A steric tethering approach enables palladium-catalyzed C–H activation of primary amino alcohols

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Aliphatic primary amines are a class of chemical feedstock essential to the synthesis of higher order nitrogen-containing molecules, commonly found in biologically active compounds and pharmaceutical agents. New methods for the construction of complex amines remain a continuous challenge to synthetic chemists. Here, we outline a general palladium-catalyzed strategy for the functionalization of aliphatic C–H bonds within amino alcohols, an important class of small molecule. Central to this strategy is the temporary conversion of catalytically incompatible primary amino alcohols into hindered secondary amines that are capable of undergoing a sterically promoted palladium-catalyzed C–H activation. Furthermore, a hydrogen-bond between amine and catalyst intensifies interactions around palladium and orients the aliphatic amine substituents in an ideal geometry for C–H activation. This catalytic method directly transforms simple, easily accessible amines into highly substituted, functionally concentrated and structurally diverse products, and can streamline the synthesis of biologically important amine-containing molecules.

Methods that enable the practical and selective functionalization of traditionally unreactive aliphatic C–H bonds have synthetic applications in fields that range from drug discovery to advanced materials[1-7]. One of the major challenges facing the continued advance of this field is the development of strategically important reactions on aliphatic molecules containing synthetically useful functional groups[8]. Over the past decade, chemists have found ways to tailor the electronic properties of directing functionalities and ligands to enable C–H activation in aliphatic hydrocarbons displaying carboxylic acid, hydroxyl groups, and derivatives of these common motifs, via a process called cyclometallation[9-19]. In light of these successful advances, it would be expected that C–H activation reactions on aliphatic amines would follow a similar pathway; the nitrogen motif in aliphatic amines is an excellent coordinating group for electrophilic transition metal complexes such as palladium (II) salts and should provide an ideal pathway to steer C–H activation via cyclometallation. However, the strong metal binding properties of the amine give rise to the formation of very stable bis(amine) palladium (II) complexes that ultimately restrict the utility of these compounds in C–H activation reactions (Figure 1a)[20]. The pathway for C–H bond cleavage with palladium (II) salts requires liberation of a coordination site occupied by one of these amines, but their strong coordinating power means that there is little driving force for the release of an amine ligand

from the bis(amine) palladium (II) complex. As a result, C–H activation reactions on aliphatic amines remain a major challenge and successful examples require electronic modification of the nitrogen with strongly electron-withdrawing sulfonyl or bespoke carbonyl groups to attenuate the metal coordinating power of the amino function[21-24]. Despite the elegance of these methods, the auxiliary function can sometimes be difficult to remove after the C–H activation step. Given the importance of aliphatic amines to biological systems[25], there is a need to develop new strategies to harness the coordinating ability of the free-(NH) amine group in order to fully explore the potential of amine directed C–H activation in complex molecule synthesis.

Steric parameters have been used to influence C–H activation reactions, although they are less common than electronic control strategies; for example, minimizing steric interactions between catalyst, substrate or ligand has been shown to steer selectivity and reactivity in arene borylation reactions[26-30]. However, the use of steric properties of a molecule to actually promote aliphatic C–H activation is a significantly less explored area.[31] Recently, we discovered that a specific class of highly hindered, secondary aliphatic amine can successfully direct palladium-catalysed C–H activation through a novel four-membered ring cyclopalladation pathway[32]. Although a useful and practical method to form a class of previously inaccessible amines, the generality of the process is currently limited by the structural requirements of the starting materials. Inspired by these discoveries, we questioned whether a new strategy could be designed for the functionalization of primary aliphatic amines (traditionally incompatible with catalytic C–H activation reactions but extremely versatile synthetic building blocks) by transiently converting these substrates into secondary amines to facilitate C–H activation (Figure 1b). In this context, we recognized three factors that should guide our C–H activation blueprint: first, that the sterically controlling component should not be a permanent aspect of the amine substrate; second, that a broad range of C–H transformations would be amenable to the C–H activation strategy; and third, that the starting amines should have well-established synthetic utility, such that the products of C–H activation could be used to streamline the synthesis of biological and pharmaceutically important molecules. Taken together, we proposed that aliphatic amino alcohols containing a fully substituted carbon atom would represent a particularly useful class of molecules upon which to test this C–H activation strategy via a broadly applicable five-membered ring cyclopalladation pathway; highly functionalized variants of this very useful building block are a common feature in many biologically important molecules (Figure 1c)[33-35].

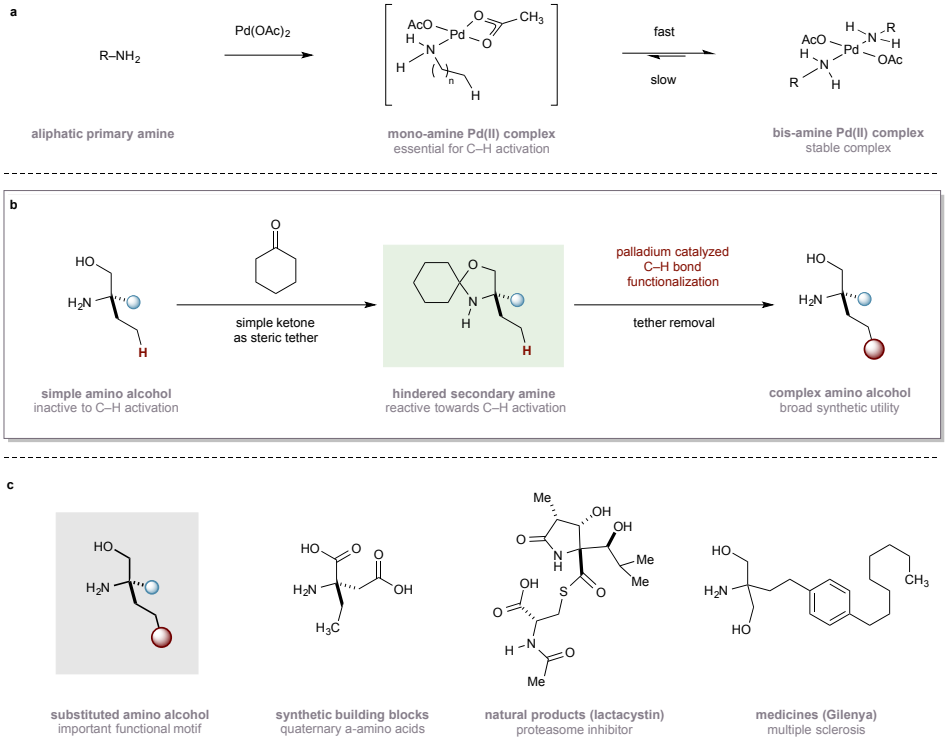


Figure 1. C–H activation on aliphatic amines. a Binding of primary amines to palladium acetate. Although the intermediate mono-amine Pd(II) complex is transiently formed, the corresponding bis-amine palladium (II) complex is stable and predominates. **b** A sterically controlled strategy to enable C–H activation in primary amino alcohols. **c** The broad utility of fully substituted primary amino alcohol derivatives.

Results and discussion

A detailed description of our working hypothesis towards the C–H activation of primary amino alcohol derivatives is outlined in Figure 2a. Central to our design was a simple ketone, deployed temporarily to bridge the oxygen and nitrogen atoms of the amino alcohol forging a hindered *N,O*-ketal motif (**1**) and masking the primary amine function. We predicted that this secondary amine (**1**) would bind to the palladium catalyst in such a way that the complexation would be accompanied by the formation of a hydrogen bond between the acetate ligand on the palladium and the free(N–H) of the amine (to ***int-I***). This non-covalent interaction would serve two important purposes: first, to orient the amines substituents in the bis-amine palladium(II) complex (***int-II***) in such a way that interactions between the aliphatic groups would be intensified, enabling amine dissociation to form the κ2-bound acetate intermediate (***int-I***) empirically required for C–H bond cleavage (to ***int-III***)[36,37]; and second, to lock the conformation of the amine with respect to the palladium center (in ***int-I***), thereby projecting the targeted C–H bond into an optimal trajectory for activation.[38] Reaction of the carbon-palladium bond in ***int-III*** can be achieved via the action of a number of external reagents, forming functionalized products (**2**).

To test this hypothesis we first prepared a representative *N,O*-ketal **1a** from a commercial amino alcohol and cyclohexanone (see supporting information for details). This ketone was selected for two reasons:

firstly, we reasoned that it should provide the requisite bulk to facilitate the amine dissociation step when bound to the palladium center; and secondly, the methylene C–H bonds in the cyclohexyl motif were less likely to undergo activation than substituents derived from a ketone containing terminal C–H bonds. In order to investigate the C–H activation step we attempted to prepare the bis-amine palladium (II) complex (corresponding to ***int-II***), which we anticipated would be the resting state of any catalytic reaction (Figure 2b). However, when we treated secondary amine **1a** with palladium acetate at room temperature, none of the expected bis-amine complex was observed, and instead we directly isolated the corresponding trinuclear cyclopalladation complex ***int-IV-1a*** (as determined by X-ray diffraction of a single crystal) in reasonable yield. Not only is this result in contrast to other amines, which readily form a stable bis-amine complex at room temperature[32], but this reaction is also a rare example of a remarkably mild palladium-mediated C–H bond cleavage within an aliphatic framework[39]. Interestingly, calculations performed on the basis of the proposed pathway concurred with the presence of a hydrogen bond between palladium-bound amine(NH) and acetate ligands, but also identified that the putative mono-amine palladium(II) complex ***int-I-1a*** was slightly lower in energy than the corresponding bis(amine) palladium(II) complex ***int-II-1a***, most likely due to the interactions between the two amines ligated to the palladium center (Figure 2c). This also supports our hypothesis that while these two species may be in equilibrium, the hindered nature of the amine means that the crucial mono-amine palladium(II) complex is both thermodynamically and kinetically favored over the bis(amine) palladium(II) complex and leads to facile C–H activation (see supporting information). Encouraged by the facile nature of the C–H activation we were able to quickly establish that the carbon–palladium bond in the cyclopalladation complex was reactive towards chemical oxidants such as iodosobenzene diacetate ($PhI(OAc)_2$) to generate the acetoxylation product **2a**, formed from a reductive elimination from a high-valent palladium-intermediate[40]. Moreover, this stoichiometric reaction could be readily converted to a catalytic process and after a brief assessment of the reaction parameters, optimal conditions enabled the conversion of amine **1a** to the acetoxylated product **2a** in 69% yield on a 3 g scale.

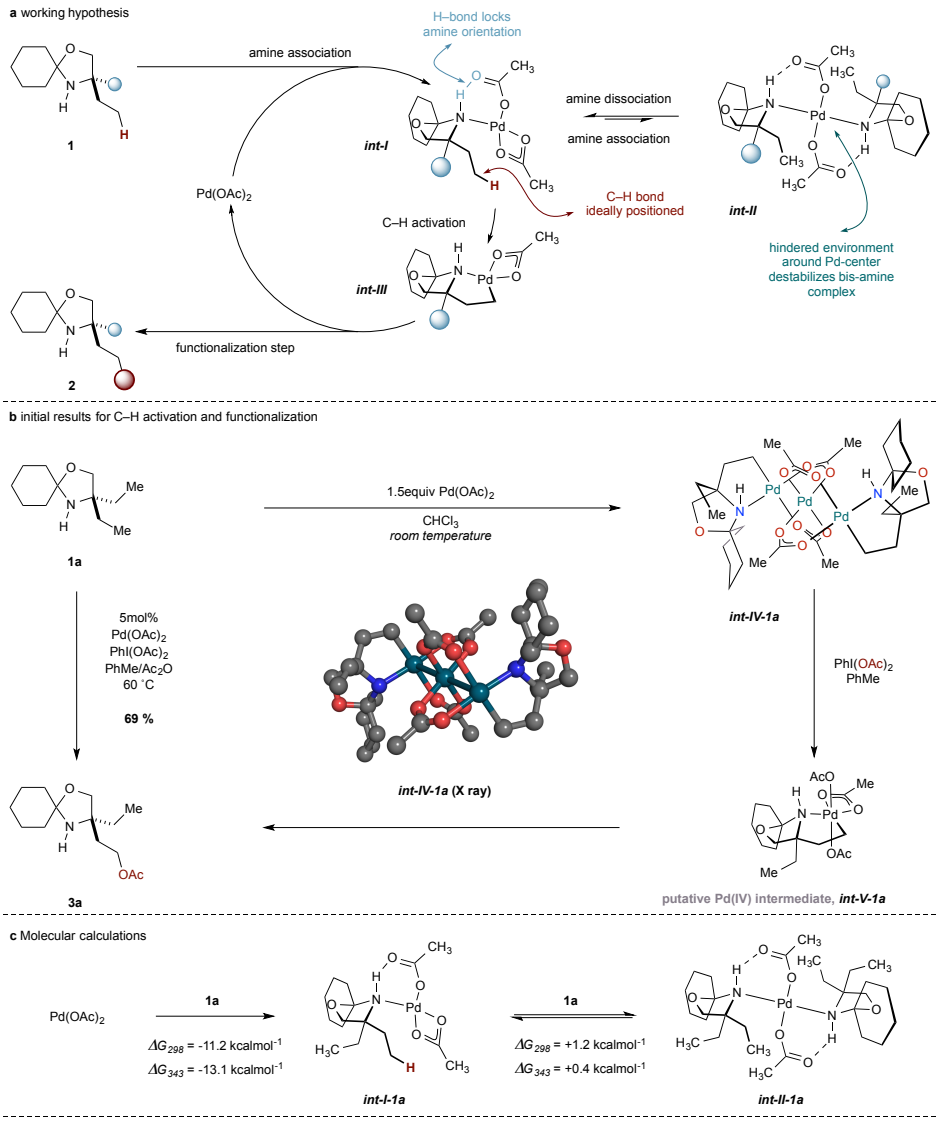
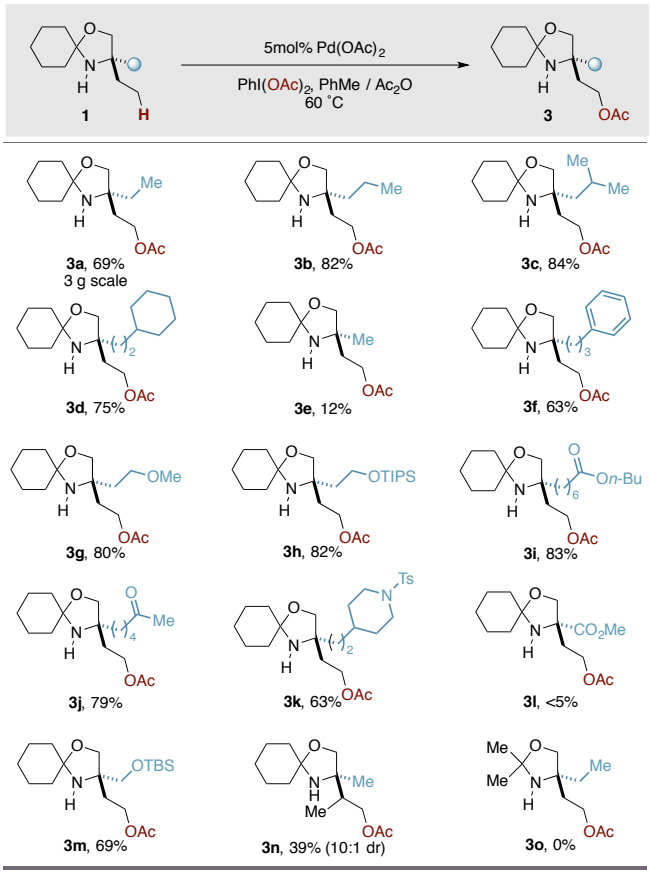


Figure 2. Conceptual approach and preliminary studies towards C–H activation of amino alcohols a Working hypothesis for the C–H activation strategy. A crucial hydrogen bond (blue) locks the conformation of the amine with respect to the palladium, positioning the C–H bond in an ideal geometry for activation, and intensifies interactions between the amine-substituents ligated across the palladium(II) centre. **b** Cyclopalladation of the amino alcohol derivative and functionalization of the resulting carbon–palladium bond leading to a catalytic C–H acetoxylation. Cyclopalladation via to a five-membered ring intermediate was confirmed by X-ray diffraction of a single crystal (***int-IV-1a***). **c** The putative bis-amine complex is disfavored on the basis of interactions between the ligated amines. Molecular calculations confirm that the mono-amine complex ***int-I-1a*** is 1.2 kcalmol^{-1} (ΔG_{298K}) lower in energy than the bisamine complex ***int-II-1a***. The bis amine complex is not observed experimentally.

The new catalytic C–H acetoxylation reaction displayed broad scope, as demonstrated by successful transformations on substrates containing simple alkyl chains of varying substitution patterns, aryl groups, protected hydroxyl functionality, carbonyl motifs and nitrogen–containing heterocycles (**3a-d**, **f-k**, Table 1). Interestingly, a methyl substituted amino alcohol derivative (forming **3e**) performed poorly in this reaction, which is possibly a reflection of the reduced steric hindrance around the nitrogen atom that precludes effective ligand dissociation from the palladium center. Notably, we do not see any products that could arise from the potentially competitive four-membered ring cyclopalladation pathway. Strongly

electron-withdrawing groups adjacent to the amine motif also failed to produce the desired product (**3l**) in acceptable yield, however, the protected hydroxymethyl motif is readily accommodated and produces the desired orthogonally protected trifunctional amine (**3m**).

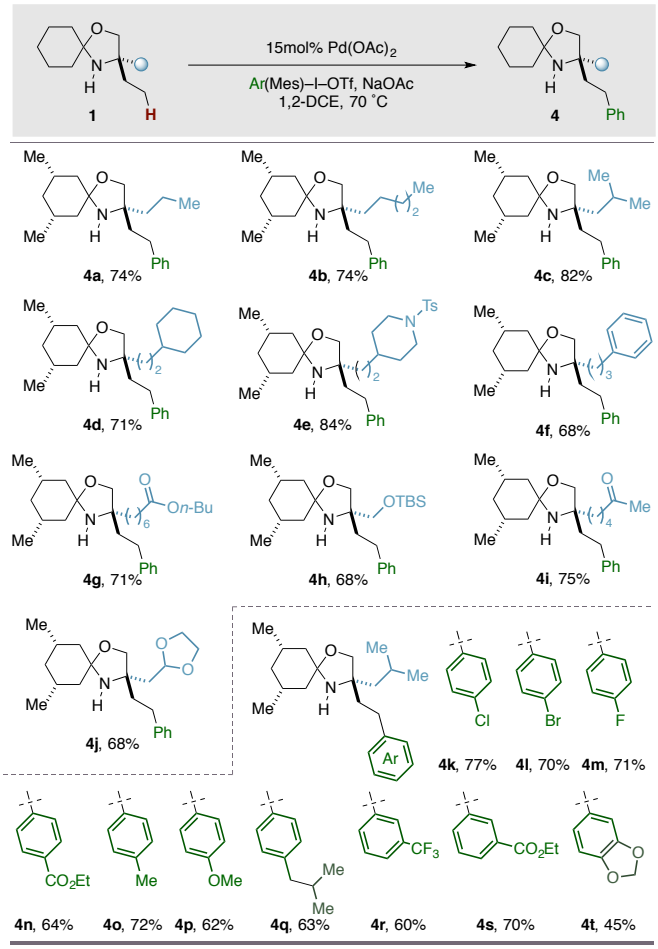
Table 1 Palladium-catalyzed C–H acetoxylation of amino alcohol derivatives.



We assumed that C–H acetoxylation most likely proceeds via a pathway involving a high-valent Pd intermediate, and hence reasoned that the strategy should be amenable to other mechanistically linked transformations and in particular, those involving carbon–carbon bond formation[40]. Accordingly, the *N,O*-ketal **1a** was treated with a related hypervalent iodine reagent, diphenyliodonium triflate and we were pleased to find that the corresponding arylated amine product was formed in modest yield. A survey of reaction conditions (not shown, see supporting information) revealed an optimal process that involved the treatment of the starting amine with 15mol% $Pd(OAc)_2$ and Ph_2IOTf in the presence of sodium acetate in 1,2-dichloroethane and stirring at 70 ˚C to yield the desired arylated product. The triflate counterion of the diaryliodonium species provided the best reaction in comparison to other salts, and the presence of a base was essential for a productive reaction and likely serves to quench the trifluoromethanesulfonic acid that is formed as a byproduct from the diaryliodonium salt. Interestingly, slight modification to the *N,O*-ketal motif proved to be most important to obtaining a good yield of the arylated products (Table 2, **4a-j**). We found that palladium-catalyzed arylation with *N,O*-ketals derived from *cis*-3,5-dimethyl cyclohexanone afforded a routinely superior yield to the parent cyclohexanone congeners; we ascribe this reactivity to a subtle conformational effect that stabilizes the *N,O*-ketal in its reactive conformation[41]. The scope of the arylation process revealed the phenylation of a range of *N,O*-ketals in good yields to provide

an interesting class of functionalized phenethyl amine derivatives. Similarly, aryl groups displaying electron-rich, electron-deficient and synthetic useful functionality could be transferred using substituted diaryliodonium triflates[42] providing further versatility to the increasingly broad activation process (Table 2, **4k-4t**).

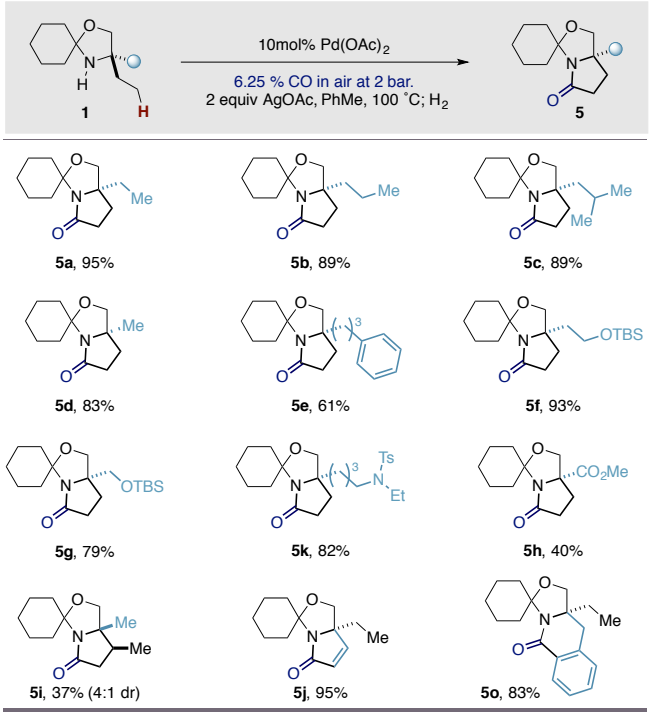
Table 2 Palladium-catalyzed C–H arylation of amino alcohol derivatives.



To further demonstrate the utility of this C–H activation strategy, we sought to adapt the reactivity of the key cyclopalladation intermediate towards a catalytic cycle involving the Pd(II)/Pd(0) redox shuttle, thereby enabling a different type of transformation on this amino alcohol scaffold (Table 2a). We reasoned that interception of the cyclopalladation complex with carbon monoxide would lead to a one carbon homologation and concomitant cyclization to form a pyrrolidinone, a five membered nitrogen-containing heterocyclic motif common to many natural products[43]. We tested this hypothesis by subjecting a solution of ***int-IV-1a*** to a CO atmosphere and found that the corresponding pyrrolidinone **5a** was formed in modest yield. A comprehensive optimization study towards a catalytic reaction revealed a number of key observations: (1) palladium acetate was the optimal catalyst; (2) silver salts were crucial to the success of the reaction; and (3) a commercial gas mixture comprised of 6.25% CO in air and used at a slight positive pressure provided the best results. Although the role of the silver salt may be solely that of a terminal oxidant, it is also possible that it forms a bi-metallic complex with the palladium, which could be important for the observed reactivity[44,45].

The scope of the carbonylation reaction proved to be general and provided good yields of pyrrolidinone products (**5**) containing a variety of useful functionality (Table 3). In addition to the routine alkyl substituents (in **5a-d**) we found that amino-alcohol derivatives displaying aryl (**5e**), protected hydroxyl (**5f-g**) and amino motifs (**5h**) all worked well in the C–H carbonylation process; the reaction proceeded diastereoselectively when presented with the choice of two methyl groups (**5i**). In the case of the formation of **5d**, the palladium has to choose between a four and five-membered ring cyclopalladation and we observe that the reaction proceeds through the larger ring pathway in contrast to our previous studies[32]. Although the reaction is less efficient when there is a strongly electron-withdrawing group adjacent to the amine function, useful yields of the desired product can still be obtained (**5j**). In all of these cases, we observe a small amount of the α,β-unsaturated pyrrolidinone product that we believe originates from C(sp^2)–H activation of an allylic amine derivative formed from β-hydride elimination of a cyclopalladation intermediate. This product can be readily processed to the saturated pyrrolidine by direct hydrogenation of the reaction mixture. The intermediacy of the allylic amine was confirmed by selective carbonylation of the sp^2 hybridized C–H bond to give the expected unsaturated pyrrolidinone product in excellent yield (**5k**).

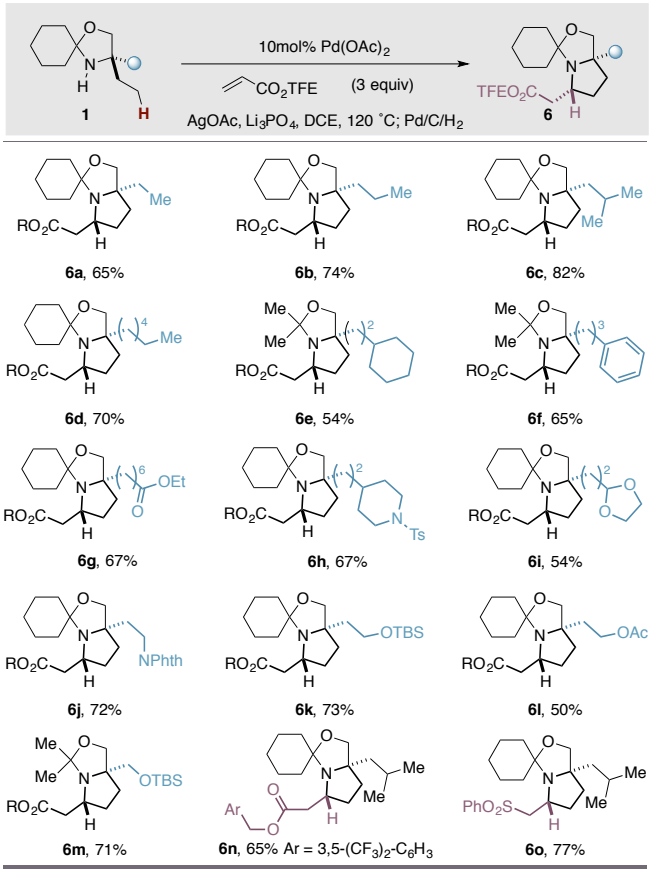
Table 3 Palladium-catalyzed C–H carbonylation of amino alcohol derivatives to pyrrolidinones



In a final venture to establish the generality of this activation strategy, we sought to address a traditionally challenging carbon-carbon forming process based on C–H alkenylation. Although examples of this coupling reaction have recently emerged for aliphatic systems, combining C(sp^3)–H bonds with alkenes remains an important goal[46,47]. Guided by our experience with the C–H carbonylation, we first assessed the reaction of amine **1a** with trifluoroethyl acrylate in the presence of palladium acetate and silver

acetate. Pleasingly, we observed the formation of pyrrolidine **6a** that formed from the C–H alkenylation reaction followed by intramolecular aza-Michael addition. After surveying a range of reaction conditions we found that Li_3PO_4 and the use of the trifluoroethyl acrylate as the alkene coupling partner were also essential for a good yield. When these were combined in an optimal process, which involved the treatment of amine **1a** with trifluoroethyl acrylate, 10mol % $Pd(OAc)_2$, AgOAc and Li_3PO_4 in 1,2-dichloroethane at 120 ˚C, pyrrolidine **6a** was isolated in 65% yield as a single diastereomer. Again, we observed a small amount of an unsaturated pyrrolidine product derived from the corresponding allylic amine and so the reaction mixture was directly hydrogenated to the form saturated pyrrolidine. We showed that the reaction displayed a broad substrate scope and supported the presence of different useful functional groups (Table 2b). We also noticed a modest improvement in yield when the size of the alkyl substituent increases (**6a-c**). In some cases, however, we found that the acetone derived *N,O*-ketal (to **6f**) performed better than the corresponding cyclohexyl group, highlighting the subtle steric balance at work in this process. In addition to the coupling with acrylates, we were also able to show that vinyl sulfones also work well in the C–H alkenylation process (to **6o**), providing useful products with opportunities for further elaboration via well-established methods.

Table 4 Palladium-catalyzed C–H alkenylation of amino alcohol derivatives to pyrrolidines



(R = TFE (2,2,2-trifluoroethyl)).

Applications of the C–H activation strategy

Taken together, the series of four amine directed C–H activation reactions enables a single amino alcohol derivative to be transformed into a diverse range of architecturally complex amines. The C–H activation strategy provides a convenient gateway to a wide range of subsequent transformations via manipulation of the intrinsic functionality within the products and could be used to readily access the core framework of various natural products, biologically relevant molecules and active pharmaceutical agents. A number of simple transformations could be applied to each of these products to formulate value-added functional molecules: first, the functional groups within the pyrrolidones (**5**) derived from the C–H carbonylation reaction can be subjected to *N,O*-ketal hydrolysis (to **7**), alkylation (to **8**), Grignard addition (to **9**) and reduction (to **10**), further modifying the heterocyclic ring; and secondly, using the symmetrical amino alcohol derivative **1a(s)**, each of the ethyl groups can be functionalized using sequential C–H activation processes via C–H acetoxylation and then C–H carbonylation (to **11**), C–H alkenylation (to **6l**) and C–H arylation (to **12**) to form complex amino alcohol derivatives form simple precursors. Finally, to illustrate the potential efficacy of this C–H activation strategy, we were able to apply the C–H arylation process to the synthesis of the Gilenya (fingolimod **16a**), Novartis' billion dollar per year drug for the treatment of multiple sclerosis. Using the new C–H arylation, we can synthesize of the active pharmaceutical agent in four steps from an inexpensive material (**13**). The C–H arylation of **14** with the readily available diaryliodonium salt **15** proceeds in high yield to construct the framework of the fingolimod **4u**. Acid hydrolysis of the protecting groups affords the active pharmaceutical ingredient **16a**. Given that fingolimod has multiple indications and is currently in seven clinical trials across a number of therapeutic areas[48], a streamlined strategy for the synthesis of analogues would be extremely useful. By changing the amine starting material, the diaryliodonium salt or using the sequential functionalization tactic (*vide supra*), we were able to rapidly access a representative selection of potentially interesting fingolimod analogues molecules using this strategy (**16b-e**).

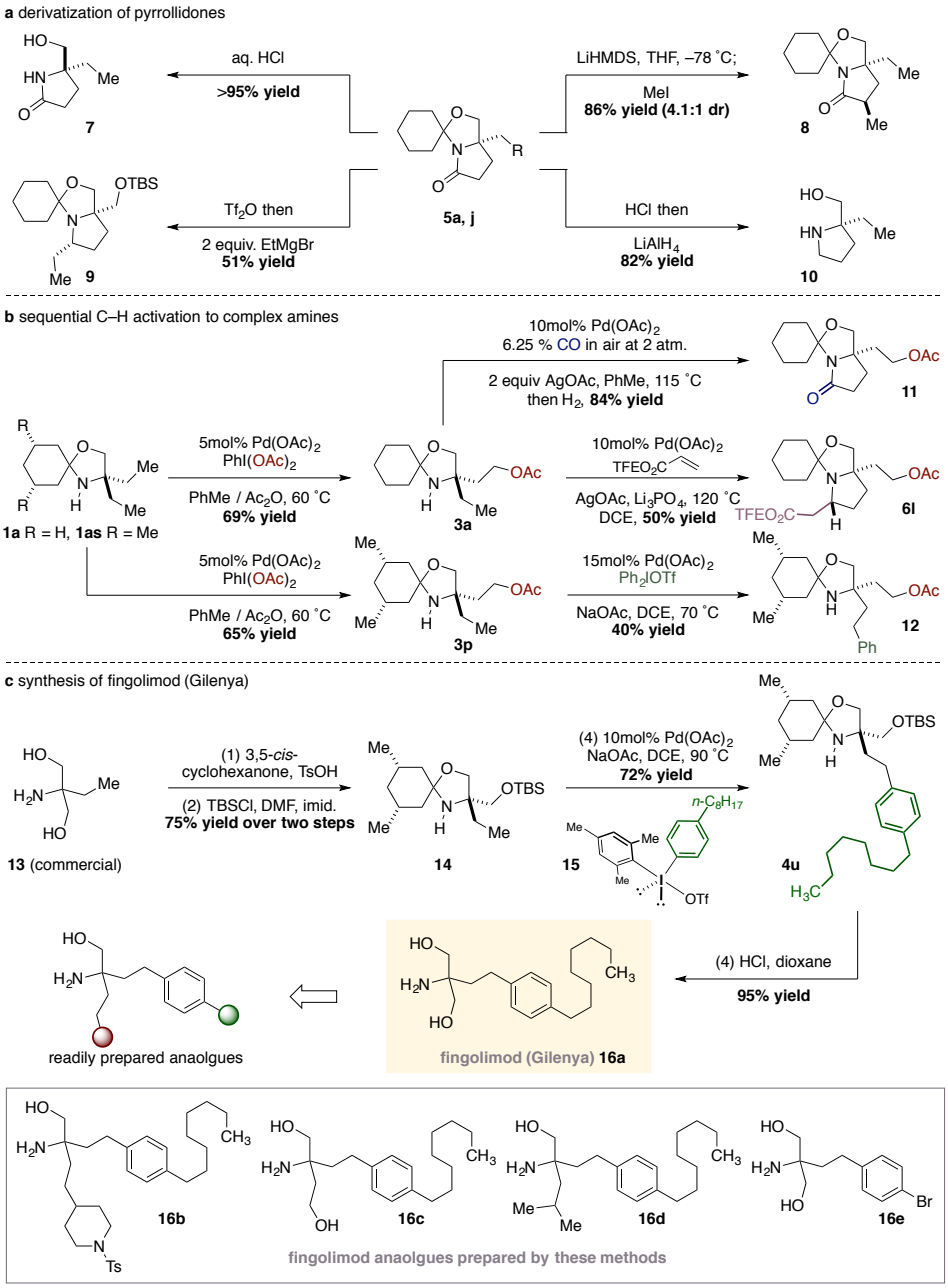


Figure 3. Synthetic applications of functionalized amino alcohol derivatives a Derivatization of pyrrolidones. A range of transformations of the pyrrolidinone core are shown including ketal-hydrolysis to **7**; diastereoselective enolate alkylation to **8**; a reductive Grignard addition to a highly substituted pyrrolidine (**9**); and direct reduction to a simple pyrrolidine (**10**). **b** Sequential C–H activation to complex amines. The new C–H activation reactions can be sequenced to convert a simple amino alcohol derivative into complex products. **c** Synthesis of fingolimod (Gilenya). A synthesis for the straightforward preparation of fingolimod (Gilenya, **16a**), a multiple sclerosis drug, is shown in four steps from commercial materials. The strategy can also be applied to the rapid synthesis of potentially interesting analogues (**16b-e**).

The advances outlined here demonstrate that amino alcohols are ideal candidates for a remarkably broad C–H activation strategy. We believe that two factors are responsible this facile C–H activation: firstly, the presence of a putative hydrogen bond between the palladium bound amine and acetate ligands is important in facilitating the C–H activation step as it locks the conformational relationship between the two groups and projects the C–H bond into an ideal trajectory for palladation; and secondly, the hindered nature of the amine substrates destabilizes the off cycle bis-amine palladium complex to favor the mono-

ligated species required for C–H activation. The range of palladium-catalyzed C–H activation reactions shown here enable either simple functional group additions or framework changing transformations on a versatile and synthetically useful amino alcohol scaffold. Taken together, the broad scope and applications of these transformations suggest that the C–H activation strategy will be beneficial to synthesis of complex amines with both established and unexplored biological properties and be of widespread utility to chemists in both academic and industrial institutions.

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

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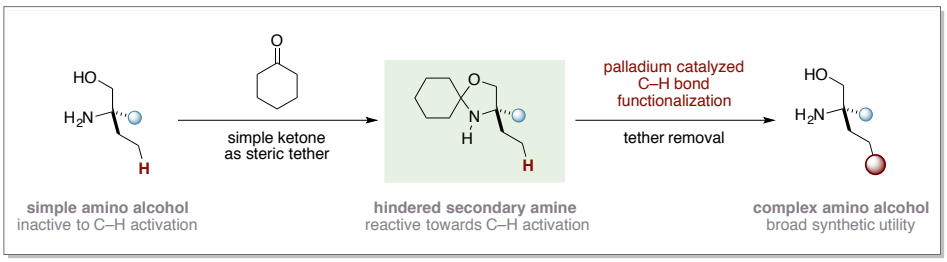
Table of contents summary

The functionalization of primary amines by C-H activation is often hindered by their strong metal-coordinating properties. Now, a steric tethering approach - that temporarily converts amino alcohols into hindered secondary amines - is described. The approach allows these amino alcohols to be transformed into structurally complex and diverse products using palladium-catalyzed aliphatic C-H activation.



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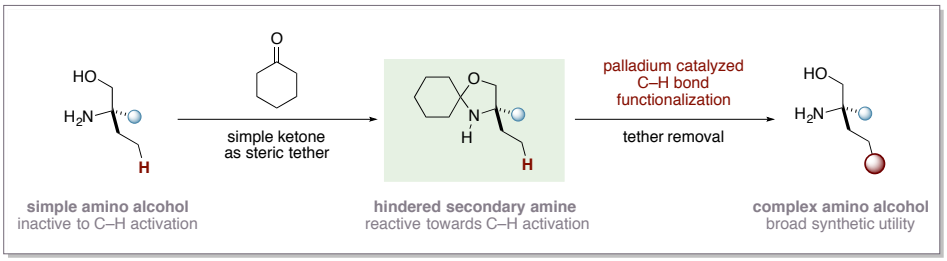

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