L. Xu, G. Wang, S. Zhang, H. Wang, L. Wang, L. Liu, P. Li, *Tetrahedron* **2017**, *73*, 7123-7157.

[22] With piperidines as the substrate, only starting material and α-functionalization was observed (see Table 3 in SI for examples).

[23] M. R. Uehling, R. P. King, S. W. Krska, T. Cernak, S. L. Buchwald, *Science* **2019**, *363*, 405-408.

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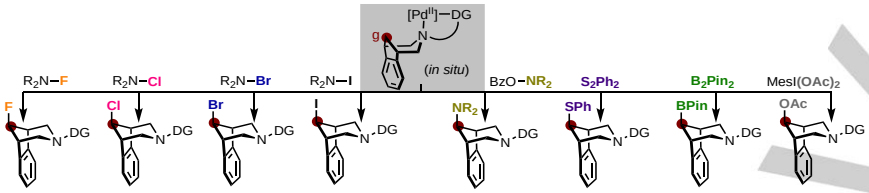

An approach to selectively transform C_γ–H bonds of alicyclic amines to $C_\gamma(sp^3)$–halogen, oxygen, nitrogen, boron, and sulfur bonds is described. This method is enabled via the pre-complexation of the amine substrate with palladium followed by the addition of oxidant to yield bioactive motifs functionalized at the γ–position.