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Selective Pd(II)-Catalyzed Carbonylation of Methylene β-C–H Bonds in Aliphatic Amines

*Jaime R. Cabrera-Pardo, Aaron Trowbridge, Manuel Nappi, Kyohei Ozaki and Matthew J. Gaunt**

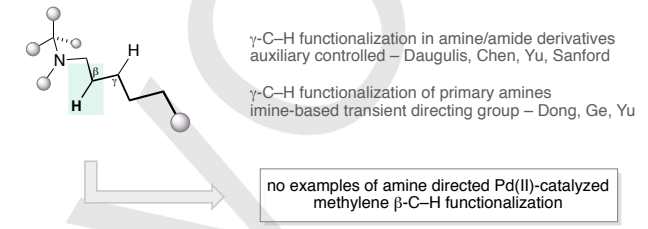
Abstract: Pd(II)-catalyzed C–H carbonylation of methylene C–H bonds in secondary aliphatic amines leads to the formation trans-disubstituted β-lactams in excellent yields and selectivities. The generality of the C–H carbonylation process is aided by the action of xantphos-based ligands and is important in securing good yields of the β-lactam products.

One of the most important developments in synthetic chemistry over the last 20 years has been the advent of transition metal catalyzed C–H activation reactions.[1] While the majority of these successful catalytic processes exploit the functionalization of C(sp^2)–H bonds, embracing C(sp^3)–H bonds as reactive entities remains a challenge to synthetic chemists and continues to inspire intensive efforts.[2] Arguably, the most successful approaches to C(sp^3)–H functionalization have exploited processes based on functional group directed C–H cleavage at methyl groups with electrophilic palladium(II) catalysts.[3] Despite this, selective Pd-catalyzed C–H functionalization at methylene sites remains particularly challenging because the increased steric interactions that result from engaging a mid-chain C–H bond can preclude proximity-driven palladation. Although, successful examples of Pd-catalyzed methylene activation usually require the appendage of an auxiliary directing group to facilitate the C–H bond cleavage, these advances have led to a range of novel transformations across a variety of substrate classes.[4,5] In contrast, the use of native directing groups to achieve related methylene C–H processes is less common.[6,7] Given the prevalence of amines in biologically active molecules,[8] we reasoned that a general strategy enabling selective activation of methylene C–H bonds directed by the intrinsic unprotected amine functionality would be of substantial utility in synthesis.

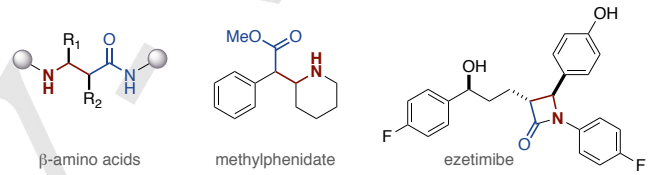
With respect to previous work on methylene C–H activation, Daugulis,[4a] Chen,[4b] Yu,[4f,7b] and Sanford[4g] have reported directed transformations with a range of aliphatic amine derivatives (eqn. 1). Each of these processes, however, requires the use of a pre-installed auxiliary group to enable functionalization and additional, often complicated, steps are always needed for its processing. More recently, Dong,[7a] Yu[7b] and Ge[7c] have reported that transiently formed catalytic auxiliaries (via imines) can be applied to methylene C–H activation in some functionally simple primary amines. In most of the aforementioned cases, auxiliary-controlled methylene C–H activation takes place at the γ-position to the amine via 'classical' 5-membered ring cyclopalladation. To the best of our knowledge, there is no direct functionalization process that selectively targets a methylene C–H bond in the β-position to an unprotected aliphatic amine;[9,10] such a transformation would give rise to a structural feature that is ubiquitous in biologically relevant complex amines (eqn. 2).

Here we report a general process for the Pd-catalyzed functionalization of methylene C–H bonds at the β-position to an unprotected aliphatic amine; no auxiliary group is required. By exploiting a novel carbonylation pathway, precluding classical cyclopalladation, the C–H functionalization process inserts CO between the β-carbon and amine to selectively form trans-disubstituted β-lactams (eqn. 3). The operationally simple reaction produces β-lactams in good yields and works for a wide range of functionally diverse and readily available amines. We believe that the versatile β-lactam products will be of significant interest to practitioners of synthetic and medicinal chemistry.

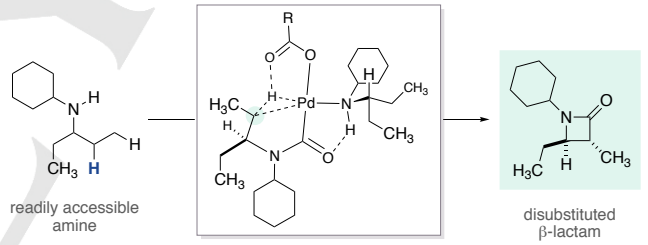
(1) State of the art in amine-directed methylene C–H functionalization with Pd(II)



(2) β-functionality is a common feature in biologically relevant aliphatic amines



(3) Pd(II)-catalyzed methylene C–H carbonylation of secondary aliphaitc amines



First, we benchmarked the C–H activation step by treating amine **1a** with a stoichiometric amount of $Pd(OAc)_2$. We found that **1a** underwent classical cyclopalladation at the γ-C–H bond to form the 5-membered ring complex, int-**I** (Scheme 1a).[11] When this complex was stirred under an atmosphere of CO, the expected γ-lactam **2a** was observed. The pathway to **2a** (via int-**I**) is consistent with cyclopalladation, followed by CO insertion and reductive elimination.[3h,3l,12] Next, we stirred a mixture of (bis)amine Pd(II) complex int-**II** (an established precursor to C–H activation)[3h] under 1 atm. of CO/air. We were surprised to find the reaction afforded a 1.3:1 mixture of γ-lactam **2a** and β-lactam **3a**, the later arising from methylene β-C–H carbonylation (Scheme 1b). We postulated that **3a** could be formed via a competitive C–H carbonylation pathway, recently outlined by our laboratory.[13] If CO is first activated by the $Pd(OAc)_2$, it could engage the amine to form a carbamoyl-Pd(II) species, from which C–H activation can occur at the β-methylene position via a 5-membered ring transition structure (eqn 3); reductive elimination from putative palladacycle int-**III** would form β-lactam **3a**. Notably, the concentration of CO appears to control the pathway of the C–H carbonylation process; only **3a** is observed if int-**II** is stirred under a purely CO atmosphere. The proposed pathway to **3a** is further supported by reaction of carbamoyl chloride **4** with $Pd(PPh_3)_4$, which presumably passes through a related carbamoyl-Pd(II) intermediate (int-**IV**) en route to the β-lactam (Scheme 1c).[10a,13,14]

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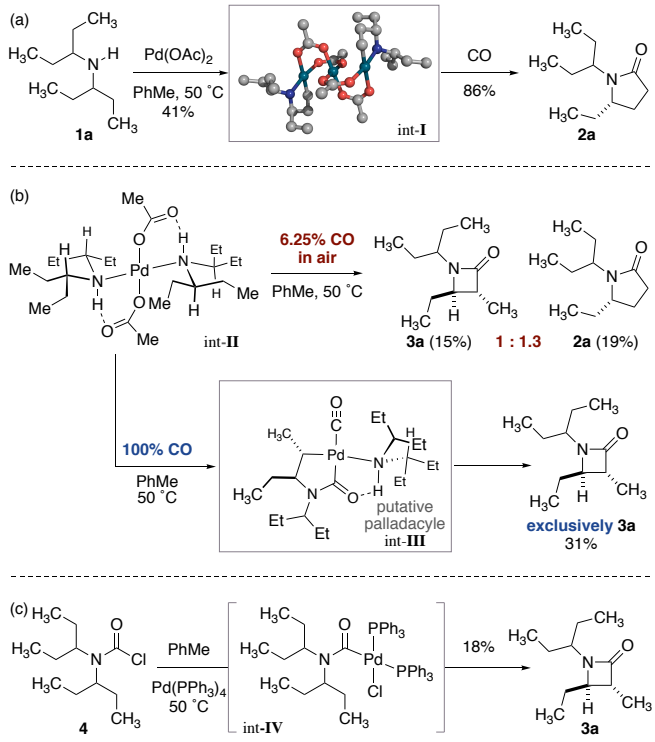
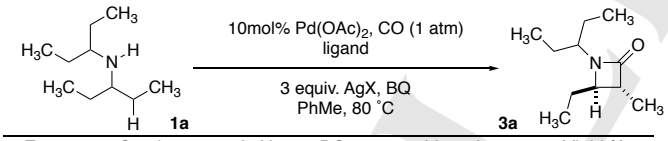


Scheme 1. Preliminary mechanistic experiments

Using amine **1a**, we assessed a catalytic methylene β-C–H carbonylation by testing the reaction conditions that were successful for our methyl β-C–H carbonylation.[13] Although the reaction produced **3a** in a capricious 23% assay yield, a significant amount of N-acetylated amine byproduct (28%) was observed. Cu(II) salts are known to catalyze N-acetylation,[15] but we found changing the oxidant from $Cu(OAc)_2$ to AgOAc increased the yield of **3a** to 42%, and reduced the amount of acetylated byproduct (Table 1, entry 1).

Table 1. Selected Optimization



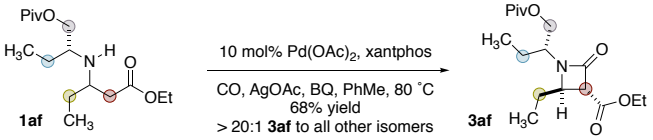
Entry	Catalyst	AgX	BQ	Ligand	Yield % (dr)
1	$Pd(OAc)_2$	OAc	2 eq.	Li-quinoline	42 (12:1)
2	$Pd(OAc)_2$	OAc	2 eq.	PPh_3	28 (12:1)
3	$Pd(OAc)_2$	OAc	2 eq.	Xantphos	82 (12:1)
4	$Pd(OAc)_2$	OPiv	2 eq.	Xantphos	54 (12:1)
5	$Pd(OAc)_2$	OBz	2 eq.	Xantphos	74 (12:1)
6	$Pd(OAc)_2$	OAc	–	Xantphos	0
7	–	OAc	2 eq.	Xantphos	0
8	$Pd(OAc)_2$	–	2 eq.	Xantphos	0
9	$Pd(OAc)_2$	OAc	2 eq.	–	23 (12:1)
10	$Pd(OAc)_2$	OAc	2 eq.	XantphosO	80 (12:1)
11	$Pd(OAc)_2$	OAc	2 eq.	Xantphos(O)$_2$	23 (12:1)

Yields and diastereoselective ratios (dr) are determined by ^{1}H NMR.

Prompted by the observation that a reaction using PPh_3 as ligand (instead of Li-quinoline) also formed **3a** (entry 2), we examined a series of phosphines and found that bidentate xantphos gave an excellent yield of **3a** (entry 3).[16] The reaction of **1a** using different Ag-carboxylates also worked well (entries 3-5). Control experiments highlighted essential roles for BQ, Pd(II)- and Ag(I)-carboxylates (entries 6-8). Optimal conditions involved treatment of amine **1a** with 10mol% $Pd(OAc)_2$, 10mol% xantphos, 3 equiv. of AgOAc, 2 equiv. of BQ under 1 atm. of CO at 80 °C in PhMe and gave **3a** in 82% yield after isolation. Interestingly, we found that reaction of **1a** using CO diluted with air (c.f. Scheme 1b), but otherwise optimal conditions, resulted in the formation of β- and γ-lactams in a 3:1 ratio, further supporting the dependence of the pathway on CO concentration. The successful use of phosphines in oxidative C–H carbonylation is surprising given their propensity oxidize to phosphine oxides; the unique effect of xantphos, compared to other phosphines, is also striking. Accordingly, we found that reaction using xantphos mono-oxide gave almost the same yield as the use of xantphos (entry 10),[17a,b] however the yield drops dramatically when xantphos dioxide was used (entry 11, c.f. entry 9).[16] Although unsure of its precise role, we believe xantphos (or its mono-oxide) most likely stabilizes Pd(0) at the end of the catalytic cycle prior to oxidation to the Pd(II) species required for reaction.[17c]

With the optimal conditions, we examined the scope of the methylene β-C–H carbonylation process. As shown in Table 2, structurally and functionally diverse amines undergo efficient β-C–H carbonylation to trans-disubstituted β-lactams. Branching at the α- and β-carbon atoms on the non-reacting side of the amine is well tolerated to provide the β-lactams in good yields (Table 2a, **3a-f**). Interestingly, we found that the use of hindered carboxylate ligands were required for amines not containing α-branching, in order to prevent the formation of the undesired N-acetylation byproducts. A variety of functional groups, including alkene, esters, arenes, alkenes, and oxetane moieties can be accommodated by the reaction, forming β-lactams in good yields (**3g-p**). Among these, we note that (a) a thioether motif neither deactivates the catalyst nor succumbs to oxidation, and β-lactam **3h** is produced in high yield, (b) the free NH-β-lactam could be revealed through photochemical cleavage of an N-benzyl derivative[18] and (c) the reaction was amenable to being performed on gram scale (**3l**). Linear substituents can be incorporated on the non-reacting side of the amine (**3q-t**), and we observed that the carbonylation is tolerant of Lewis basic heteroarenes (**3s**,**t**) thereby enhancing the utility of this process towards medicinal chemistry applications.[8,19] A range of functional groups can also be included on the reacting side of the amine (Table 2b, **3u-3ae**). Substrates derived from protected amino alcohols work well to provide functionalized β-lactams in good yields and diastereoselectivities (**3w-z**); interestingly, C–H carbonylation is not observed at the β-position bearing the O-substituent, thereby conveying useful selectivity in more heavily functionalized systems. Selective carbonylation at the benzylic position in phenylalanine- and tryptophan-derived substrates gave highly functionalized α-aryl-β-hydroxymethyl-β-lactams (**3y-z**); importantly, no competitive C(sp^2)–H carbonylation was observed in these β-arene-containing amines. Unfortunately, reaction was not observed when the amine was unbranched on the reacting side,[15] however C–H carbonylation onto cycloalkanes worked well to reveal a useful class of fused ring β-lactams (**3aa-ab**). A selection of heteroarenes on the reacting side of the amine are compatible in the C–H carbonylation (**3ac-2ae**).

To test the limits of selectivity in this C–H carbonylation, we prepared **1af**, wherein four different β-C–H bonds are accessible to the Pd-carboxamide activation (Scheme 2). Remarkably, reaction was selective at one C–H bond (next to the ester, possibly reflecting C–H acidity or importance of a Pd-enolate) to form **3af**.



Scheme 2. Regioselective C–H carbonylation

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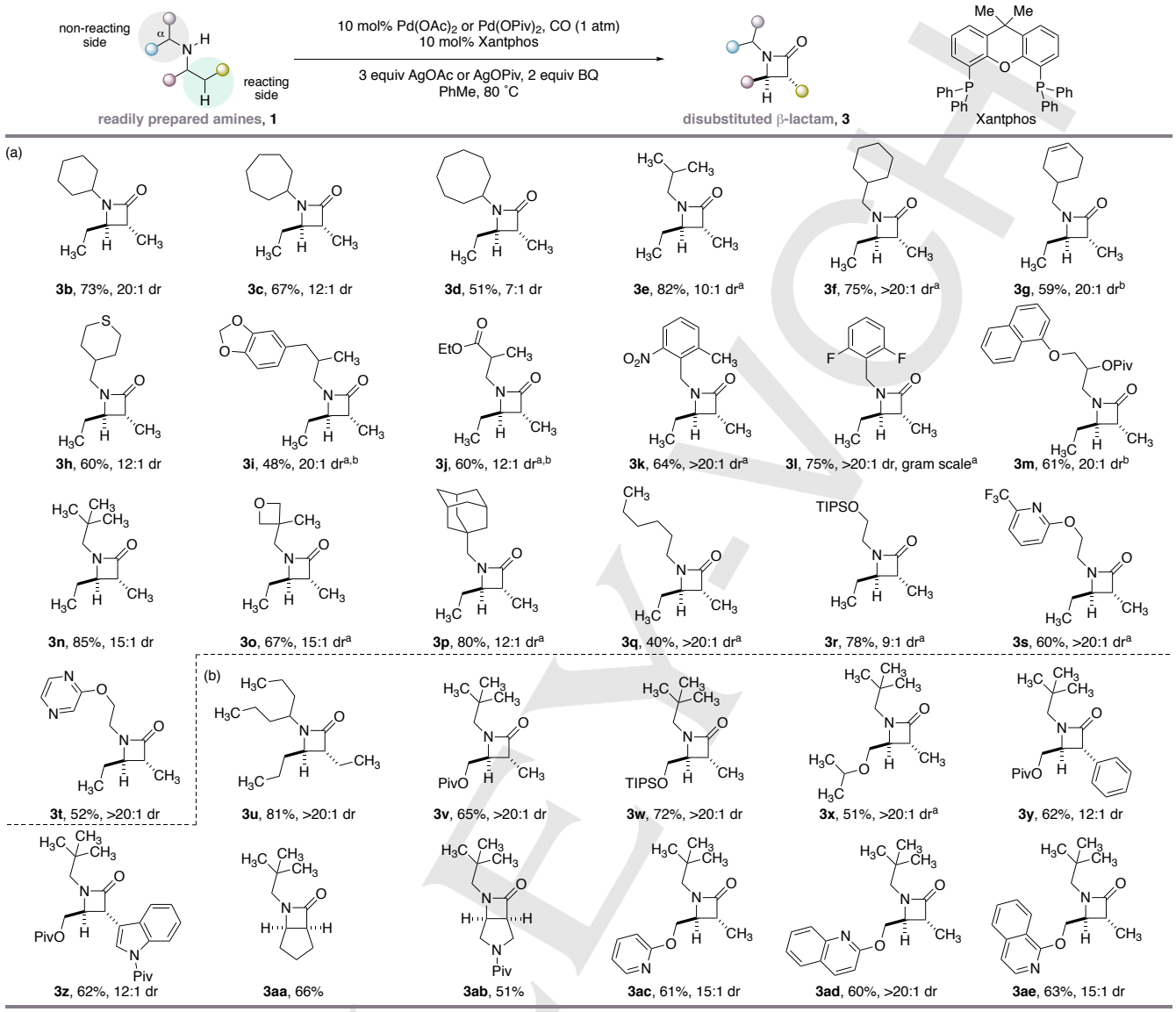
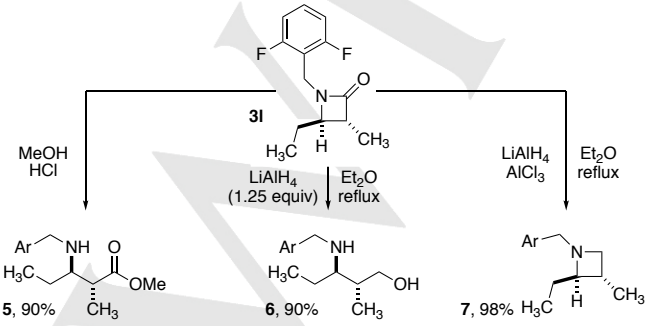
Table 2 Scope of methylene C–H carbonylation



[a] reaction with 10mol% Pd(OPiv)2, 3 equiv AgOPiv. [b]. product exists as a 1:1 mixture of diasteromers, each with diastereoselectivity across the β-lactam as stated

The β-lactams could be readily transformed into useful building blocks. Acidic methanolysis formed the β-amino ester **5**; exhaustive reduction afforded the amino alcohol **6**; and treatment with alane delivered the azetidine **7** (Scheme 3).



Scheme 3. Derivatization of β-lactams

In conclusion, we have developed a C–H carbonylation of the methylene β-C–H bonds in secondary aliphatic amines to form trans-disubstituted β-lactams. We believe the reaction proceeds via a carbamoyl–Pd(II) intermediate, from which C–H activation is selective for the β-C–H bond via a 5-membered ring cyclopalladation. The bis-phosphine, xantphos, was important for achieving the high yields of the β-lactams. Given the broad tolerance of this reaction to useful functional groups, we believe that this C–H carbonylation process will be of significant interest to practitioners of synthesis and medicinal chemistry.[8]

Acknowledgements

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acquired at the EPSRC UK National Mass Spectrometry Facility at Swansea University.

Keywords: C–H activation • methylene • aliphatic amines • carbonylation • palladium catalysis

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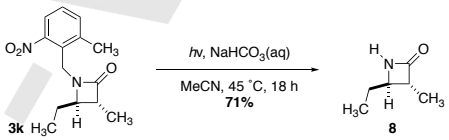

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