Palladium-catalyzed C(sp^3)–H activation of amines to strained nitrogen heterocycles

Andrew McNally, Benjamin Haffemayer, Beatrice S. L. Collins and Matthew J. Gaunt

The development of new chemical transformations based on catalytic functionalization of unactivated C–H bonds holds great potential for complex molecule synthesis. Transition metal catalysis has emerged as a powerful tool to convert these traditionally unreactive C–H bonds into useful carbon–carbon and carbon–heteroatom bonds[1-6]. While this strategy has been particularly important in functionalizing aromatic molecules, the selective functionalization of aliphatic C–H bonds remains a significant challenge. The majority of successful processes are facilitated by a directing group, a polar functionality that positions the metal catalyst in proximity to a particular C–H bond, thereby enabling the C–H functionalization step via cyclometallation[7]. Strikingly, almost all of these aliphatic directed C–H activation processes proceed through a 5-membered ring cyclometallated intermediate[8-10]. Considering the number of new reactions that have evolved from 5-membered ring cyclometallated intermediates, the discovery of distinct cyclometallation pathways could lead to the development of many useful chemical transformations.[11] Herein, we report an unprecedented palladium-catalyzed C–H bond activation mode that proceeds through a 4-membered ring cyclopalladation pathway and enables the selective transformation of a methyl group adjacent to an unprotected secondary amine into synthetically versatile strained nitrogen heterocycles. The scope previously of this unknown bond disconnection is highlighted through the development of C–H amination and carbonylation processes leading to the synthesis of aziridines and β–lactams respectively and is suggestive of a generic C–H functionalization platform that could simplify the synthesis of aliphatic secondary amines, a universally important class of molecules.

Several classes of directing group can participate in directed C–H activation with aliphatic systems and include functionalities such as carbonyl derivatives, aromatic nitrogen heterocycles and hydroxyl motifs[12-18]. Palladium salts have been particularly successful at affecting cyclometallation with these functional groups; coordination of the palladium centre to the Lewis basic heteroatom within the directing motifs is assumed to lower the entropic and enthalpic costs of the C–H bond cleavage and ring closure, and accounts for why kinetically favoured 5-membered ring intermediates are preferred over other cyclopalladation pathways. Reaction of the resulting carbon-palladium bond with an external reagent leads to an overall chemical transformation that sees a carbon-hydrogen bond converted into a synthetically versatile functional group. As a result, this type of cyclopalladation event has led to a number of useful catalytic C–H bond functionalization processes that have expanded the synthetic chemists toolbox of available reactions (Fig. 1a). Despite their success, one limitation of catalytic cyclopalladation is that the exquisite selectivity displayed through 5-membered ring intermediates means that the generic strategic bond disconnection enabled by directed C–H activation is often restricted to a single position with respect to the controlling functional group. As part of an overarching goal to develop new activation modes for catalytic C–H activation, we questioned whether cyclopalladation could function in systems that do not possess C–H bonds in the positions that would facilitate classical, kinetically favoured insertion processes. Furthermore, we reasoned that C–H activation directed by common functional groups represents an important challenge to the continued advance of this field; while native functionalities such as carboxylic acids and hydroxyl groups have been shown to participate in catalytic cyclopalladallation[17,18], there are no examples of directed catalytic C–H activation with unprotected aliphatic amines[19-23]. Herein, we report the successful realization of these ideas via a new C–H activation strategy that uses unprotected aliphatic secondary amines to direct a palladium-catalyzed C–H activation event that transforms an adjacent methyl groups into synthetically versatile nitrogen heterocycles (Fig. 1b). This novel palladium catalyzed

activation process proceeds through a remarkable 4-membered ring cyclometallation pathway and enables a broad scope for catalytic C–H functionalization through both Pd(II) or Pd(IV) intermediates.

At the outset of our studies, we selected an amine substrate displaying a series of C–H bonds positioned in such a way that they could not engage in classical 5-membered ring cyclopalladation (Fig. 2a). When the aliphatic secondary amine **1a** was treated with a stoichiometric amount of palladium(II) acetate, we were delighted to observe a new trinuclear organopalladium complex (***int-I***) where C–H activation had taken place at one of the unactivated methyl groups proximal to the amine and formed a 4-membered ring intermediate (as determined by single crystal X-ray diffraction of a phosphine dertivative **2a**). To the best of our knowledge, this is the first example of an amine directed 4-membered ring cyclopalladation event[24,25]. Excited by this novel C–H activation mode, we next probed the reactivity of these strained cyclopalladation complexes. We questioned whether mild chemical oxidants, such as the hypervalent iodine compound $PhI(OAc)_2$, might allow access to C–H functionalization pathways proceeding through high-valent Pd(IV) cyclometallated intermediates[26], as well as formulating the basis of a catalytic transformation. When we treated cyclopalladation complex (***int-I*** or **2a**) with $PhI(OAc)_2$ we were surprised to discover aziridine **3a**, presumably formed via C–N bond forming reductive elimination from a high oxidation state Pd(IV) intermediate (***int-III***, Fig. 2b-c). We were able to quickly establish a catalytic transformation based on this unusual in this C–H functionalization event; after optimization, the Pd-catalyzed C–H process requires only 5 mol% catalyst to produce aziridine **3a** on a multigram scale. Furthermore, the reaction is also selective between the two different types of methyl groups (red & blue in Fig. 1a), indicating a subtle stereoelectronic differentiation imparted by the nearby carbonyl group. The distinctive nature of the directed cyclopalladation pathway was further evidenced when we tested amine **1b**, where cyclopalladation can proceed through a 4-membered ring (activation on methyl group) or the conventional 5-membered ring pathway (activation on ethyl group) (Fig. 2d). Remarkably, we still observe activation through the 4-membered ring pathway forming the related strained complexes (***int-II***, **2b**) – we do not believe that such selectivity has been observed before. We also found that the amine **1b** underwent the same catalytic transformation in very good yield, forming the corresponding aziridine **3b** (Fig. 2e). Not only does this catalytic cyclopalladation pathway contrast classical directed C–H activation, it also reveals novel chemical reactivity that underpins a conceptually distinct disconnection to synthesise strained nitrogen heterocycles directly from simple aliphatic amines displaying methyl groups adjacent to an unprotected nitrogen motif.

In assessing the scope of the catalytic reaction, a range of amines displaying a variety of substituents were found to be suitable substrates (Figure 3). For example, simple alkyl–(methyl) substituted morpholinones undergo the C–H aziridination process in high yield (**3a–e**) and are always selective for the 4-membered ring C–H activation pathway. Substituents containing aromatic rings, protected hydroxyl groups, sensitive chloromethyl and fluoromethyl motifs, esters and protected amines all work well underlying a broad tolerance to a variety of useful functional groups (**3f**-**k**). The C–H aziridination reaction can be applied to methylene C–H bonds, albeit in lower yield, to form **3l**, further expanding the potential efficacy of this process. Morpholinones that display only three substituents around the secondary amine motif, thus far, do not react under the standard conditions. Substrates containing substituents other than methyl groups distal to the carbonyl motif can be accommodated; a piperidine substituted morpholinone undergoes smooth C–H aziridination to form a product (**3n**) displaying a high density of useful functionality. Interestingly, we found that amine derivatives not possessing the lactone framework also underwent catalytic C–H activation through the 4-membered ring cyclopalladation pathway in the presence of $PhI(OAc)_2$ but formed acetoxylation product (**5**) rather than an aziridine. This again suggests that the carbonyl group in the morpholinones may play a subtle controlling role, this time steering the reactivity of the putative organo-Pd(IV) intermediate. Importantly, acyclic amines also undergo directed C–H activation to form an amino alcohol derivative (**6**) is reasonable yield.

One of the most important uses of aziridines is their ring opening reactions with nucleophiles[27]. Despite the non-activated and hindered nature of these aziridines (**3**), we found that a range of nucleophiles can open this strained heterocycle to form complex amine products (Fig. 3c). For example, heteroatom nucleophiles such as azide, thiol, chloride and water open the aziridine in good yield under acidic conditions (**4a-d**). Notably, fluoride can also be used as a nucleophile, forming amine **4e**. The aziridine motif can also be opened with a carbon nucleophile (*N*-methylindole) to form **4f**. To further demonstrate the synthetic versatility of these products, the functionalized aziridine **3g** can also be opened with pyrazole followed by saponification-oxidative cleavage of the cyclic framework reveals a highly functionalized quaternary amino acid **7a**, characteristic of a class of molecule that would be difficult to make by conventional synthetic methods (Fig. 3d). Moreover, the C–H activation strategy also provides access to a previously inaccessible class of fully substituted secondary aliphatic amines. The lactone motif in morpholinones such as **4f** can be transformed into useful functionality (**7a**-**b**) that is representative of a class of complex fully substituted aliphatic secondary amine with unexplored biological properties. This class of sterically hindered amine is underrepresented because of the limited number of ways through which they can be synthesised and have therefore been largely ignored as pharmaceutical candidates. However, we believe the privileged nature of aliphatic nitrogen-containing compounds motif will generate significant interest in this elusive class of amines.

Intrigued by the different outcome observed in forming amines **3a** and **5** under the same conditions, we next explored the reactivity of these molecules under a complemetary palladium manifold. Replacing $PhI(OAc)_2$ with carbon monoxide and a suitable oxidant would lead to a potential carbonylation process through a Pd(II)-Pd(0) catalytic cycle[28]. We found that mixing commercial amine (tetramethylpiperidine, TMP) with stoichiometric $Pd(OAc)_2$ gave rise to a 4-memebered ring palladacycle (**8**) that could be directly characterized by X-ray diffraction (Fig. 4a). Furthermore, when we treated this complex with carbon monoxide, a β–lactam (**9a**) was formed in high yield (Fig. 4b). Yet again, a strained nitrogen heterocycle can be formed form a methyl group adjacent to a secondary amine and further underlines the synthetic versatility of this new directed C–H activation mode. Assessment of a range of reaction parameters led to an optimized catalytic process that required treatment of TMP with 10 mol% of $Pd(OAc)_2$, 10 mol% of $Cu(OAc)_2$ as oxidant in toluene at 120 ˚C under an atmospheric pressure of CO/air (for 22 hours) to form β–lactam **9a** in 87% yield. As shown in Fig. 1b, an array of commercial or readily available piperidine derivatives are competent substrates. Not only does this reaction produce a series of novel β–lactams that may themselves have interesting biological properties, many of the products also display orthogonal and versatile functionality that can be easily transformed into more complex amines. In addition to standard piperidine derivatives (**9a**-**b**), a number of other heterocylces could also be readily tolerated: morpholine and piperizine scaffolds, fluorinated piperidines and a 7-memebered ring azepine all productively form the corresponding β–lactams and display the type of structural motifs that are frequently considered important in the design of pharmaceutical agents (**9c**-**f**). The morpholinone **1a** also undergo carbonylation, but, in contrast to the C–H aziridnation process, a 2:1 ratio of a mixture of separable β–lactams, in favour of **9g**, is formed. This result is surprising given the selectivity of the cyclopalladation with this substrate and suggests that the C–H palladation step may be reversible under carbonylation conditions. Pleasingly, acyclic amines are also effective substrates producing the monocyclic β–lactam **9h** in good yield.

Given the broad utility and application of aliphatic amines, it is surprising that they are seldom employed in C–H bond functionalization reactions, especially considering that secondary amines are excellent coordinating groups for palladium salts. When treated with palladium (II) salts most amines rapidly form square planar, coordinately saturated bis-amine palladium (II) complexes, however, the pathway for C–H bond functionalization requires liberation of a coordination site occupied by one of these amines[21]. As the palladium(II) complexes formed from these amines are typically very stable, there is little driving force for the release of an amine

ligand. This generally renders the bis-amine palladium species catalytically inactive unless they are subjected to thermal activation that can also lead to unwanted side reactions. The hindered secondary amines used in this study, that contain two fully substituted carbon atoms bonded to nitrogen, also form bis-amine complexes with $Pd(OAc)_2$ (**10**, Fig 5). We propose that the steric hindrance around the Pd(II) centre results in more facile dissociation. This weaker binding would therefore facilitate the release of one of the amines to create the essential vacant coordination site (***int-IV***) and enabling C–H activation to take place[29]. We speculated that if secondary amines that do not possess two fully substituted carbon groups directly attached to the NH motif could be accommodated (as represented by amine **11**), then the efficacy of this new C–H activation mode would be significantly expanded. Although we were conscious such amines might be prone to competitive decomposition pathways potentially via β–hydride elimination, we found that these less hindered amines, comprised of a fully substituted carbon atom on one side of the NH motif and a tertiary carbon atom on the other, undergo the palladium catalyzed C–H carbonylation reaction to form the corresponding β–lactams **12a-c** (Fig. 5b). The C–H activation pathway was even viable on amines displaying two tertiary substituents (hence a C–H bond adjacent to nitrogen on both substituents), and although the yield is low, this initial result suggests that the generic activation pathway could be possible on many classes of secondary amine. Finally, we were also able to demonstrate that more classical five membered ring cyclopalladation pathways can also be initiated by this type of secondary aliphatic amine. On treatment of ethyl-substituted morpholinone **3o** with $Pd(OAc)_2$ and $PhI(OAc)_2$ as oxidant we observed a 55% of the C–H acetoxylation product **13** that is presumably derived from the 5-memebered ring palladacycle **14**. Based on the extensive number of transformations available to related 5-memebred ring cyclopalladation pathways, this result suggests that aliphatic amines could be amenable to a range of new reactions through this well established activation mode.

Taken together, these exciting results represent an important initial advance that could dramatically broaden this directed C–H activation methodology to further classes of secondary amine and further re-enforces the potential of a new strategic bond disconnection, which converts simple methyl groups into a range of versatile strained nitrogen heterocycles. As the physical and biological properties of aliphatic amines are central to the function of many important pharmaceuticals, chemical reagents and polymeric materials, we expect that such an approach to amine synthesis will be broadly useful to the synthesis complex functional amines.

METHODS SUMMARY

Pd(II)-catalyzed C–H amination to aziridines. An oven dried round bottom flask, equipped with stir bar, was charged with the amine (1.0 equiv), $Pd(OAc)_2$ (0.05 equiv) and iodobenzene diacetate (1.5-2.5 equiv). The solvent (0.1-0.05 M) was added followed by acetic anhydride (2.0 equiv) and the flask capped under an air atmosphere. The flask was placed in a pre-heated oil bath at the 70 ˚C and stirred for the given time. The reaction was then cooled to room temperature, filtered through Celite, eluting with ethyl acetate, and concentrated *in vacuo*. The residue was purified by flash column chromatography to provide the pure aziridine product.

Pd(II)-catalyzed C–H carbonylation to β-lactams. An oven dried round bottom flask, equipped with stir bar, was charged with $Pd(OAc)_2$ (0.1 equiv.), $Cu(OAc)_2$ (0.1 equiv.), the amine (as a 0.1 M solution in toluene) and then fitted with a reflux condenser and rubber septa. A balloon of air and a balloon filled with carbon monoxide were fitted and then the flask was placed in a pre-heated oil bath at 120 ºC such that the oil level matched the level of solvent in the flask and stirred for 22-24 h. The reaction mixture was then cooled to room temperature and filtered through Celite, eluting with ethyl acetate. The filtrates were washed with a 0.1 M solution of hydrochloric acid (20 mL), a saturated aqueous solution of $NaHCO_3$ (20 mL) and brine (20 ml). The organic phase was dried

($MgSO_4$), filtered and concentrated *in vacuo*. The residue was then purified by flash column chromatography to provide the pure β-lactam product.

1. Jia, C., Kitamura, T. & Fujiwara, Y. Catalytic functionalization of arenes and alkanes via C–H bond activation. *Acc. Chem. Res.* **34**, 633-639 (2001).
2. Godula, K. & Sames, D. C–H bond functionalization in complex organic synthesis. *Science* **312**, 67 (2006).
3. Davies, H. M. L. & Manning, J. R. Catalytic C–H functionalization by metal carbenoid and nitrenoid insertion. *Nature*, **451**, 417 (2008).
4. Davies, H. M. L., Du Bois, J., Yu, J. –Q. C–H functionalization in organic synthesis. *Chem. Soc. Rev.* **40**, 1855-1856 (2011).
5. Yamaguchi, J., Yamaguchi, A. D. & Itami, K. C–H bond functionalization: emerging synthetic tools for natural products and pharmaceuticals. *Angew. Chem. Int. Ed.* **51**, 8960-9009 (2012).
6. Mkhalid, I. A. I., Barnard, J. H., Marder, T. B., Murphy, J. M. & Hartwig, J. F. C–H activation for the construction of C–B bonds. *Chem. Rev.* **110**, 890-931 (2010).
7. Dupont, J., Consorti, C. C. & Spencer, J. The potential of palladacycles: more than just precatalysts. *Chem. Rev.* **105**, 2527-2572 (2005)
8. Lyons, T. W. & Sanford, M. S. Palladium-catalyzed ligand-directed C–H functionalization reactions. *Chem. Rev.* **110**, 1147-1169 (2010).
9. Ackermann, L. Carboxylate-assisted transition-metal-catalyzed C–H bond functionalizations: mechanism and scope. *Chem. Rev.* **111**, 1315-1345 (2011).
10. Colby, D. A., Bergman, R. G. & Ellman, J. A. Rhodium-catalyzed C–C bond formation via heteroatom directed C–H bond activation. *Chem. Rev.* **110**, 624-655 (2010).
11. Leow, D. Li, G. Mei, T.-S. Yu, J.-Q. Activation of Remote meta-C-H Bond Assisted by an End-on Template. *Nature* **486**, 518-521 (2012)
12. Desai, L. V., Hull, K. L. & Sanford, M. S. Palladium-catalyzed oxygenation of unactivated sp^3 hybridized C–H bonds. *J. Am. Chem. Soc.* **126**, 9542-9543 (2004).
13. Zaitsev, V. G., Shibashov, D. & Daugulis, O. Highly regioselective arylation of sp^3 C–H bonds catalyzed by palladium acetate. *J. Am. Chem. Soc.* **127**, 13154-13155 (2005).
14. Wang, D.-H., Wasa, M., Giri, R. & Yu, J.-Q. Pd(II)-catalyzed cross-coupling of sp^3 C–H bonds with sp^2 and sp^3 boronic acids using air as the oxidant. *J. Am. Chem. Soc.* **130**, 7190-7191 (2008).
15. Giri, R., Chen, X. & Yu, J.-Q. Palladium-catalyzed asymmetric iodination of unactivated C–H bonds under mild conditions. *Angew. Chem. Int. Ed.* **44**, 2112-2115 (2005).
16. Campeau, L.-C., Schipper, D. J. & Fagnou, K. Site-selective sp^2 and benzylic sp^3 palladium-catalyzed direct arylation. *J. Am. Chem. Soc.* **130**, 3266-3267 (2008).
17. Giri, R., Maugel, N. L., Li, J.-J., Wang, D.-H., Breazzano, S. P., Saunders, L. B. & Yu, J.-Q. Palladium-catalyzed methylation and arylation of sp^2 and sp^3 C–H bonds in simple carboxylic acids. *J. Am. Chem. Soc.* **129**, 3510-3511 (2007).
18. Simmons, E. M. & Hartwig, J. F. Catalytic functionalization of unactivated primary C–H bonds directed by an alcohol. *Nature* **483**, 70-73, (2012).

19. He, G., Zhao, Y., Zhang, S., Lu, C. & Chen. G. Highly efficient syntheses of azetidines, pyrrolidines, and indulines via palladium-catalyzed intramolecular amination of C(sp^3)–H and C(sp^2)–H bonds at the g and d positions. *J. Am. Chem. Soc.* **134**, 3-6 (2011).
20. Zhang, S.-Y., He, G., Nack, W. A., Zhao, Y., Li, Q. & Chen. G. Palladium-catalyzed picolinamide-directed alkylation of unactivated C(sp^3)–H bonds with alkyl iodides. *J. Am. Chem. Soc.* **135**, 2124-2127 (2013).
21. Ryabov, A. D. Mechanisms of intramolecular activation of carbon-hydrogen bonds in transition-metal complexes. *Chem. Rev.* **90**, 403-424 (1990).
22. Chan, K. S. L., Wasa, M., Chu, L., Laforteza, B. N., Miura, M., & Yu, J.-Q. Ligand-enabled cross-coupling of C(sp3)-H bonds with arylboron reagents via Pd(II)/Pd(0) catalysis. *Nat. Chem.* **6**, 146-150 (2013).
23. Wehn, P. M., Lee, J., Du Bois, J. Stereochemical models for Rh-catalysed amination reactionsof chrial sulfamates. *Org. Lett.* **5**, 4823-4826 (2005).
24. Tan, Y., Barrios-Landeros, F. & Hartwig, J. F. Mechanistic studies on direct arylation of pyridine N-oxide: evidence for cooperative catalysis between two distinct palladium centers. *J. Am. Chem. Soc.* **134**, 3683-3686 (2012).
25. Agnus, Y., Gross, M., Labarelle, M., Louis, R. & Metz, B. *J.* Unusual double palladium(II) cyclometallation in a tweezer-like receptor with stacked arms: synthesis, properties and X-ray structure. *J. Chem. Soc. Chem. Commun.* 939-940 (1994).
26. A. J. Hickman, M. S. Sanford, High-valent organometallic copper and palladium in catalysis. *Nature* **484**, 177-185 (2012).
27. Hu, X. E. Nucleophilic ring openings of aziridines. *Tetrahedron* **60**, 2701-2743 (2004).
28. Yoo, E. J. Wasa, M. & Yu, J.-Q. Pd(II)-catalyzed carbonylation of C(sp^3)–H bonds: a new entry to 1,4-dicarbonyl compounds. *J. Am. Chem. Soc.* **132**, 17378-17380 (2010).
29. Engle, K. M., Wu, H.-C. & Yu, J.-Q. Weak coordination as a powerful means for developing broadly useful C–H functionalization reactions. *Acc. Chem. Res.* **45**, 788-802 (2012).

Supplementary Information is available in the online version of the paper.

Acknowledgments We are grateful to the EPSRC (A. M.), GSK for Case Award (B. H.), University of Cambridge (B. S. L. C.), and the ERC and EPSRC for Fellowships (M. J. G.). Mass spectrometry data was acquired at the EPSRC UK National Mass Spectrometry Facility at Swansea University. The authors declare no competing financial interests.

Author Contributions A.M., B.H. and B.S.L.C. discovered and developed the reactions. M.J.G. conceived, designed and directed the investigations and wrote the manuscript with revisions provided by A.M. and B.S.C.L. All correspondence should be sent to M. J. G. (mjg32@cam.ac.uk).

Figure 1. Palladium-catalyzed directed C–H activation modes. **a**, classical directed C–H activation via kinetically favoured 5-membered ring cyclopalladation. X, directing group; FG, new functional group. **b**, new aliphatic secondary amine directed C–H activation to a 4-membered ring cyclopalladation complex and novel reactivity to form synthetically versatile strained nitrogen heterocycles. $R^{1,2,3}$, general aliphatic substituents.

Figure 2. A new amine directed, palladium-catalyzed directed C–H activation mode. **a**, coordination of amine to the Pd(II) centre facilitates a cyclopalladation to a 4-membered ring complex. Proof of structure is obtained through X-ray diffraction of a phosphine derivative, **b** and **e**, palladium-catalyzed C–H aziridination of secondary amines, **c**, reaction most likely proceeds through the oxidation of ***int-I*** to the Pd(IV) intermediate (***int-III***) before a reductive elimination to form a C–N bond. L, undefined neutral ligand, **d**, the novel cyclopalladation pathway when a classical, kinetically favoured 5-membered ring cyclopalladation is possible. For X-ray structures, grey = C, red = O, dark blue = N, aquamarine = Pd, orange = P, green = Cl, light blue = F

Figure 3. Scope of palladium-catalyzed C–H aziridination process. **a**, transformation of amine to aziridine and then ring opening with nucleophiles (Nu–H), **b**, scope of azirindation reaction, **c**, scope of azirindine ring opening (see SI for experimental procedures), **d**, synthesis of a functionally complex quaternary amino acid. [i] mass balance comprises of a complex mixture of polyacetoxylated products, **e**, representative transformations of the aziridine ring opening products into highly functionalized fully substituted secondary aliphatic amines.

Figure 4. Palladium-catalyzed C–H carbonylation of aliphatic amines. **a**, similarly to amine **1a**, treatment of TMP with $Pd(OAc)_2$ generates the 4-membered ring cyclopalladation complex **8**, whose structure was directly determined by X-ray diffraction, **b**, scope of the C–H carbonylation reaction. [a] 2:1 mixture of regioisomers observed in favour of the one shown. [b] Reaction conducted with AgOAc in dioxane at 125 ˚C.

Figure 5. Towards a general strategy for C–H activation of aliphatic amines. **A**, amines bind strongly to palladium(II) salts to form stable bis-amine complexes. Dissociation of one of the amine ligands leads to C–H activation to the cyclopalladation complex. The steric properties of these hindered amine are likely to be responsible for the facile dissociation, **b**, shows that less hindered amines can also undergo the directed C–H activation through the 4-membered ring, **c**, demonstration that C–H activation on unprotected aliphatic secondary amines can also proceed through 5-membered ring cyclopalladation pathways.

Figure 1

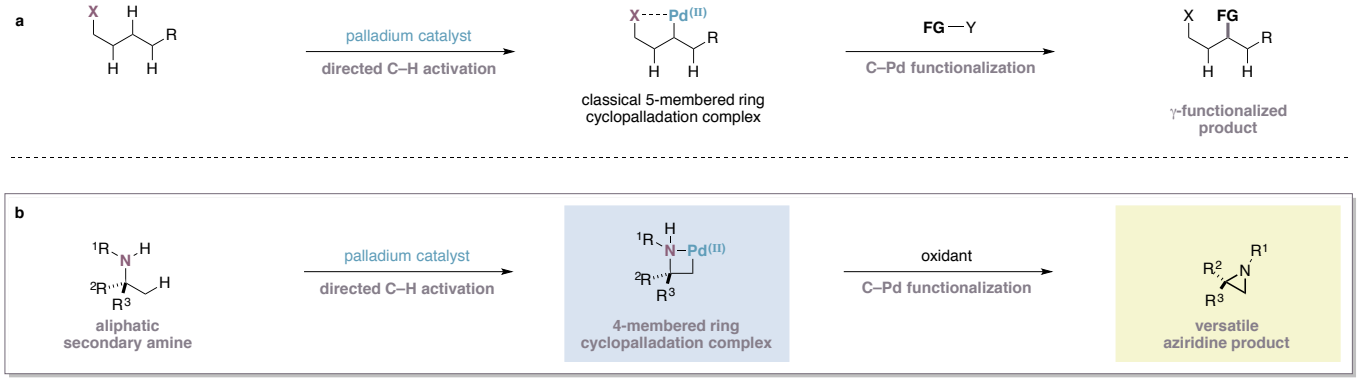


Figure 2

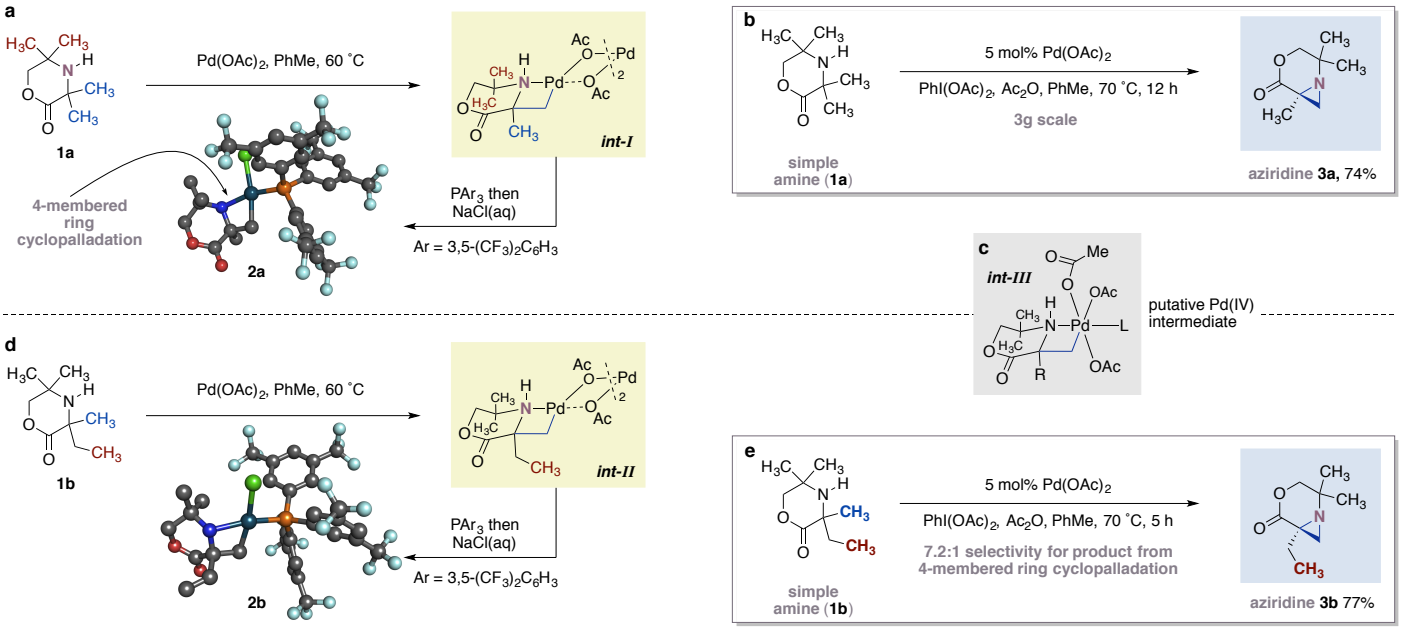


Figure 3

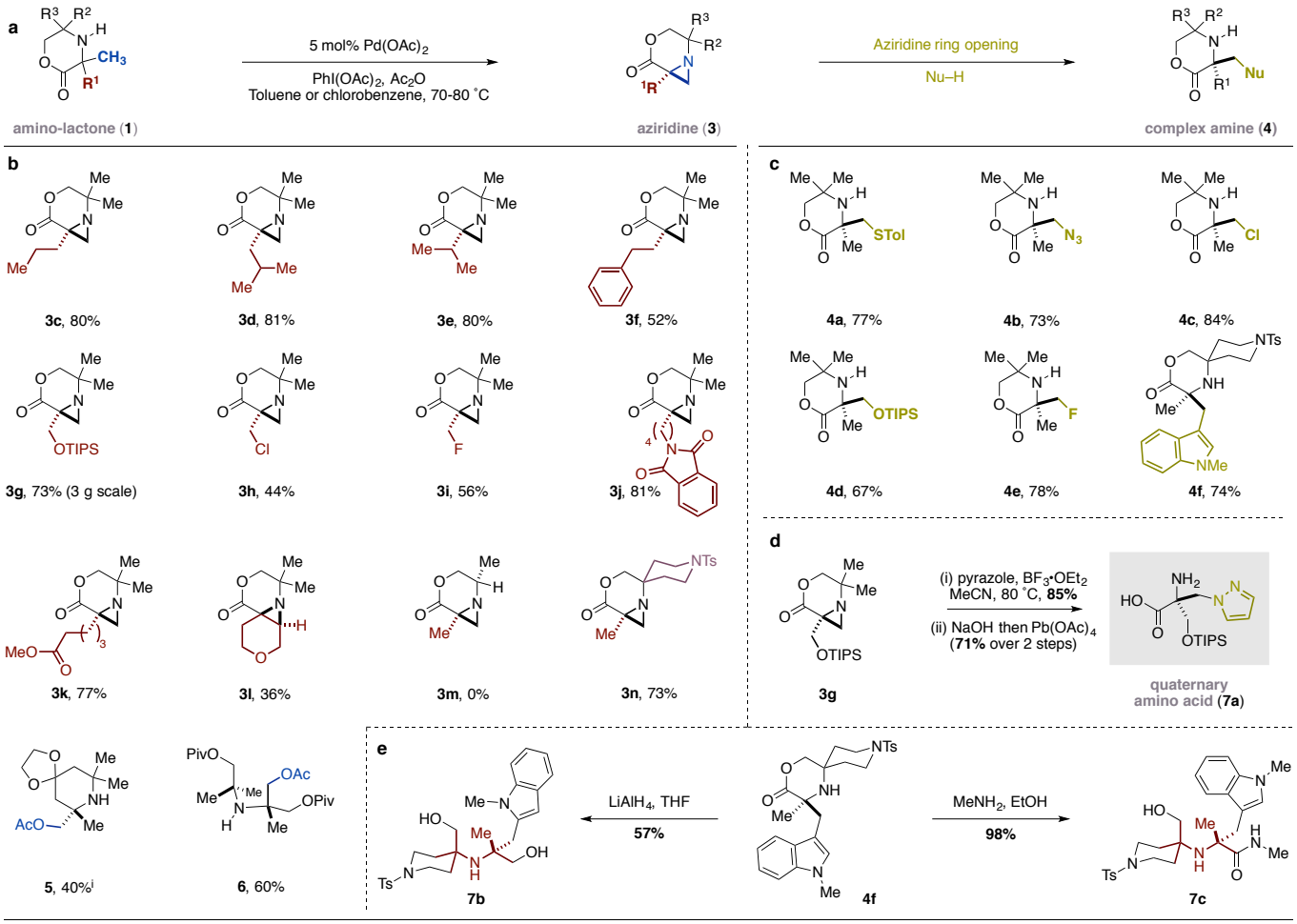


Figure 4

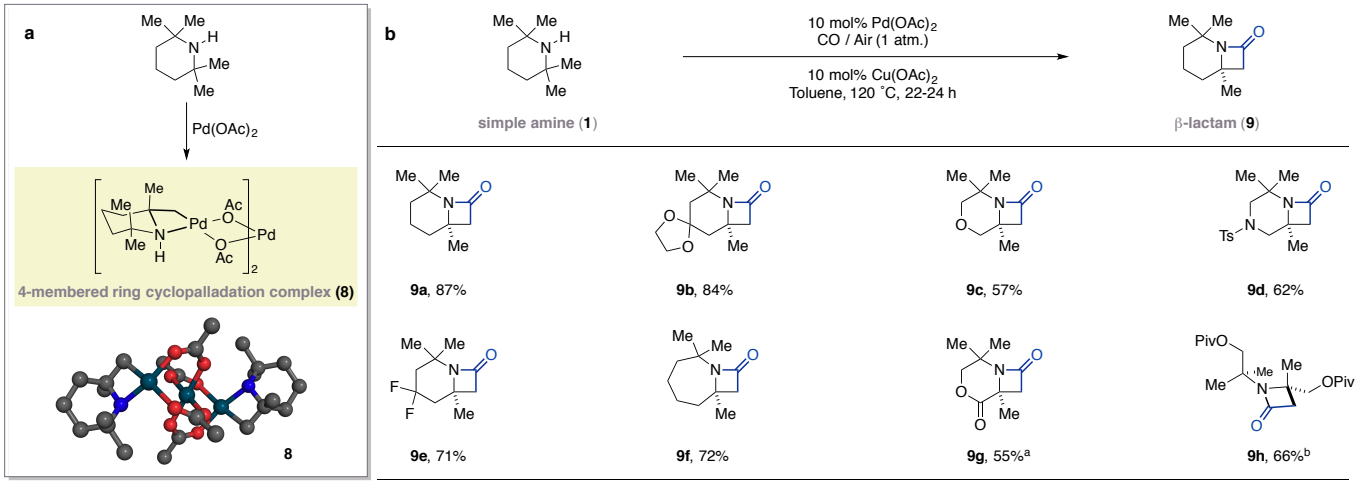
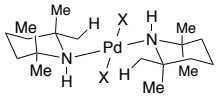


Figure 5

a

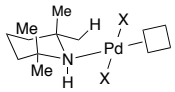


bis(amine) – Pd(II) complex (**10**)

amine dissociation to tri coordinate 14e complex

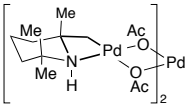
ligated sterically hindered amines may more readily dissociate from Pd(II)

Pd(II) center is projected directly into a high concentration of aliphatic C–H bonds



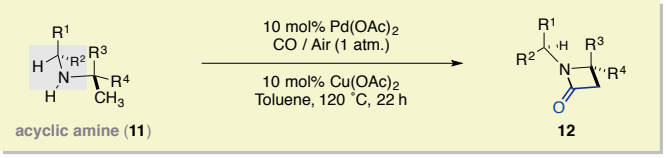
mono(amine) – Pd(II) complex, ***int-IV***

distinct cyclopalladation activation mode



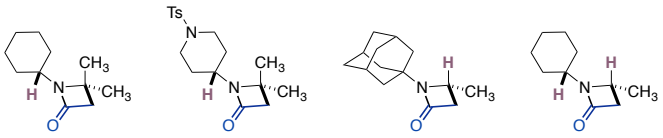
4-membered ring cyclopalladation complex (**8**)

b



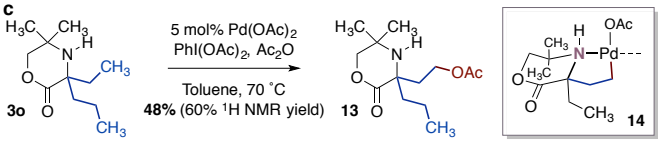
acyclic amine (**11**)

12



12a, 45% **12b**, 37% **12c**, 53% **12d**, 19%

c



3o **48%** (60% ^{1}H NMR yield) **13**

14