A General Catalytic β-C–H Carbonylation of Aliphatic Amines to β-Lactams

Authors: Darren Willcox,† Ben G. N. Chappell,† Kirsten Hogg, Jonas Calleja, Adam P. Smalley & Matthew J Gaunt*

Affiliations: Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge, United Kingdom CB2 1EW.
† D.W. and B.C. contributed equally to the manuscript.

Abstract: Methods for the synthesis and functionalization of amines are intrinsically important to a variety of chemical applications. We present a general C–H activation process that combines readily available aliphatic amines and the feedstock gas carbon monoxide to form synthetically versatile value-added amide products. The operationally straightforward palladium-catalyzed process exploits a distinct reaction pathway, wherein a sterically hindered carboxylate ligand orchestrates amine attack on a palladium anhydride to transform aliphatic amines into β-lactams. The reaction is successfully applied to a wide range of secondary amines and can be used as a late-stage functionalization tactic to deliver advanced, highly functionalized amine products of utility for pharmaceutical research and other areas.

One Sentence Summary: Palladium catalysts can insert carbon monoxide into aliphatic amines via a novel C–H activation process, delivering a broad range of synthetically useful products

Main Text:

The preparation and functionalization of amines is fundamental to a variety of chemical applications such as the synthesis of medicinal agents, biologically active molecules and functional materials *(1)*. The best-established methods for amine synthesis involve carbon–nitrogen bond forming processes based on alkylation *(2)*, carbonyl reductive-amination *(3)* and cross coupling *(4-6)*. Although recent advances in olefin hydroamination *(7,8)* and biocatalysis *(9,10)* have further expanded the toolbox of available transformations, the need for functional amines keeps the development of increasingly general catalytic

reactions for amine synthesis at the forefront of synthetic organic chemistry. We reasoned that a catalytic process capable of selectively transforming the traditionally unreactive C–H bonds in aliphatic amines into functionalized variants of these important molecules would be valuable to practitioners of synthetic and medicinal chemistry (Figure 1A).

Transition metal catalysts capable of C–H activation have inspired intense research efforts within the synthetic community *(11-14)*. Although many advances have been made in the field of aromatic C(sp^2)–H bond activation, functionalization of less reactive C(sp^3)–H bonds in aliphatic molecules continues to present a challenge *(15)*. Due to the lower reactivity of C(sp^3)–H bonds, their activation often relies on proximity to polar functional groups such as carboxylic acids *(16,17)*, heteroarenes *(18)* and hydroxyl functionalities *(19)*.aliphatic hydrocarbons containing the free(NH) amino group continuously cause problems that restrict wider application *(20)*.

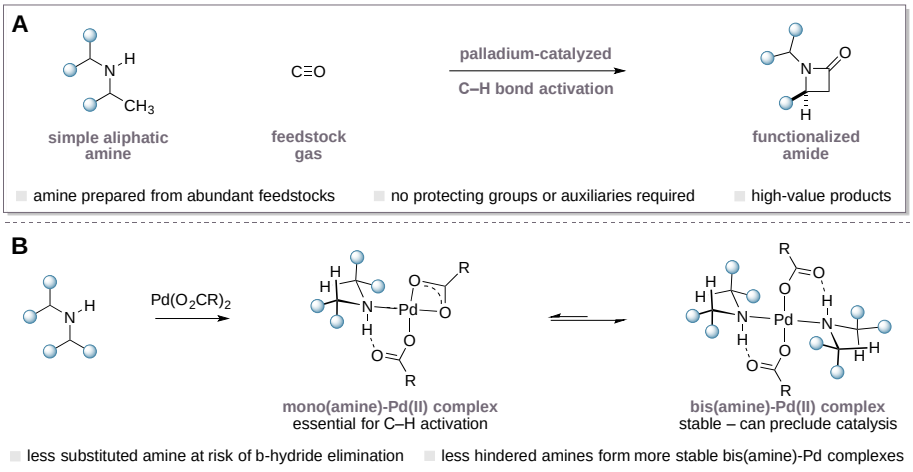
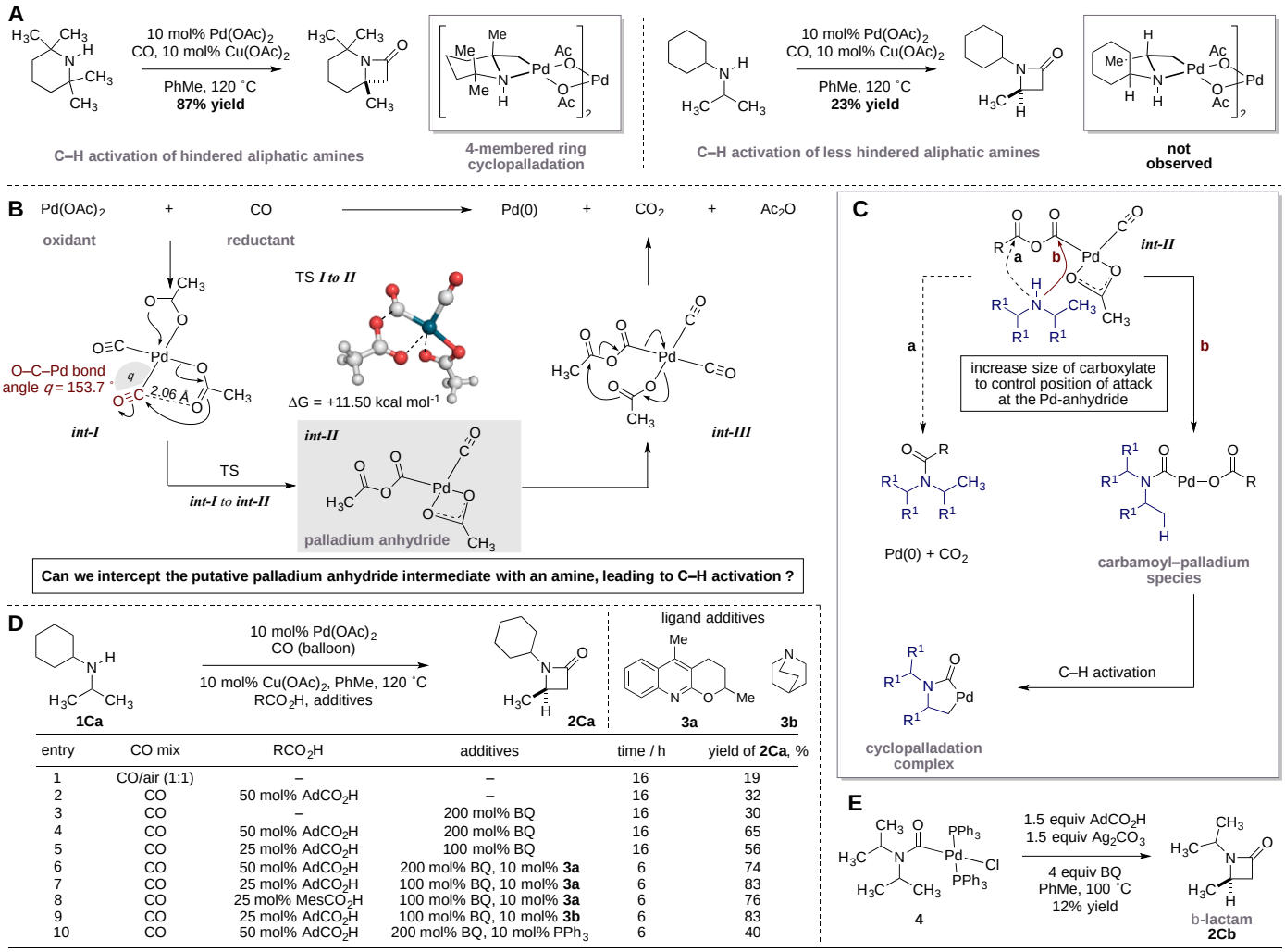


Fig. 1. (**A**). Pd-catalyzed C(sp^3)–H carbonylation of free(NH) amines. (**B**) Secondary aliphatic amines react with $Pd(O_2CR)_2$ to form mono(amine)- and bis(amine)-Pd(II) complexes, in favor of the latter species.

A number of factors can be identified which impede the development of free(NH) amine-directed aliphatic C–H activation with catalysts such as Pd(II) salts (Figure 1B): the high affinity of a free(NH) amine for Pd(II) salts leads to the formation of stable bis(amine)-Pd complexes and can preclude catalysis; β-hydride elimination pathways often lead to oxidative degradation of the amine and catalyst reduction; and other polar functional groups can compete with the amine for coordination to the Pd-catalyst leading to poorly reactive or unselective systems. As a result, successful aliphatic amine directed C–H activation typically requires the nucleophilicity of the nitrogen atom to be modulated by strongly electron withdrawing protecting groups *(21)*, directing auxiliaries *(22-25)* or an intensified steric environment around the NH-motif *(26,27)*. Despite the success of these methods, the additional functional and structural features that need to be incorporated into the amine framework for successful C–H activation can sometimes preclude downstream operations. Taken together, the limitations of current methods give weight to the appeal of a free(NH) aliphatic amine directed C–H activation process (Figure 1A). First, such a method would enable readily available amines to be directly converted into highly functionalized and versatile small-molecule building blocks. Second, by obviating the need for nitrogen protecting or auxiliary groups, the number of synthetic steps required to access functional amines would be greatly reduced. Third, C–H activation directed by free(NH) amine motifs in pharmaceutical agents or natural products could be used as a potentially powerful late-stage functionalization approach to analogue synthesis. Here, we report the successful realization of these aspirations in the development of a general process for the catalytic C–H carbonylation of free(NH) aliphatic amines, wherein readily available unprotected amines are combined with carbon monoxide to generate synthetically versatile amides in the form of β-lactams. The design of a

reaction pathway for C–H carbonylation controlled by a sterically hindered carboxylate ligand was crucial in overcoming the incompatibility of aliphatic free(NH) amines and Pd(II) catalysts.



entry	CO mix	RCO_2H	additives	time / h	yield of **2Ca**, %
1	CO/air (1:1)	–	–	16	19
2	CO	50 mol% $AdCO_2H$	–	16	32
3	CO	–	200 mol% BQ	16	30
4	CO	50 mol% $AdCO_2H$	200 mol% BQ	16	65
5	CO	25 mol% $AdCO_2H$	100 mol% BQ	16	56
6	CO	50 mol% $AdCO_2H$	200 mol% BQ, 10 mol% **3a**	6	74
7	CO	25 mol% $AdCO_2H$	100 mol% BQ, 10 mol% **3a**	6	83
8	CO	25 mol% $MesCO_2H$	100 mol% BQ, 10 mol% **3a**	6	76
9	CO	25 mol% $AdCO_2H$	100 mol% BQ, 10 mol% **3b**	6	83
10	CO	50 mol% $AdCO_2H$	200 mol% BQ, 10 mol% PPh_3	6	40

Fig. 2. Towards an activation mode for C–H carbonylation of unhindered aliphatic amines. (**A**) Previous work: C–H carbonylation of hindered aliphatic amines via a four-membered cyclopalladation pathway; poor yielding C–H carbonylation of less hindered amines (**B**) Reduction of $Pd(OAc)_2$ by CO. (**C**) Design hypothesis – a sterically-controlled ligand-enabled C–H activation. (**D**) Optimization studies. (**E**) C–H activation from a de novo carbamoyl Pd complex. BQ, benzoquinone; Ad, adamantyl.

Carbon monoxide (CO) is an abundant chemical feedstock, and metal-catalyzed carbonylation reactions are integral to the laboratory and manufacturing scale synthesis of chemical products. Most of these processes involve CO-binding to a metal to form a metal-carbonyl complex with well-established reactivity *(28)*. Recently, our group described a sterically controlled C–H activation strategy for carbonylation of(?)

free(NH) aliphatic amines. Highly hindered amines, displaying fully substituted carbon atoms on either side of the nitrogen motif underwent C–H carbonylation to afford β-lactams (Fig. 2A). A key factor in the success of this strategy was the sterically-induced destabilization of the readily formed bis(amine)-Pd(II) complex (as shown in Figure 1A) resulting from a clash between the two highly hindered amines, which promotes the mono(amine)-Pd(II) species required for C–H activation. The anticipated pathway for these amine-directed reactions had been based on seminal studies by Fujiwara who had outlined a mechanistic blueprint that has underpinned most subsequent directed C–H carbonylation reactions with Pd(II) catalysts: in this case, amine-directed cyclopalladation of the C–H bond formed a four-membered ring complex and was followed by coordination of CO, 1,1-migratory insertion to an acyl-Pd species and reductive elimination to generate the carbonyl product *(29)*. However, when the same reaction concept was applied to more commonly encountered, less hindered amines, the reaction failed or was low-yielding and resulted in oxidative degradation and acetylated amine products (Fig. 2A). Furthermore, we were not able to observe any trace of the corresponding four-membered ring cyclopalladation complex, in contrast to reactions with the hindered amine counterparts. Indeed, we calculated that a transition state for four-membered ring cyclopalladation on these less hindered amines was too high to be a realistic pathway *(30)*. Based on these observations, we reconsidered the classical mechanism for C–H carbonylation. CO is a strongly binding ligand and it is perhaps surprising that it does not interact with the Pd-catalyst prior to C–H activation. Moreover, $Pd(OAc)_2$ and CO display contrasting redox properties, and their combination predictably leads to catalyst reduction, which can complicate a catalytic process. Intrigued by the apparent paradox of the redox properties of the reagents, we became interested in the mechanism of CO-mediated reduction of $Pd(OAc)_2$, outlined in Fig. 2B. Although there is little known about this pathway, studies by Moiseev provided clues that led us to propose a simplified model that we supported through computation *(31)*. Two molecules of CO coordinate to monomeric $Pd(OAc)_2$ (***int-I***) and a calculated Pd–C–O angle of 153.7˚, with

a bond distance between the carboxylate and CO of 2.06 Å, suggested an interaction between the two ligands. Attack on one of these CO ligands by a neighboring carboxylate was energetically favorable, leading to a Pd-anhydride type species ***int-II***. The transition state for this step (***int-I*** to ***int-II***) was calculated to be +11.50 kcal mol^{-1} relative to ***int-I***. Coordination of a further CO (***int-III***) could trigger an intermolecular attack of the κ^1-bound acetate onto the distal carbonyl group of the anhydride causing the release of CO_2, acetic anhydride and Pd(0). Attracted by the potential reactivity of the putative Pd-anhydride ***int-II***, we postulated that attack by an amine on the proximal carbonyl would lead to a carbamoyl-Pd species (Fig. 2C), from which C–H activation would be possible. This unorthodox cyclopalladation pathway would lead to C–H activation two carbon atoms away from the nitrogen group, and is distinct from classical cyclopalladation processes that usually result in activation three carbons from the directing motif.

Mechanistic studies

To test our hypothesis, we reacted amine **1Ca** under anticipated conditions for C–H carbonylation (Fig. 2D) *(32-33)*. Although we observed the desired product (β-lactam **2Ca**) in low yield, the reaction was capricious and accompanied by the formation of acetylated amine and oxidative degradation products (Entry 1). On the basis of our mechanistic blueprint, attack on the Pd-anhydride species at position **a** would lead to CO_2 release, reduction of the Pd-catalyst and acetylated amine side product (Fig. 2B). We speculated that a larger carboxylate would generate a sterically biased Pd-anhydride, steering amine attack to position **b** to form the carbamoyl-Pd species and precluding the deleterious reduction pathway. Accordingly, addition of adamantanoic acid ($AdCO_2H$) to the standard reaction resulted in an increase in yield to 32% (Entry 2). A similar improvement was observed when the original reaction was conducted in the presence of benzoquinone (BQ) (Entry 3) *(34)*. We were delighted to find that addition of both $AdCO_2H$ and BQ resulted in a dramatic increase in yield, with the β-lactam isolated in 65% yield (Entry 4). The addition of

nitrogen-containing ligands, such as quinoline **3a** or quinuclidine **3b**, enabled us to lower the amounts of the other reagents (Entries 6,7,9) *(35)*. We also found that other hindered carboxylic acids were effective in the reaction (Entry 8). Taken together, an optimized procedure involved stirring a 0.1 M solution of amine **1Ca** in toluene with 10 mol% $Pd(OAc)_2$, 10 mol% $Cu(OAc)_2$, 100 mol% BQ, 25 mol% adamantanoic acid and 10 mol% of **3a** at 120 ˚C under an atmosphere of CO, and gave an 83% yield of β-lactam **2Ca** after isolation. To probe the nature of the C–H activation step, we synthesized a derivative (**4**) of the proposed carbamoyl-Pd species (Fig. 2E). Under conditions that would create a similar chemical environment to the reaction (c.f. Figure 2B, entry 10, where PPh_3 is used as an additive), we showed that the β-lactam **2Cb** could be formed, albeit in low yield, supporting our hypothesis that C–H activation can occur through this carbamoyl-Pd intermediate.*(36)*

A number of further preliminary mechanistic experiments were conducted to ascertain the role of the distinctive components of this C–H carbonylation process. First, we confirmed the importance of the sterically bulky carboxylate by comparing the reaction of the acetate and adamantanoate-derived bis(amine)-Pd(II) carboxylate complexes (**5a** and **5b** in Fig. 3A) in the presence of BQ under a CO atmosphere; the yield of β-lactam from the acetate complex (**5a**) was 25% compared to 89% from the adamantanoate complex (**5b**), supporting our hypothesis of a sterically controlled attack on the putative Pd-anhydride species (Fig. 3A). Second, we identified that BQ is essential for the high yielding formation of **2Ca** from **5b:** in its absence the yield drops from 89% to 26%, suggesting that BQ may play a mechanistic role in the pathway beyond that of an oxidant *(35)*. Third, we deduced that although quinoline **3a** and quinuclidine **3b** additives increase the yield of β-lactam, they do not significantly affect the rate of the catalytic reaction. Finally, we observed a kinetic isotope effect of 1.14 from parallel reaction of **1Ca** and ***d*^{6}-1Ca**, suggesting that C–H activation is not the rate-determining step (Fig. 3B). A close inspection of the reaction of ***d*^{6}-1Ca**, using NMR, revealed that H/D scrambling had occurred in the product lactam **2Ca** at

the methyl group and at the position adjacent to the carbonyl of the amide. However, no H/D scrambling was observed in the recovered starting material ***d*^{6}-1Ca**. These observations suggest that C–H activation is reversible and takes place after an irreversible step.

Taken together, these observations suggest a simplified catalytic cycle for this C–H carbonylation reaction *(30)*, which we have supported with a computational study of a simplified system using pivalic acid and without the involvement of **3a** or **3b** (Fig. 3C). The process begins with carboxylate exchange on $Pd(OAc)_2$: coordination of the sterically hindered acid (RCO_2H) forms $Pd(O_2CR)_2$ or a mixed carboxylate complex. Next, amine coordination forms the mono(amine)-Pd(II) complex ***int-IV***, which is in equilibrium with the off-cycle bis(amine)-Pd(II) complex (***int-V***); ***int-V*** is deemed to be the energetic reference point as the catalyst resting state. CO-binding then forms ***int-VI***, from which a viable transition state (**TS1**) to the Pd-anhydride complex ***int-VII*** was determined. Consistent with our kinetic isotope effect and computational studies, we suggest that attack of the amine at the internal carbonyl of ***int-VII*** (via **TS2**) to form carbamoyl-Pd species ***int-VIII*** is irreversible, from which reversible C–H activation takes place through a concerted metallation deprotonation pathway (**TS3**) to form a 5-membered ring cyclopalladation intermediate ***int-IX*** (see also Fig. 2E). Finally, BQ-assisted reductive elimination (via **TS4**) leads to β-lactam **2Cb**, after decomplexation from Pd(0); oxidation of the Pd(0) species with $Cu(OAc)_2$ regenerates the active Pd(II) species. We believe that the amine additives **3a/b** may stabilize the Pd(0) species prior to oxidation by preventing deactivating aggregation *(37).* This effect may be more pronounced towards the end of the reaction when the concentration of the amine substrate **1** will be lower and possibly explains why **3a/b** have an affect on yield but not the rate of reaction.

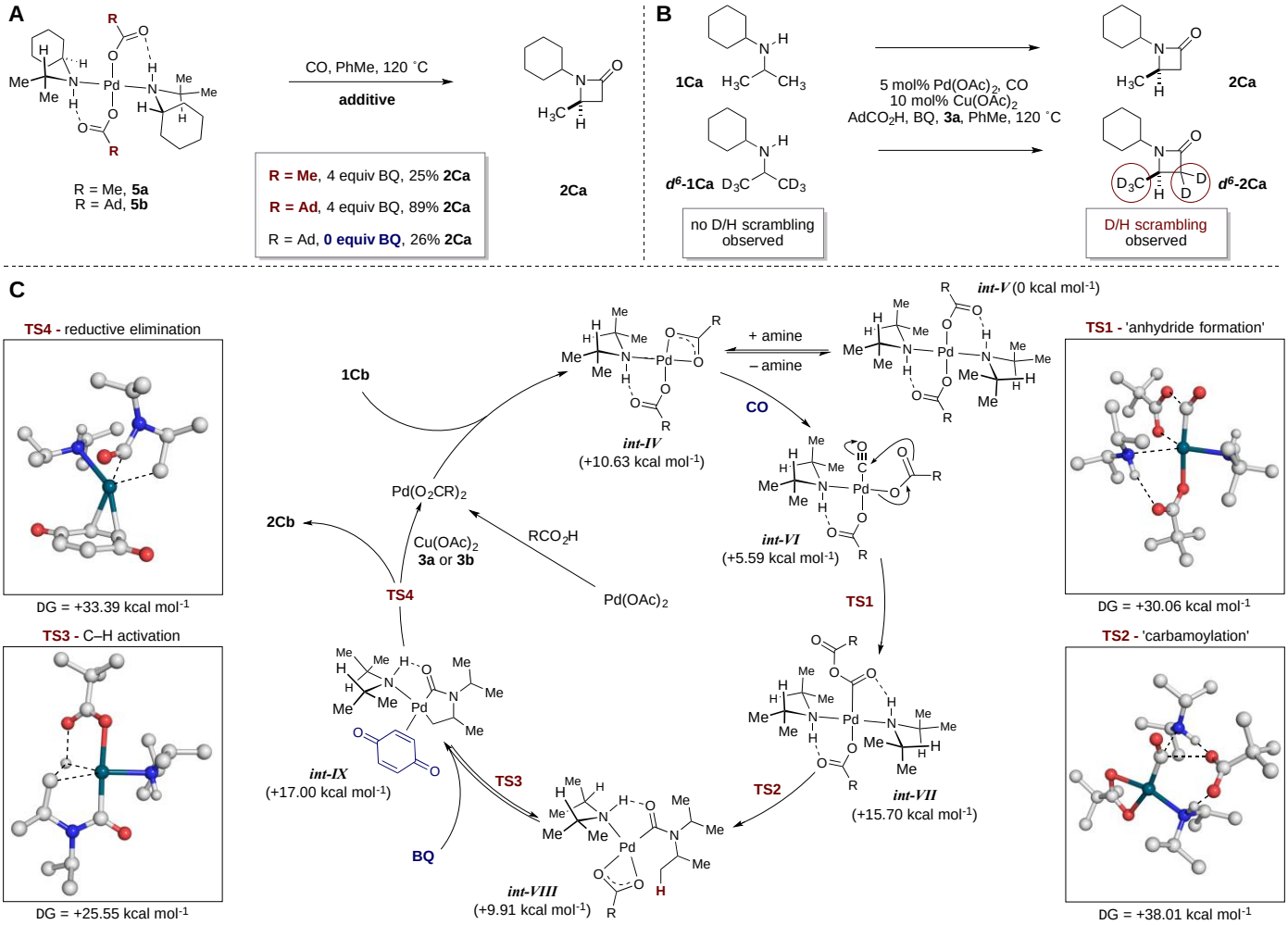


Fig. 3. Mechanistic evaluation of the new C–H carbonylation reaction. (**A**) Stoichiometric studies. (**B**) Kinetic isotope effect studies. (**C**) Proposed mechanism for C–H carbonylation of aliphatic amines. Computational studies were conducted using Amsterdam Density Functional (ADF) at the ZORA:BLYP-D3/TZ2P level using COSMO solvation model (PhMe).

Substrate scope with simple amines

Having established optimal reaction conditions and validated a possible reaction mechanism, we focused our efforts on establishing the scope of the C–H carbonylation process. In setting a benchmark, we targeted a substrate scope that would encompass all structural classes of aliphatic secondary amine with respect to substitution at the carbon atoms directly connected to the free(NH) group. By this criterion, aliphatic

secondary amines can be divided into six classes that we call type A–F amines (Figure 4): type A is the least sterically hindered and type F being fully-substituted secondary aliphatic amines. We previously reported a C–H activation strategy for type F amines that proceeds via 4-membered ring cyclopalladation – a pathway distinct from this process *(26)*. However, the majority of amines in everyday use can be represented by amines of type A–E. Each class of these amine starting materials can be prepared by classical C–N bond forming methods, thereby linking the C–H activation process to well established preparative methods and reliable chemical feedstocks. Figure 4 shows the remarkable breadth of substrate scope for this aliphatic amine C–H activation process. We began by assessing type E amines and found that these hindered secondary amines are compatible with the reaction conditions and could be efficiently converted into the corresponding β-lactams in good yields (**2Ea-g**). In the case of **2Eb**, classical amine-directed 5-membered ring cyclopalladation could potentially lead a γ-lactam product; however, only the product formed via the new carbonylation pathway was observed. Type D amines, displaying an unsymmetrical arrangement of substituents around the NH-motif, also work very well in the C–H activation process (**2Da-j**). A variety of useful functional groups are amenable to the reaction conditions, producing the β-lactam products in good yields. The reaction with type C amines, displaying two substituents on either side of the free(NH) amine motif (**2Ca-p**), tolerated the incorporation of protected hydroxyl motifs (**2Cd**,**o**), carbonyls (**2Cf**), and amine motifs (**2Cg**,**k**,**m**,**n**) into the β-lactam products, providing opportunities for downstream synthetic manipulations of these valuable products. Pyridines (**2Ch**,**i**) and thioethers (**2Cl**) were tolerated as well, with no adverse effects on regioselectivity or catalyst poisoning, *(38)*. The reaction of an *N*-aryl amine (to **2Cp**), however, was unsuccessful under these conditions and the starting material was returned unchanged *(39)*.

Having demonstrated that the reaction works well on substituted type E-C secondary amines, we next sought to investigate the process with less hindered substrates. Type A and B amines would be expected to

form stable bis(amine)-Pd(II) complexes and their high nucleophilicity suggested that selective attack on the putative Pd-anhydride complex might be difficult to control. Additionally, each substrate contains up to four C–H bonds that can readily undergo β-hydride elimination side reactions. Despite these potential pitfalls, we were pleased to find that a range of type B amines worked very well in the C–H carbonylation (**2Ba-j**) when the reaction was conducted using phenylbenzoquinone, a hindered variant of BQ that prevents deleterious oxidative amination of the quinone scaffold. A variety of functional groups on the amine substituents were tolerated, including sulfones (**2Bc**), esters (**2Bd**), aromatic heterocycles (**2Be**) and alkenes (**2Bg**), producing the β-lactams in high yields. Our C–H carbonylation even producedunsubstituted β-lactams products from type A amines, albeit in lower yields (due in part to *N*-acylation and β-hydride elimination by-products) compared to the other amine types (**2Aa**,**b**). Taken together, our studies across type A-E amines led us to observe several additional features of this C–H activation process. First, substrates displaying unfunctionalized alkyl groups worked well (**2Ea**, **2Dg**, **2Cb** and **2Ba**), demonstrating that the success of the reaction is not the result of remote functionality influencing the reactivity. Second, C–H activation is also possible on either the branched or unbranched substituent of the amine without a change in outcome (for example **2Ba** and **2Bh**). Third, aliphatic heterocycles are also competent substrates for this reaction (**2Bj**), thereby providing a simple method by which to functionalize readily available amine building blocks suitable for complex molecule synthesis. Finally, the reaction tolerates a remarkable range of synthetic versatile functional groups across more than 40 examples highlighting the generality of this transformation.

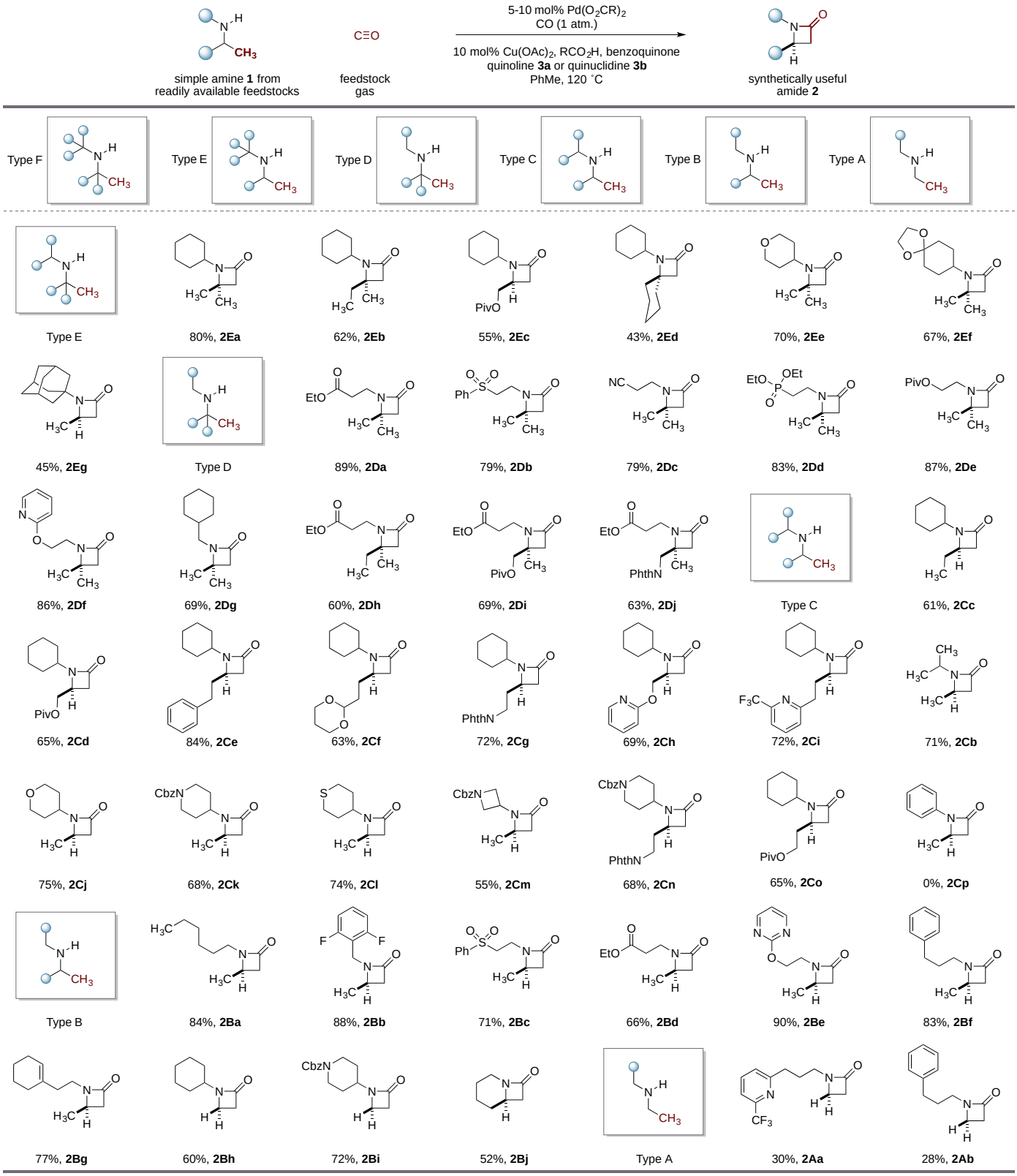


Fig. 4. The scope of the aliphatic amine C–H carbonylation.

Application to complex molecules

Aliphatic amine motifs are present in at least 30% of small-molecule pharmaceutical agents and are heavily represented in preclinical candidates. Therefore a major benefit of our aliphatic amine C–H carbonylation process is its potential amenability to mid and late-stage functionalization applications *(40).* In more complex molecules, the competition between numerous Lewis basic functionalities capable of steering C–H activation could cause deactivation or selectivity issues. To test this, we prepared an amine (**1Dk**) with three possible sites of C–H activation and were delighted to find that C–H carbonylation was directed by the aliphatic amine motif (to form **2Dk**) without any trace of the competitive pyridine directed C–H activation product (Fig. 5A). To further the potential for late-stage functionalization, we subjected a selection of pharmaceutical derivatives and biologically active molecules to our C–H carbonylation protocol (Figure 5B). Salbutamol and propranolol are β2-adrenergic receptor agonists and representative of a huge range of marketed pharmaceutical agents with a distinctive secondary amino alcohol. Simple derivatives of these molecules (**6a**,**b**) effectively underwent C–H carbonylation to form β-lactams (**7a**,**b**) in synthetically useful yields. A derivative of the acute heart failure drug, dobutamine (**6c**), reacted smoothly to afford the β-lactam in 72% yield (**7c**). Fenfluramine (**6d**), part of an anti-obesity treatment was successfully carbonylated to yield a separable mixture of regioisomeric β-lactams (**7d**, 2.5:1), highlighting a moderate selectivity for the branched methyl group. Finally, C–H carbonylation on the aza-sterol **6e**, an inhibitor of the hedgehog-activating transmembrane protein Smoothened *(41),* formed the β-lactam **7e** in useful yield, providing access to valuable analogs of this molecule that would be difficult to obtain by other means. A successful late-stage functionalization program would require delivery of multiple analogs in order to get maximum benefit from the strategy; β-lactams support a rich array of chemistry that can transform the amide function into pharmaceutically relevant motifs *(42)*. Removal of the hydroxyl protecting group from β-lactam **7b** yielded alcohol **8**, reductive ring opening afforded β-amino alcohol **9** and esterification yielded β-amino

ester **10** (Figure 5C). Under certain reductive conditions, the β-lactam could be transformed into azetidine **11**, an important structural feature that is common in many drug development programs (Figure 5C), underlining the diversity of structural motifs readily available from this aliphatic C–H activation tactic.

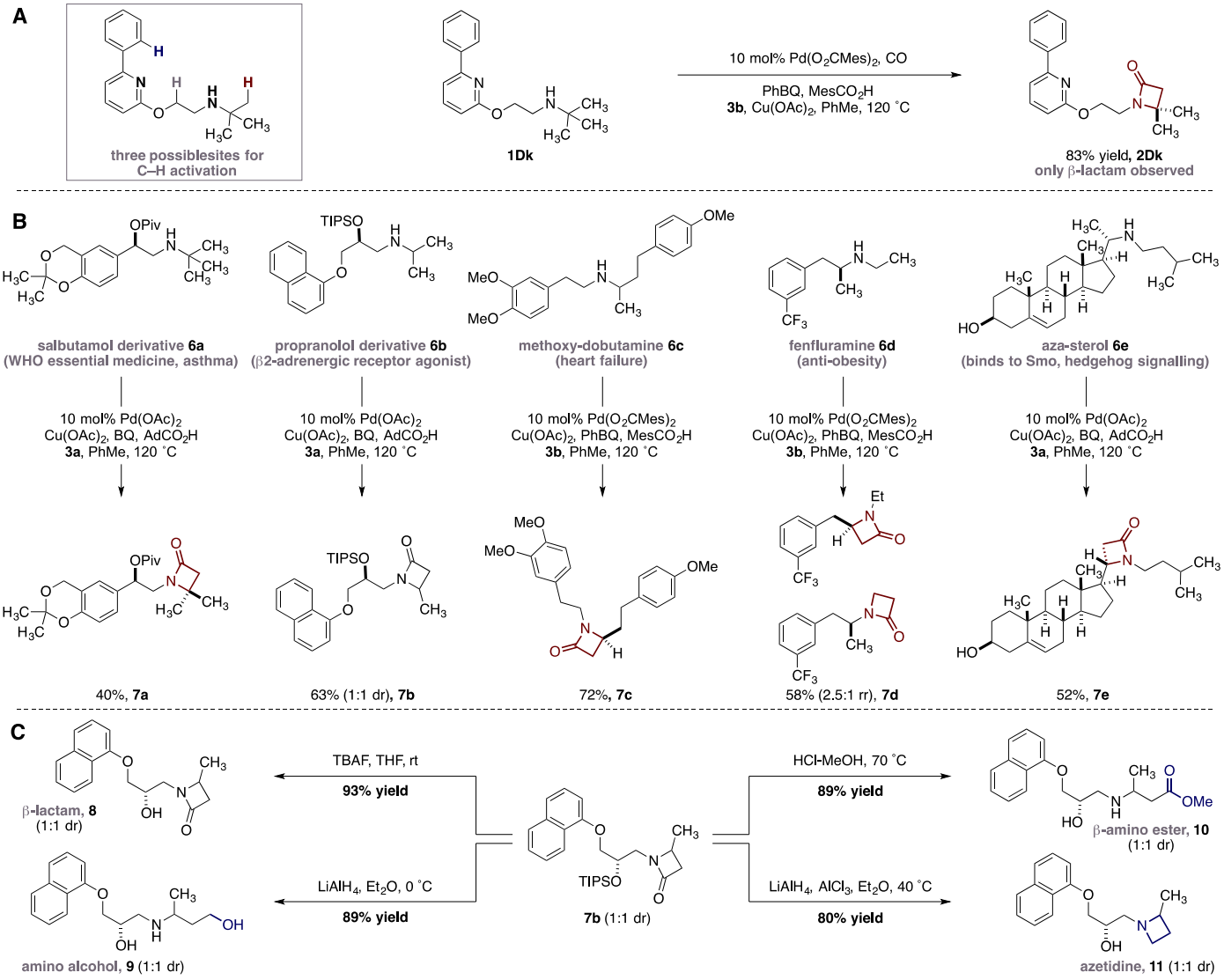


Fig. 5. Application to complex substrates. (**A**) Regioselective C–H activation in the presence of competing directing groups; (**B**) Late stage C–H functionalization on biologically active molecules. (**C**) Derivatizations of the β-lactam framework. [Pls define Mes, TIPS]

OUTLOOK

We expect this general C–H carbonylation process for aliphatic secondary amines to find broad application among practitioners of synthetic and pharmaceutical chemistry. In addition to the utility of this protocol, we anticipate that the distinct reactivity of free(NH) aliphatic amines in combination with Pd-catalysts will inspire further advances in a range of C–H activation processes. Moreover, this C–H carbonylation pathway is conceptually distinct from classical cyclopalladation-related approaches and may lead to opportunities for C–H activation reactions in other classes of functionalized aliphatic and aromatic molecules.

References and Notes:

1. S. D. Roughley, A. M. Jordan, The medicinal chemist's toolbox: An analysis of reactions used in the pursuit of drug candidates. *J. Med. Chem.* **54**, 3451–3479 (2011).

2. R. N. Salvatore, C. H. Yoon, K. W. Jung, Synthesis of secondary amines. *Tetrahedron* **57**, 7785–7811 (2001).

3. E. W. Baxter, A. B. Reitz, Reductive aminations of carbonyl compounds with borohydride and borane reducing agents. *Org. React.* **59**, 1–714 (2004).

4. J. Bariwal, E. Van der Eycken, C–N bond forming cross-coupling reactions: an overview. *Chem. Soc. Rev.* **42**, 9283–9303 (2013).

5. D. S. Surry, S. L. Buchwald, Biaryl phosphane ligands in palladium-catalyzed amination. *Angew. Chem. Int. Ed*. **47**, 6338–6361 (2008)

6. J. F. Hartwig, Evolution of a fourth generation catalyst for the amination and thioetherification of aryl halides. *Acc. Chem. Res*. **41**, 1534–1544 (2008)

7. Y, Yang, S. –L. Shi, D. Niu, P. Liu, S. L. Buchwald, Catalytic asymmetric hydroamination of unactivated internal olefins to aliphatic amines. *Science* **349**, 62–66 (2015).

8. J. Gui, C.-M. Pan, Y. Jin, T. Qin, J. C. Lo, B. J. Lee, S. H. Spergel, M. E. Mertzman, W. J. Pitts, T. E. La Cruz, M. A. Schmidt, N. Darvatkar, S. R. Natarajan, P. S. Baran, Practical olefin hydroamination with nitroarenes. *Science* **348**, 886–891 (2015).

9. C. K. Savile, J. M. Janey, E. C. Mundorff, J. C. Moore, S. Tam, W. R. Jarvis, J. C. Colbeck, A. Krebber, F. J. Fleitz, J. Brands, P. N. Devine, G. W. Huisman, G. J. Hughes, Biocatalytic asymmetric synthesis of chiral amines from ketones applied to Sitagliptin manufacture. *Science* **329**, 305–309 (2010).

10. F. G. Mutti, T. Knaus, N. S. Scrutton, M. Breuer, N. J. Turner, Conversion of alcohols to enantiopure amines through dual-enzyme hydrogen-borrowing cascades. *Science* **349**, 1525–1529 (2015).

11. J. Yamaguchi, A. D. Yamaguchi, K. Itami, C–H bond functionalization: emerging synthetic tools for natural products and pharmaceuticals. *Angew. Chem. Int. Ed.* **51**, 8960–9009 (2012)

12. T. W. Lyons, M. S. Sanford, Palladium-catalyzed ligand-directed C–H functionalization reactions. *Chem. Rev.* **110**, 1147–1169 (2010).

13. I. A. I. Mkhalid, J. H. Barnard, T. B. Marder, J. M. Murphy, J. F. Hartwig, C–H activation for the construction of C–B bonds. *Chem. Rev*. **110**, 890–931 (2010)

14. J. Wencel-Delord, T. Dröge, F. Liu, F. Glorius, Towards mild metal-catalyzed C–H bond activation. *Chem. Soc. Rev*. **40**, 4740–4761 (2011)

15. R. Jazzar, J. Hitce A. Renaudat J. Sofack-Kreutzer, O. Baudoin, Functionalization of Organic Molecules by Transition-Metal-Catalyzed C(sp^3)–H Activation *Chemistry – A European Journal*, **16**, 2654–2672 (2010).

16. H. A. Chiong, Q. N. Pham, O. Daugulis, Two methods for direct ortho-arylation of benzoic acids. *J. Am. Chem. Soc.* **129**, 9879–9884 (2007).

17. K. M. Engle, T. S. Mei, M. Wasa, J. –Q. Yu, Weak coordination as a powerful means for developing broadly useful C–H functionalization reactions. *Acc. Chem. Res.* **45**, 788–802 (2012).

18. K. J. Stowers, K. C. Fortner, M. S. Sanford, Aerobic Pd-catalyzed sp^3 C–H olefination: a route to both N-heterocyclic scaffolds and alkenes. *J. Chem. Am. Soc.* **133**, 6541–6544 (2011).

19. E. M. Simmons, J. F. Hartwig, Catalytic functionalization of unactivated primary C–H bonds directed by an alcohol. *Nature* **483**, 70–73 (2012).

20. A. D. Ryabov, Mechanisms of intramolecular activation of C–H bonds in transition-metal complexes. *Chem. Rev.* **90**, 403–424 (1990).

21. K. S. L. Chan, M. Wasa, L. Chu, B. N. Laforteza, M. Miura, J. –Q. Yu, Ligand-enabled cross-coupling of C(sp^3)–H bonds with arylboron reagents via Pd(II)/Pd(0) catalysis. *Nat. Chem.* **6**, 146–150 (2014).

22. V. G. Zaitsev, D. Shabashov, O. Daugulis, Highly regioselective arylation of sp^3 C–H bonds catalyzed by palladium acetate. *J. Chem. Am. Soc.* **127**, 13154–13155 (2005).

23. G. He, G. Chen, A practical strategy for the structural diversification of aliphatic scaffolds through the palladium-catalyzed picolinamide-directed remote functionalization of unactivated C(sp^3)–H bonds. *Angew. Chem. Int. Ed.* **50**, 5192–5196 (2011).

24. C. Wang, L. Zhang, C. Chen, J. Han, Y. Yao, Y. Zhao, Oxalyl amide assisted palladium-catalyzed synthesis of pyrrolidones via carbonylation of γ-C(sp^3)–H bonds of aliphatic amine substrates. *Chem. Sci.* **6**, 4610–4614 (2015).

25. J. J. Topczewski, P. J. Cabrera, N. I. Saper, M. S. Sanford, Palladium-catalysed transannular C–H functionalization of alicyclic amines. *Nature* **531**, 220–224 (2016).

26. A. MacNally, B. Haffemayer, B. S. L. Collins, M. J. Gaunt, Palladium-catalysed C–H activation of aliphatic amines to give strained nitrogen heterocycles. *Nature* **510**, 129–133 (2014).

27. J. Calleja, D. Pla, T. W. Gorman, V. Domingo, B. Haffemayer, M. J. Gaunt, A steric tethering approach enables palladium-catalysed C–H activation of primary amino alcohols. *Nature Chem.* **7**, 1009–1016 (2015).

28. X-. F. Weng, H. Neumann, M. Beller, Palladium catalyzed oxidative carbonylation reactions. *ChemSusChem.* **6**, 229–241 (2013).

29. C. Jia, T. Kitamura, Y. Fujiwara, Catalytic functionalization of arenes and alkanes via C–H bond activation. *Acc. Chem. Res.* **34**, 633–639 (2001).

30. We considered a number of alternative pathways as part of our assessment of possible catalytic cycle. See supplementary material for details of these calculations.

31. T.A. Stromnova, M.N. Vargaftik, I.I. Moiseev, Mechanism of reaction of palladium(II) carboxylates with carbon monoxide in nonaqueous media. *J. Organomet. Chem.* **252**, 113–120 (1983).

32. K. Orito, A. Horibata, T. Nakamura, H. Ushito, H. Nagasaki, M. Yuguchi, S. Yamashita, M. Tokuda, Preparation of benzolactams by $Pd(OAc)_2$-catalyzed direct aromatic carbonylation. *J. Chem. Am. Soc.* **126**, 14342–14343 (2004).

33. E. J. Yoo, M. Wasa, J. –Q. Yu, Pd(II)-catalyzed carbonylation of $C(sp^3)$ –H Bonds: a new entry to 1,4-dicarbonyl compounds. *J. Chem. Am. Soc.* **132**, 17378–17380 (2010).

34. K. Hull, M. S. Sanford, Mechanism of benzoquinone-promoted palladium-catalyzed oxidative cross coupling reactions. *J. Am. Chem. Soc*. **131**, 9651–9653 (2009).

35. J. He, S. Li, Y. Deng, H. Fu, B. N. Laforteza, J. E. Spangler, A. Homs, J. –Q. Yu, Ligand-controlled $C(sp^3)$–H arylation and olefination in synthesis of unnatural chiral α–amino acids. *Science* **343**, 1216–1220 (2014).

36. C. Tsukano, M. Okuno, Y. Takemoto, Y. Palladium-Catalyzed Amidation by Chemoselective $C(sp^3)$–H Activation: Concise Route to Oxindoles Using a Carbamoyl Chloride Precursor. *Angew. Chem. Int. Ed*. **51**, 2763–2766 (2012).

37. B. V. Popp, S. S. Stahl Mechanism of $Pd(OAc)_2$/Pyridine Catalyst Reoxidation by O_2: Influence of Labile Monodentate Ligands and Identification of a Biomimetic Mechanism for O_2 Activation. *Chem. Eur. J.* ***15***, 2915-2922 (2009).

38. Y-. J. Liu, H. Xu, W.- J. Kong, M. Shang, H.- X. Dai, J-. Q. Yu Overcoming the limitations of directed C–H functionalization of heterocycles. *Nature*, **515**, 389-393 (2015).

39. W. Li, Z. Duan, X. Zhang, H. Zhang, M. Wang, R. Jiang, H. Zeng, C. Liu, A. Lei, From anilines to isatins: Oxidative palladium-catalyzed double carbonylation of C–H bonds. *Angew. Chem. Int. Ed.* **54**, 1893–1896 (2015).

40. J. Wencel-Delord, F. Glorius, C–H bond activation enables the rapid construction and late-stage diversification of functional molecules. *Nat. Chem.* **5**, 369–375 (2013).

41. D. Nedelcu, J. Liu, Y. Xu, C. Jao, A. Salic, Oxysterol binding to the extracellular domain of Smoothened in Hedgehog signaling. *Nat. Chem. Bio.* **9**, 557–564 (2013).

42. B. K. Banik, Ed., *β-Lactams: unique structures of distinction for novel molecules* (Springer, Berlin, 2013).

Acknowledgments:

We gratefully acknowledge the ERC and EPSRC (D.W., K.H., A.S., M.J.G.), the Herchel Smith Trust (B.C.) and the Marie Curie Foundation (J.C.) for funding. Mass spectrometry data were acquired at the EPSRC UK National Mass Spectrometry Facility at Swansea University. Computational work was performed using the Darwin Supercomputer of the University of Cambridge High Performance Computing Service (http://www.hpc.cam.ac.uk/), provided by Dell, Inc., using Strategic Research Infrastructure Funding from the Higher Education Funding Council for England. Supplementary Material contains ^{1}H and ^{13}C NMR spectra and computational details. Crystallographic data are available free of charge from the Cambridge Crystallographic Data Centre under reference CCDC-####.

Supplementary Materials
Materials and Methods
Figs. 1 to #
Tables 1 to #
References (43-#)
NMR Spectra

Notes on the supplementary material (not supporting information or any other permutation of those 4 words): Pls make a single integrated pdf file that includes both the synthetic and computational methods. There should also be one integrated reference list, reproduced in full both above in this main file, as well as at the very end of the supplement file (after the spectra). References cited exclusively in the supplement should be numbered consecutively at the end of the list (ie, 43, 44, etc). Please use Science citation style in the supplement (ie, (#), not superscripts). Finally, pls use *, †, ‡ for table footnotes, rather than letters.