

ORGANIC CHEMISTRY

A general catalytic β -C-H carbonylation of aliphatic amines to β -lactams

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Methods for the synthesis and functionalization of amines are intrinsically important to a variety of chemical applications. We present a general carbon-hydrogen bond 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 an amine attack on a palladium anhydride to transform aliphatic amines into β -lactams. The reaction is successful with 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.

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. Inspired by the efficacy with which these well-established methods produce amines, we recognized the potential utility of a general catalytic process capable of directly introducing new functionality onto the framework of readily accessible and simple amines. In particular, we envisioned that their union with carbon monoxide through a selective amine-directed C–H carbonylation would produce a β -lactam feature, the versatile reactivity and biological relevance of which would make the method valuable to practitioners of synthetic and medicinal chemistry (Fig. 1A).

Transition metal catalysts capable of C–H activation have inspired intense research efforts within the synthetic chemistry community (11–14). Although many advances have been made in the field of aromatic sp^2 -hybridized C–H [$C(sp^2)$ –H] bond activation, functionalization of less reactive $C(sp^3)$ –H bonds in aliphatic molecules continues to present a challenge (15). Because of the lower reactivity of $C(sp^3)$ –H bonds, their activation often relies on the 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, however, continue to cause problems that restrict wider application (20).

A number of factors can be identified that impede the development of free-NH aliphatic amine-directed C–H activation with catalysts such as Pd(II) salts (Fig. 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 (Fig. 1A). Here we report the development of a general process for the catalytic C–H carbonylation of aliphatic amines, wherein readily available unprotected amines are combined with carbon monoxide to generate 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 free-NH aliphatic amines and Pd(II) catalysts. There are a number of specific advantages of this method: First, readily available aliphatic amines can be directly converted into highly functional-

ized and synthetically versatile small-molecule lactam building blocks; second, by obviating the need for nitrogen-protecting or auxiliary groups, the number of synthetic steps required to access functional amines is greatly reduced; third, C–H carbonylation directed by free-NH amine motifs in pharmaceutical agents or natural products could be used as a potentially powerful late-stage functionalization approach to analog synthesis.

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 (26). Highly hindered amines, displaying fully substituted carbon atoms on either side of the nitrogen motif, underwent C–H carbonylation to yield 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, resulting from a clash between the two highly hindered amines, which shifts the equilibrium toward a 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 and colleagues (29), who outlined a mechanistic blueprint that has underpinned most subsequent directed C–H carbonylation reactions with Pd(II) catalysts: In our 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. 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 the case for 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). On the basis of 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 before C–H activation. Moreover, Pd(OAc)₂ (Ac, acetate group) 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 little is known about this pathway, studies by

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Moiseev and colleagues (31) provided clues that led us to propose a simplified model that we supported through computation. Two molecules of CO coordinate to monomeric $\text{Pd}(\text{OAc})_2$ (**int-I**) and a calculated Pd–C–O angle of 153.7° , along with a bond distance between the carboxylate and CO of 2.06 \AA , suggested an interaction between the two ligands. An 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 $+11.50 \text{ kcal mol}^{-1}$ 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(O). Motivated 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—distinct from classical cyclopalladation processes that usually result in activation three carbons from the directing motif.

Reaction development and mechanistic studies

To test our hypothesis, we reacted amine **1a** under anticipated conditions for C–H carbonylation (Fig. 2D) (32, 33). Although we observed the desired product (β -lactam **2a**) in low yield, the re-

action was capricious and accompanied by the formation of acetylated amine and oxidative degradation products (entry 1). On the basis of our mechanistic blueprint, we expected that the attack on the Pd anhydride species at position **a** would lead to CO_2 release, reduction of the Pd catalyst, and an acetylated amine side product (Fig. 2B). We speculated that a larger carboxylate would generate a sterically biased Pd anhydride, steering the 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 found that the 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, and 9) (35). We also found that other hindered carboxylic acids were effective in the reaction (entry 8). An optimized procedure thus involved stirring a 0.1 M solution of amine **1a** in toluene with 10 mole (mol) % $\text{Pd}(\text{OAc})_2$, 10 mol % $\text{Cu}(\text{OAc})_2$, 100 mol % BQ, 25 mol % adamantanoic acid, and 10 mol % **3a** at 120°C under an atmosphere of CO; this gave an 83% yield of β -lactam **2a** 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 (see Fig. 2D, entry 10, where PPh_3 is used as an additive), we showed that the β -lactam **2b** 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 with 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 BQ as essential for the high-yielding formation of **2a** 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 substantially affect the rate of the catalytic reaction. Last, we observed a kinetic isotope effect of 1.14 from parallel reaction of **1a** and **d⁶-1a**, suggesting that C–H activation is not the rate-determining step (Fig. 3B). A close inspection of the reaction of **d⁶-1a**, using nuclear magnetic resonance (NMR), revealed that hydrogen-deuterium scrambling had occurred in the lactam product **2a** at the

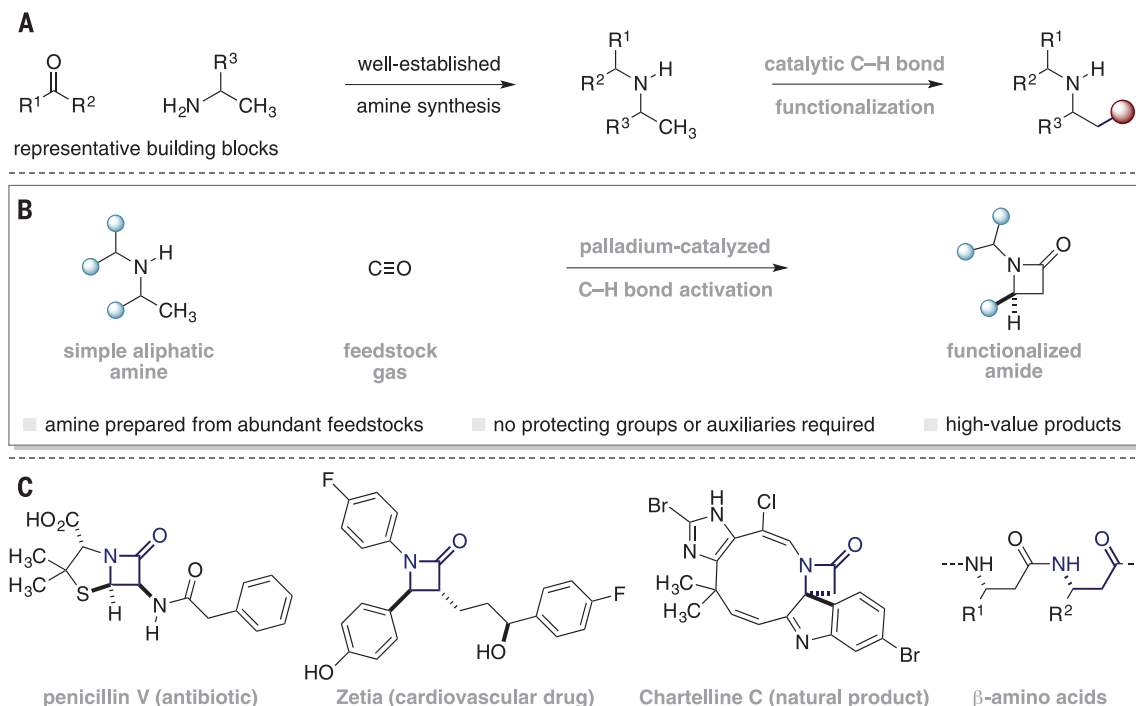


Fig. 1. A strategy for the catalytic synthesis of functionalized aliphatic amines. (A) Hypothesis: Combining well-established amine synthesis with metal-catalyzed C–H functionalization will lead to the rapid synthesis of functionalized amides. (B) Pd-catalyzed $\text{C}(\text{sp}^3)\text{--H}$ carbonylation of free-NH amines. A blue circle or R denotes a general organic group. (C) The importance of β -lactams.

methyl group and at the position adjacent to the carbonyl of the amide. However, no hydrogen-deuterium scrambling was observed in the recovered starting material **4^a**-**1a**. These observations indicate that C–H activation is reversible and takes place after an irreversible step.

Taken together, these observations suggest a catalytic cycle for this C–H carbonylation reaction (30), which we have supported with a computational study of a simplified system using diisopropylamine **1b** and 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 (RCO₂H) (R, *t*-butyl group) forms Pd(O₂CR)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**); we deemed **int-V**, as the

catalyst resting state, to be the energetic reference point. CO binding then forms **int-VI**, from which a viable transition state (**TS1**) to the Pd anhydride complex **int-VII** was determined. On the basis of our kinetic isotope effect and computational studies, we suggest that the attack of the amine at the internal carbonyl of **int-VII** (via **TS2**) to form carbamoyl-Pd species **int-VIII** is irreversible, and from this point, reversible C–H activation takes place through a concerted metalation-deprotonation pathway (**TS3**) to form a five-membered-ring cyclopalladation intermediate **int-IX** (see also Fig. 2E). Last, BQ-assisted reductive elimination (via **TS4**) leads to β-lactam **2b** after decomplexation from Pd(0); oxidation of the Pd(0) species with Cu(OAc)₂ regenerates the active Pd(II) species. The amine additives **3a** and **3b** may stabilize the Pd(0) species before oxidation by preventing deactivating aggregation (37).

This effect may be more pronounced toward the end of the reaction, when the concentration of the amine substrate **1** is lower, and possibly explains why **3a** and **3b** have an effect on yield but not on the rate of reaction.

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 amines with respect to substitution at the carbon atoms directly connected to the free-NH group. We previously reported a C–H activation strategy for fully substituted aliphatic secondary amines that proceeds via four-membered-ring cyclopalladation—a pathway distinct from

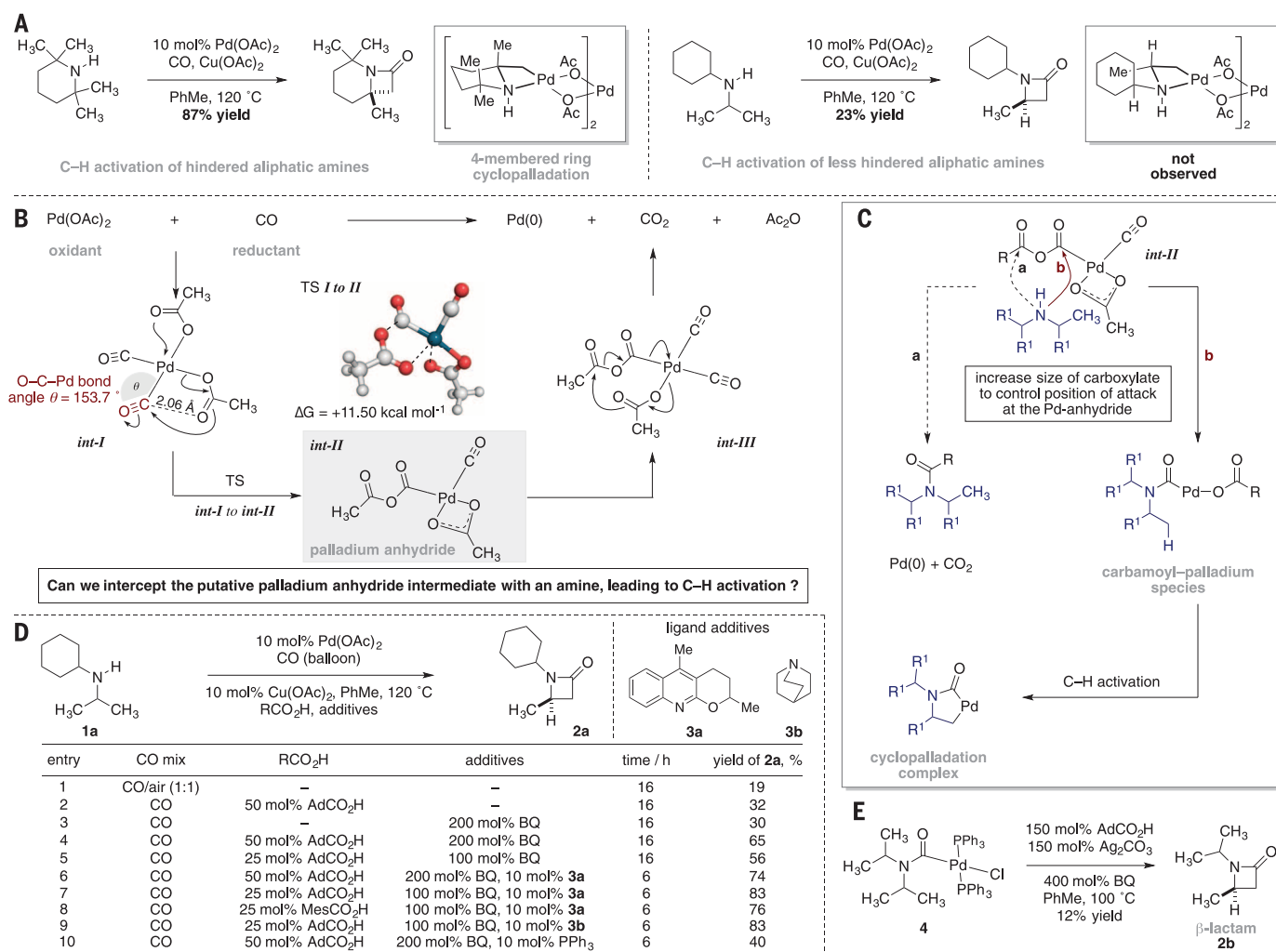


Fig. 2. Toward an activation mode for C–H carbonylation of unhindered aliphatic amines. (A) Previous work: C–H carbonylation of hindered aliphatic amines via a four-membered-ring cyclopalladation pathway (left) and poor-yielding C–H carbonylation of less hindered amines (right). (B) Reduction of Pd(OAc)₂ by CO. (C) Design: A sterically controlled ligand-enabled C–H activation. (D) Optimization studies. (E) C–H activation from a de novo carbamoyl-Pd complex.

Computational studies were conducted using Amsterdam Density Functional software at the ZORA:BLYP-D3/TZ2P level with the COSMO solvation model (PhMe) (supplementary materials). Ph, phenyl group; Me, methyl group; Ac, acetate group; BQ, benzoquinone; Ad, adamantyl group; MesCO₂H, 2,4,6-trimethylbenzoic acid; ΔG, change in Gibbs free energy; TS, transition state; int, intermediate; h, hours; equiv, equivalent.

this process (26). However, the majority of amines in everyday use are represented by less substituted variants. Each class of these amine starting materials can be prepared by classical methods of C–N bond formation, thereby linking the C–H activation process to well-established preparative methods and reliable chemical feedstocks. Figure 4 shows the wide breadth of the substrate scope for this aliphatic amine C–H activation process. We began by assessing amines with five substituents around the nitrogen motif and found that these hindered secondary amines were compatible with the reaction conditions and could be efficiently converted into the corresponding β -lactams in good yields (**2c** to **2i**). In the case of **2d**, classical amine-directed five-membered-ring cyclopalladation could potentially lead to a γ -lactam product; however, only the product formed via the new carbonylation pathway was observed. Amines with an unsymmetrical arrangement of four substituents around the NH motif also worked very well in the C–H activation process (**2j** to **2s**). A variety of useful functional groups were amenable to the reaction conditions, produc-

ing the β -lactam products in good yields. The reaction with amines containing two substituents on either side of the free-NH amine motif (**2a**, **2b**, and **2t** to **2af**) tolerated the incorporation of protected hydroxyl motifs (**2u** and **2af**), carbonyls (**2w**), and amine motifs (**2ab**, **2ad**, and **2ae**) into the β -lactam products, providing opportunities for downstream synthetic manipulations of these valuable products. Pyridines (**2y** and **2z**) and thioethers (**2ac**) were tolerated as well, with no adverse effects on regioselectivity or catalyst poisoning (38). The reaction of an *N*-aryl amine (to **2ag**), however, was unsuccessful under these conditions, and the starting material was returned unchanged (39).

Having demonstrated that the reaction works well on heavily substituted secondary amines, we next sought to investigate the process with less hindered substrates. These types of amines would be expected to form stable bis(amine)-Pd(II) complexes (compare with **int-V**, Fig. 3C), 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 found that a range of amines with three substituents worked very well in the C–H carbonylation (**2ah** to **2aq**) when the reaction was conducted using phenylbenzoquinone, a hindered variant of BQ that prevents deleterious oxidative amination of the quinone scaffold. A substrate with only unfunctionalized alkyl groups worked well (**2ah**), demonstrating that the success of the reaction is not the result of remote functionality influencing the reactivity. A variety of functional groups on the amine substituents were tolerated, including sulfones (**2aj**), esters (**2ak**), aromatic heterocycles (**2al**), and alkenes (**2an**), producing the β -lactams in high yields. Aliphatic heterocycles were also competent substrates for this reaction (**2aq**), thereby providing a simple method by which to functionalize readily available amine building blocks suitable for complex molecule synthesis. Our C–H carbonylation even produced unsubstituted β -lactam products from unbranched secondary amines, albeit in lower

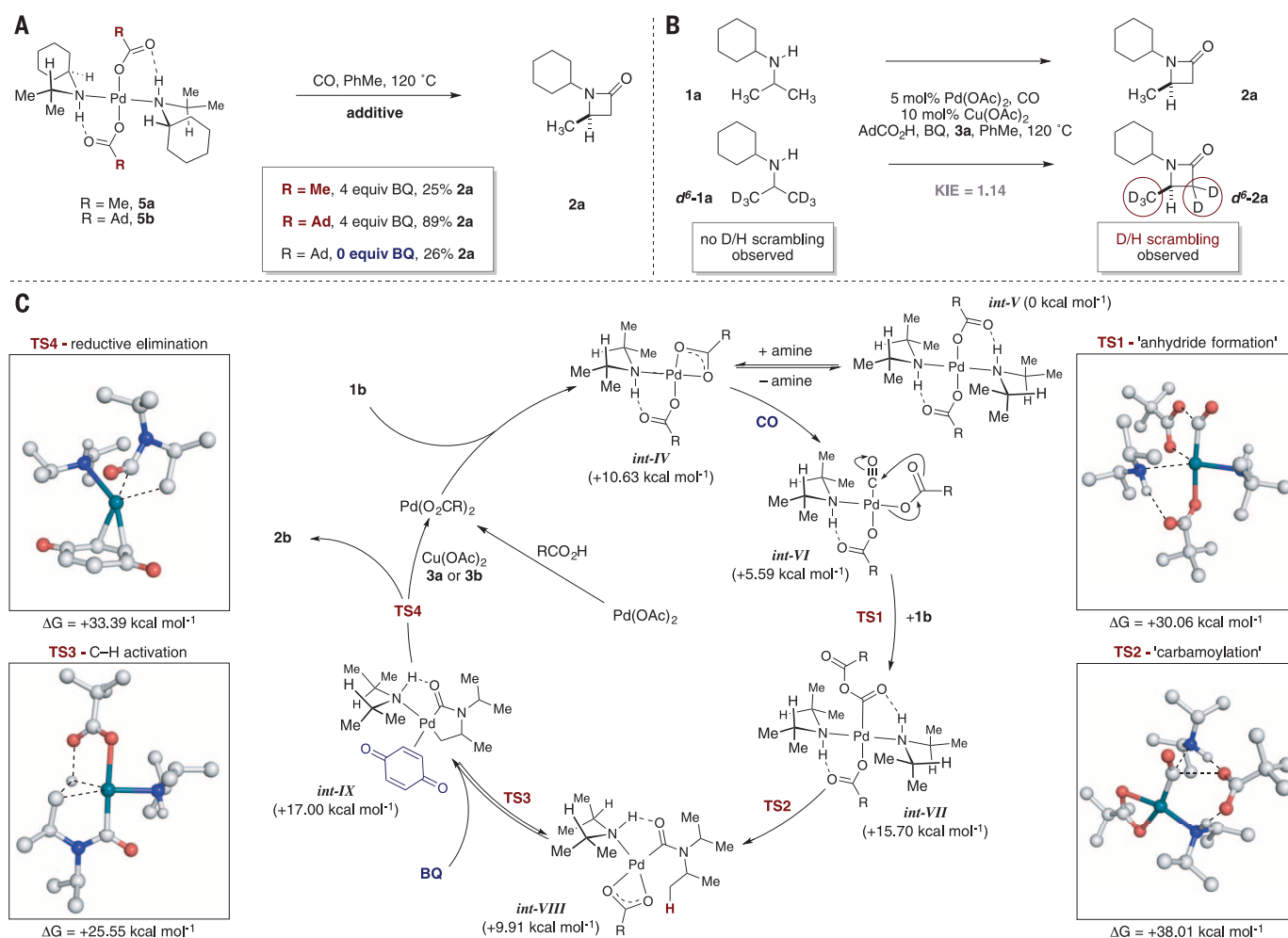


Fig. 3. Mechanistic evaluation of the C–H carbonylation reaction. (A) Stoichiometric studies. (B) Kinetic isotope effect (KIE) studies. (C) Proposed mechanism for C–H carbonylation of aliphatic amines. In the insets, blue is nitrogen, teal is palladium, red is oxygen, and light gray is carbon. Dotted lines indicate breaking and forming bonds. Computational studies were conducted as in Fig. 2.

yields (due in part to by-products formed from *N*-acylation and β -hydride elimination) compared with those from the other amine types (**2ar** to **2as**). As a whole, our scope studies demonstrate that the C–H carbonylation reaction tolerates a wide range of synthetic versatile functional groups spanning more than 40

examples, highlighting the generality of this transformation.

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 (**40**).

Therefore, a major benefit of our aliphatic amine C–H carbonylation process is its potential amenability to mid- and late-stage functionalization applications (**41**). In more complex molecules, the competition between numerous Lewis basic functionalities capable of steering C–H activation could cause deactivation or selectivity issues.

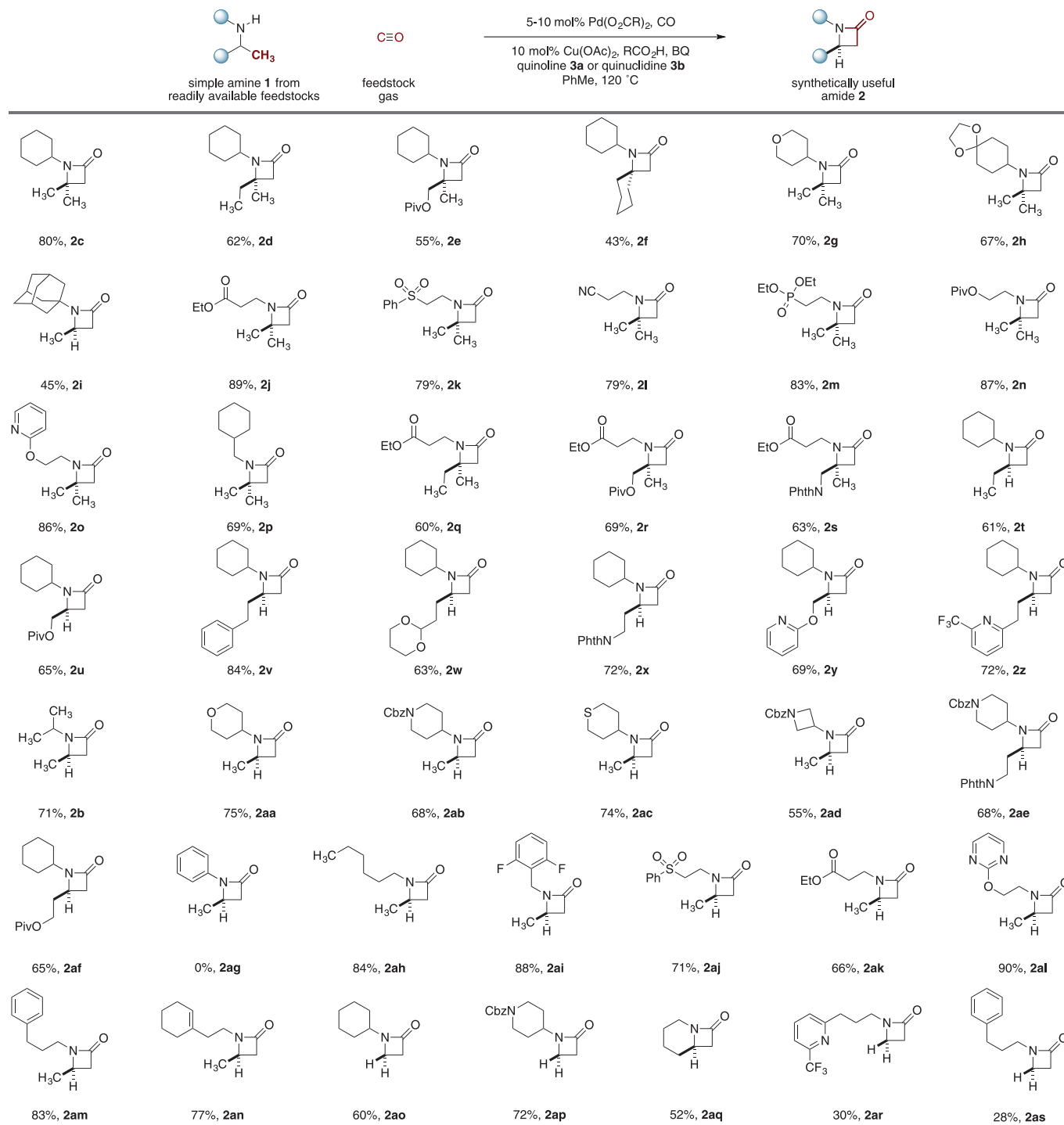


Fig. 4. The scope of the aliphatic amine C–H carbonylation. Yields of isolated products are shown. All compounds are racemic. Piv, pivaloyl group; Et, ethyl group; Phth, phthalimido group; Cbz, carbobenzyloxy group.

To test this, we prepared an amine (**1at**) with three possible sites of C–H activation and found that C–H carbonylation was directed by the aliphatic amine motif (to form **2at**) 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 (Fig. 5B). Salbutamol and propranolol are β_2 -adrenergic receptor agonists and are representative of a huge range of marketed pharmaceutical agents with a distinctive secondary amino alcohol. Simple derivatives of these molecules (**6a** and **6b**) effectively underwent C–H carbonylation to form β -lactams (**7a** and **7b**) in synthetically useful yields. A derivative of the acute heart failure drug dobutamine (**6c**) reacted smoothly to afford β -lactam in 72% yield (**7c**). Fenfluramine (**6d**), part of an anti-obesity treat-

ment, 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. Last, C–H carbonylation on the aza-sterol **6e**, an inhibitor of the hedgehog-activating transmembrane protein Smoothened (**42**), 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 the delivery of multiple analogs to get the maximum benefit from the strategy; β -lactams support a rich array of chemistry that can transform the amide function into pharmaceutically relevant motifs (**43**). 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** (Fig. 5C). Under certain reductive conditions, the β -lactam could be trans-

formed into azetidine **11**, an important structural feature that is common in many drug development programs (Fig. 5C), underlining the diversity of structural motifs readily available from this aliphatic C–H activation tactic.

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.

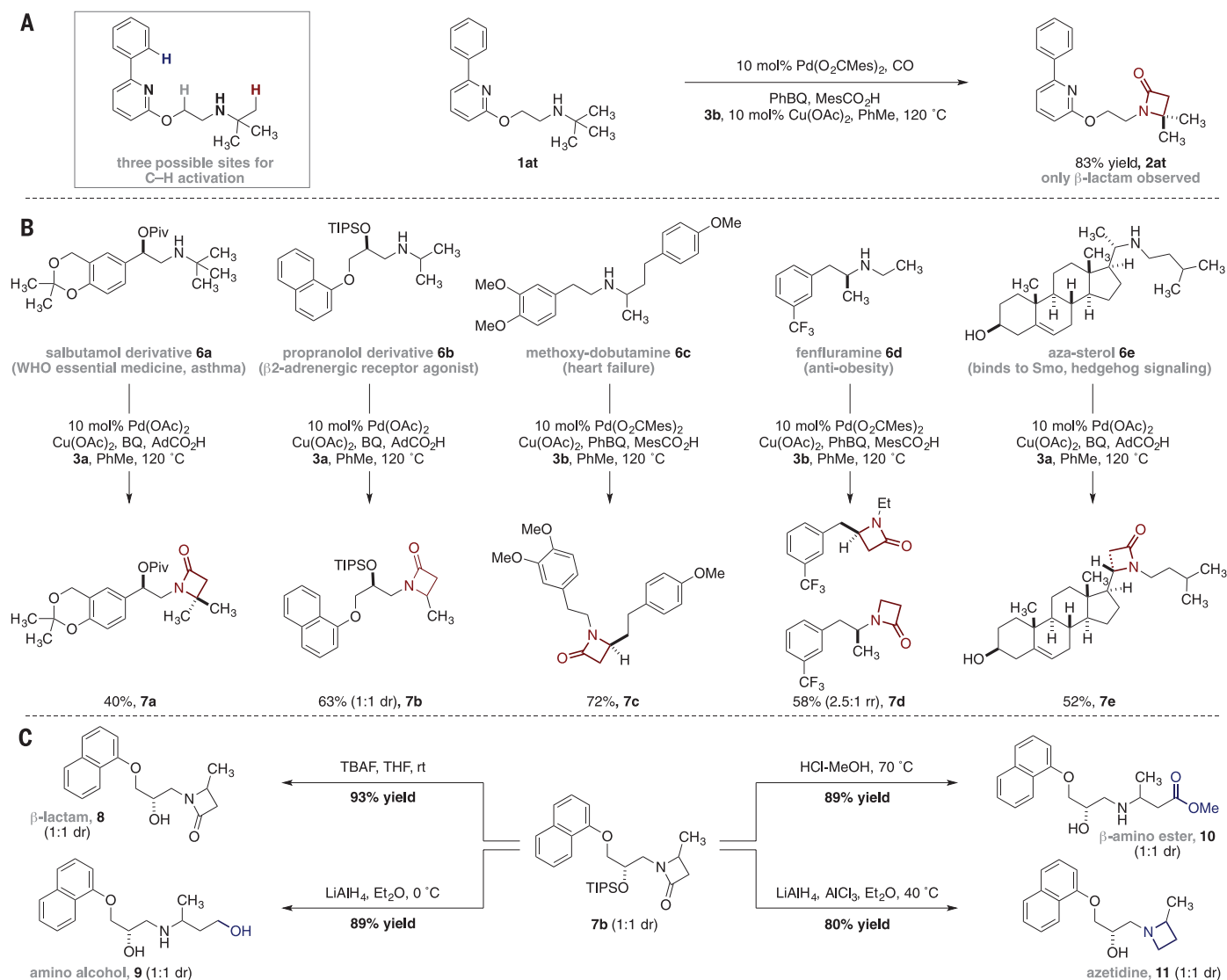


Fig. 5. Application to complex substrates. (A) Regioselective C–H activation in the presence of competing directing groups. (B) Late-stage C–H functionalization on biologically active molecules. (C) Derivatizations of the β -lactam framework. TIPS, triisopropylsilyl; WHO, World Health Organization; Smo, Smoothened (protein); TBAF, tetrabutylammonium fluoride; THF, tetrahydrofuran; dr, diastereoisomeric ratio; rr, regioisomeric ratio; rt, room temperature.

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Crystallographic Data Centre under reference numbers CCDC-1508626 to CCDC-1508631.

SUPPLEMENTARY MATERIALS

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Materials and Methods
Figs. S1 to S3
NMR Spectra
References (44–55)

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Improving photosynthesis and crop productivity by accelerating recovery from photoprotection

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Crop leaves in full sunlight dissipate damaging excess absorbed light energy as heat. When sunlit leaves are shaded by clouds or other leaves, this protective dissipation continues for many minutes and reduces photosynthesis. Calculations have shown that this could cost field crops up to 20% of their potential yield. Here, we describe the bioengineering of an accelerated response to natural shading events in *Nicotiana* (tobacco), resulting in increased leaf carbon dioxide uptake and plant dry matter productivity by about 15% in fluctuating light. Because the photoprotective mechanism that has been altered is common to all flowering plants and crops, the findings provide proof of concept for a route to obtaining a sustainable increase in productivity for food crops and a much-needed yield jump.

According to detailed forecasts of future global food demand, current rates of increase in crop yields per hectare of land are inadequate. Prior model predictions have suggested that the efficiency of the photosynthetic process and thereby crop yield could be improved (1). Here, we show improvement of photosynthetic efficiency and crop productivity through genetic manipulation of photoprotection.

Light in plant canopies is very dynamic, and leaves routinely experience sharp fluctuations in levels of absorbed irradiance. When light intensity is too high or increases too fast for photochemistry to use the absorbed energy, several photoprotective mechanisms are induced to protect the photosynthetic antenna complexes from overexcitation (2). Excess excitation energy in

the photosystem II (PSII) antenna complex can be harmlessly dissipated as heat, which is observable as a process named nonphotochemical quenching of chlorophyll fluorescence (NPQ) (3). Changes in NPQ can be fast but are not instantaneous and therefore lag behind fluctuations in absorbed irradiance. In particular, the rate of NPQ relaxation is slower than the rate of induction, and this asymmetry is exacerbated by prolonged or repeated exposure to excessive light conditions (4). This slow rate of recovery of PSII antennae from the quenched to the unquenched state implies that the photosynthetic quantum yield of CO_2 fixation is transiently depressed by NPQ upon a transition from high to low light intensity (Fig. 1). When this hypothesis was tested in model simulations and integrated for a crop canopy over a diurnal course, corresponding losses of CO_2 fixation were estimated to range between 7.5 and 30% (5–7). On the basis of these computations, increasing the relaxation rate of NPQ appeared to be a very promising strategy for improving crop photosynthetic efficiency and in turn yield (8).

Although the exact NPQ quenching site and nature of the quenching mechanisms involved are still debated (9), it is clear that for NPQ to occur, PSII-associated antennae need to undergo a conformational change to the quenched state,

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A general catalytic β -C–H carbonylation of aliphatic amines to β -lactams

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Editor's Summary

CO takes the lead to make β -lactam rings

Strained β -lactam rings are a key feature of penicillin and some other drugs. Willcox *et al.* designed a versatile route to these four-membered ring motifs through the palladiumcatalyzed coupling of carbon monoxide with secondary amines. The bulky carboxylate ligand appears to facilitate preliminary CO incorporation into a Pd anhydride, which is then attacked by the amine to set up ring closure via C–H activation. This approach broadens the substrate scope compared with a previous scheme in which C–H activation preceded CO insertion.

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