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Palladium(II)-Catalyzed C(sp^3)–H Activation of N,O-Ketals towards a Method for the β-Functionalization of Ketones

Danny K. H. Ho
Jonas Calleja
Matthew J. Gaunt*

Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge, CB2 1EW, UK
mjg32@cam.ac.uk

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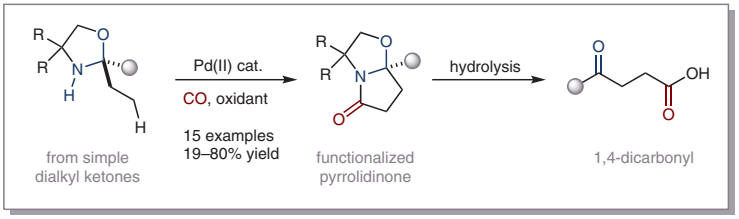

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Abstract A method for the formal β-functionalization of aliphatic ketones via a palladium-catalyzed sp^3 C–H activation pathway is reported. An N,O-ketal directs an aliphatic C–H carbonylation to form γ-lactams which upon hydrolysis generate γ-keto carboxylic acids. This C–C bond-forming reaction is tolerant of a range of functional groups, enabling the synthesis of a range of synthetically important building blocks. Furthermore, the concepts underlying this transformation have also enabled the development of a related C–H alkenylation process to highly functionalised heterocycles.

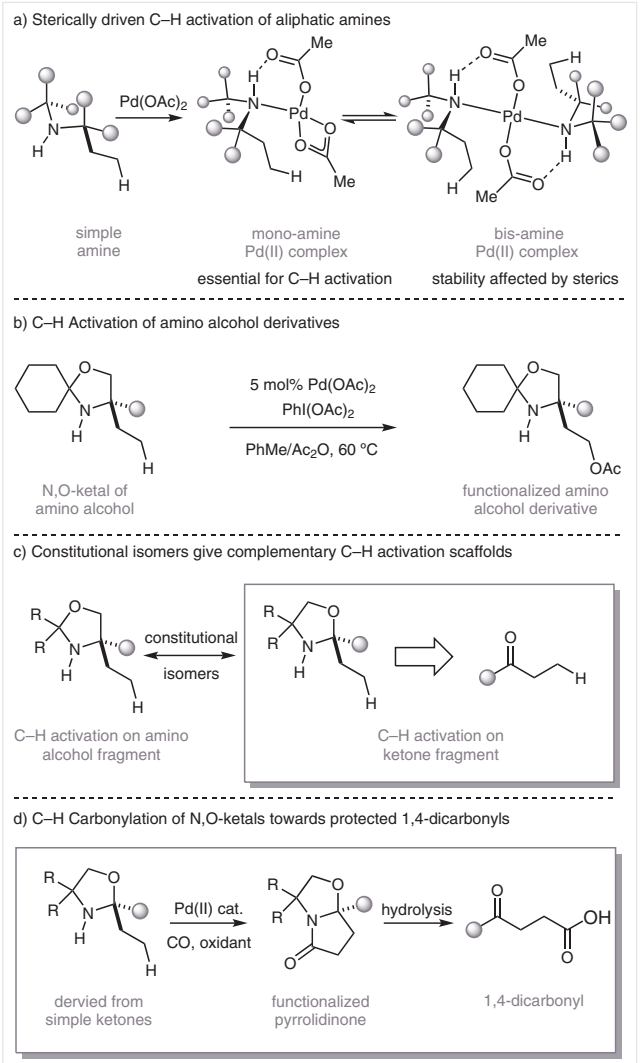
Key words oxazolidine, palladium, carbonylation, lactam, ketone, C–H activation

Methods for directly functionalizing C–H bonds represent ideal reactions for synthetic chemists, with the appeal of such transformations lying in their ability to enable the rapid build-up of molecular complexity from simple and readily accessible building blocks.[1] Despite recent advances in the field of palladium-catalyzed aromatic C–H functionalization, the development of methods for the selective functionalization of unactivated sp^3 C–H bonds remains an ongoing challenge.[2] In this regard, the functionalization of aliphatic C–H bonds in the β-position to a carbonyl group has been the subject of sustained interest.[3] Seminal contributions from the group of Yu have led to the development of a variety of palladium-catalyzed reactions for the functionalization of sp^3 C–H bonds at the β-position of carboxylic acids[4] and their derivatives,[5] however, the development of palladium-catalysed C–H activation processes involving the analogous ketones remains a challenge.[6] In particular, the development of methodology for the β-carbonylation of ketones would provide access to structurally important 1,4-dicarbonyl compounds,[7] a class of molecules used extensively as precursors to pharmaceuticals and other value-added products.[8] The development of a broadly applicable method for accessing β-functionalised ketones would therefore be of interest to the synthetic community.

We recently reported the application of hindered aliphatic amines as directing groups in a palladium-catalyzed C–H activation reaction proceeding through a previously unknown 4-membered ring cyclopalladation pathway (Scheme 1).[9] This strategy used the steric properties of the amine to favour the formation of a catalytically active mono(amine)-Pd(II) complex necessary for C–H activation (Scheme 1, a).

More recently, we utilised the concepts underlying this sterically promoted C–H activation protocol to enable the functionalization of primary amino alcohols, through their transient conversion into hindered N,O-ketals (Scheme 1, b).[10] This catalytic strategy led to the development of a number of useful reactions, providing a means by which simple, readily accessible amines could be converted into structurally complex products.

Inspired by these discoveries, we questioned whether this sterically controlled, amine-directed C–H activation methodology could be extended to encompass other functional groups of synthetic importance. In particular, we questioned whether we could exploit the structural features of the N,O-ketal functionality to develop a strategy for the functionalization of ketones. Analysis of the molecular constitution of the N,O-ketal scaffold revealed that simply switching the position of the oxygen atom in the oxazolidine ring would enable the C–H activation to occur on the ketone component of the heterocycle, which upon hydrolysis would reveal a β-functionalised ketone (Scheme 1, c).

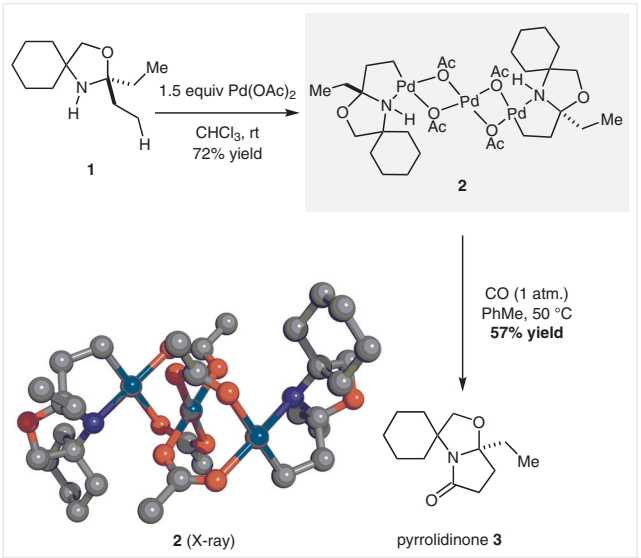


Scheme 1 Sterically promoted C–H activation of amines

Herein, we report a palladium-catalyzed C–H carbonylation of N,O-ketal-protected ketones, enabling the synthesis of substituted pyrrolidinones which are readily transformed into 1,4-dicarbonyl compounds upon hydrolysis (Scheme 1, d). Furthermore, we demonstrate that this formal β-functionalization of ketones is not limited to C–H carbonylation; a related sp^3 C–H alkenylation protocol is also reported.

To commence our investigations, we chose to prepare N,O-ketal **1**, formed via condensation of 3-pentanone with the corresponding amino alcohol (see Supporting Information for details). We reasoned that the cyclohexyl substituent would provide the steric bulk required to favour the formation of a mono-(amine)-Pd(II) complex, a pre-requisite for C–H activation. Furthermore, we speculated that the methylene C–H bonds of the cyclohexyl group would be less likely to undergo activation than the terminal C–H bonds on the ketone component.

Upon treatment of N,O-ketal **1** with $Pd(OAc)_2$ (1.5 equiv.) at room temperature, the trinuclear cyclopalladation complex **2** was isolated in 72% yield. Structural analysis by single-crystal X-ray diffraction confirmed that the C–H activation had occurred on the methyl group of the ketone component. The reactivity of the C–Pd bond was subsequently demonstrated through carbonylation of the cyclopalladated intermediate (CO, PhMe, 50 °C) which furnished the desired lactam **3** in 57% yield (Scheme 2).[11]

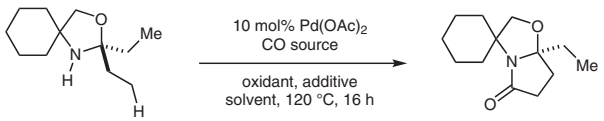


Scheme 2 Cyclopalladation and carbonylation of **1**

Encouraged by these initial results, we sought to develop a catalytic variant of this transformation. Evaluation of the critical reaction parameters revealed that treatment of N,O-ketal **1** with $Pd(OAc)_2$ (10 mol%), AgOAc (2.0 equiv.) as the oxidant in toluene at 120 °C under an atmosphere of CO gave lactam **3** in an optimal 77% yield. Increasing the loading of AgOAc, changing the oxidant, or the addition of a weak base were found to have a deleterious effect on the reaction efficiency (Table 1, entries 6–11). Pleasingly, modifications to the N,O-ketal core were tolerated; upon replacement of the cyclohexyl ring with a *gem*-dimethyl group, the desired carbonylation product was obtained in 76% isolated yield (Table 1, entry 14). Notably, no evidence of carbonylation on the oxazolidine methyl groups via a competitive 4-membered ring cyclopalladation pathway nor via β-C–H methylene carbonylation were observed.[11]

With optimised reaction conditions in hand, we set out to explore the scope of the reaction for the cyclohexyl N,O-ketal analogues (Scheme 3). A range of substituted 2,2-oxazolidines were carbonylated to give the corresponding γ-lactams in good yield. Pleasingly, *gem*-dimethyl N,O-ketals

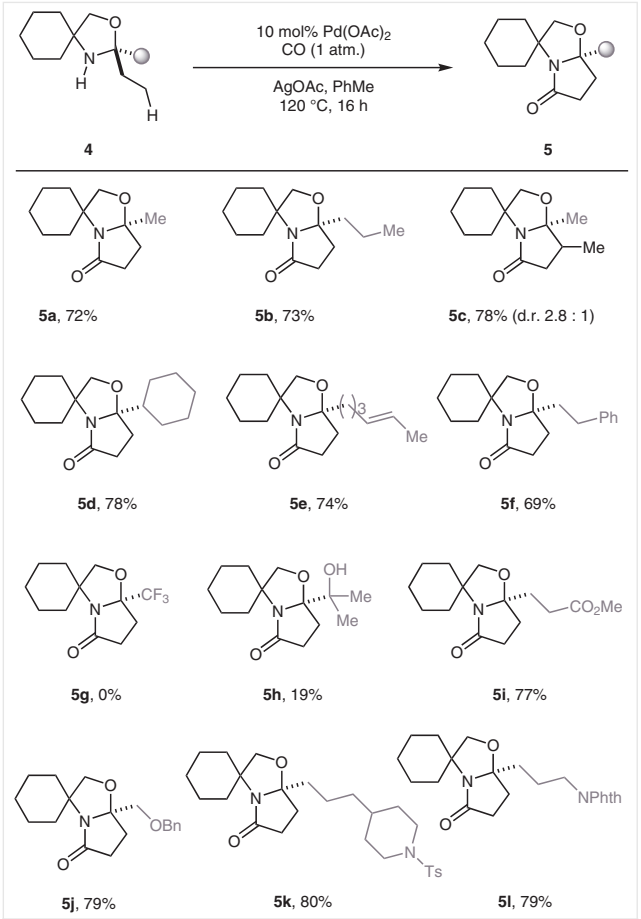
Table 1 Optimization of the Pd(II)-Catalyzed Carbonylation



1 3

Entry	CO source[a]	Oxidant (equiv.)	Additive	Solvent	Yield **3** (%)[b]
1	6.25% CO	AgOAc (2)	–	toluene	22
2	6.25% CO	AgOAc (2)	NaOAc	toluene	59
3	6.25% CO	$Cu(OAc)_2$(2)	–	toluene	39
4	6.25% CO	BQ (2)	–	toluene	13
5	CO balloon	AgOAc (2)	–	toluene	84 (77)[c]
6	CO balloon	AgOAc (2)	NaOAc	toluene	63
7	CO balloon	AgOAc (2) / O_2	–	toluene	48
8	CO balloon	$Cu(OAc)_2$(2)	–	toluene	18
9	CO balloon	AgOAc (2.5)	–	toluene	70
10	CO balloon	AgOAc (3.5)	–	toluene	68
11	CO balloon	AgOAc (2)	–	dioxane	32
12	CO balloon	AgOAc (2)	–	$PhCF_3$	50
13	CO balloon	AgOAc (2)	–	*n*-PrOH	0
14	CO balloon	AgOAc (2)	–	toluene	76[d]

[a] Reaction with 6.25% CO was conducted at 2 bar pressure.
[b] Yield determined by ^{1}H NMR spectroscopy with 1,1,2,2-tetrachloroethane as the internal standard.
[c] Yield of isolated product.
[d] Oxazolidine cyclohexyl substituent replaced with a *gem*-dimethyl group.



Scheme 3 Substrate scope

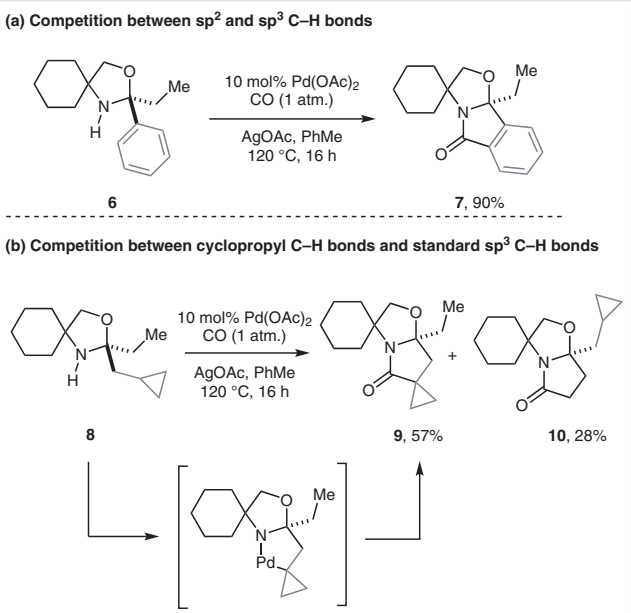
were also found to give similar yields under the standard reaction conditions (see Supporting Information for details). In all cases, exclusive activation of the terminal ethyl sp^3 C–H bonds was observed with no evidence of activation on the amino alcohol component of the N,O-ketal or the β-methylene C–H bonds.

A range of simple aliphatic ketones were tolerated under the standard reaction conditions (Scheme 3, 5a–d). A reaction employing an isopropyl-substituted oxazolidine proceeded in good yield with moderate levels of diastereoselectivity (**5c**, dr = 2.8:1). In addition, olefins and aryl rings could also be incorporated into the ketone component with no deleterious effects on the reaction efficiency (**5e** and **5f**). Disappointingly, a substrate with a strongly electron-withdrawing trifluoromethyl group in close proximity to the nitrogen atom gave only recovered starting material even after prolonged heating at 120 °C (**5g**). Importantly, heteroatom-containing ketones could also be employed in the transformation. A low yield was observed for a substrate containing an unprotected tertiary alcohol (**5h**), which was attributed to an undesired bidentate coordination of the substrate to the palladium forming a coordinatively saturated palladium complex precluding the C–H activation event.

Pleasingly, other oxygen and nitrogen-containing groups were readily tolerated giving the desired γ-lactams in good yield (**5i–l**).

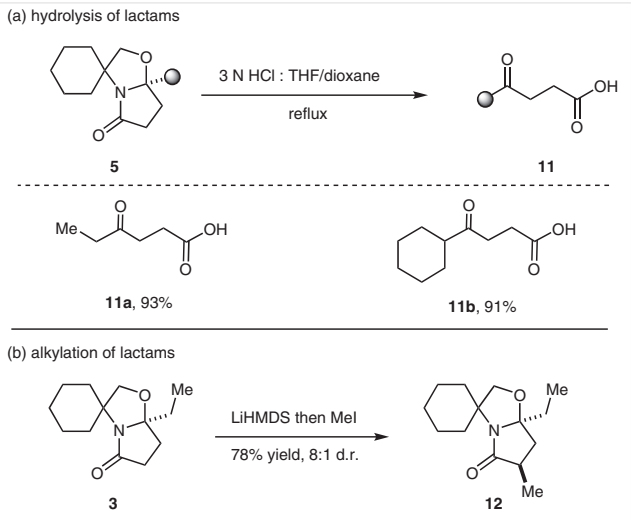
We next sought to apply the methodology to substrates containing multiple sites for C–H activation in order to investigate the regioselectivity of the transformation (Scheme 4). Unsurprisingly, when an aromatic ketone was used to prepare the oxazolidine (i.e., a phenyl group was incorporated at the 2-position), the inherently more facile aryl sp^2 C–H activation pathway predominated to give exclusively the isoindolinone product **7** in excellent yield. In contrast, when the cyclopropyl-substituted oxazolidine **8** was subjected to the reaction conditions, a mixture of two products was obtained: The major product, spirocyclic oxindole **9** (57% yield), formed through activation of the cyclopropyl methine C–H bond, and the expected γ-lactam **10** (28% yield). Whilst methine C–H functionalization is known under palladium catalysis, it remains relatively uncommon compared to methyl and methylene activation.[12] This methodology represents a rare example of a methine C–H bond being activated in preference to a methyl C–H bond. Notably, only products arising from a 5-membered ring pallada-

cycle intermediate were obtained; in no instances were products arising from competitive β- or δ-membered ring cyclopalladation pathways observed.[13]



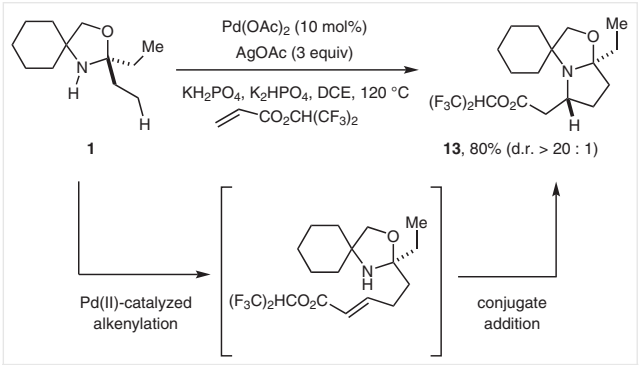
Scheme 4 Pd(II)-catalyzed carbonylation of a) aryl C–H and b) methine C–H

Having demonstrated the scope of the transformation, we next sought to demonstrate the practicality of this methodology for accessing β-functionalised ketones. A selection of the γ-lactams products was subjected to acid-mediated ring opening to obtain the desired γ-keto carboxylic acids in excellent yields (Scheme 5, a). We also found that the bicyclic lactam core underwent diastereoselective alkylation to **12**, further functionalizing this heterocyclic framework (Scheme 5, b).



Scheme 5 Ring opening of γ-lactams to reveal γ-keto carboxylic acids

Finally, in order to highlight the broader scope of this methodology, we set out to explore other transformations involving N,O-ketal-protected ketones. Pleasingly, initial results have shown that N,O-ketal **1** participates in a C–H alkenylation reaction using a modified set of reaction conditions.[14] The product was isolated as the corresponding substituted pyrrolidine **13**, formed via a conjugate addition of the oxazolidine nitrogen into the newly incorporated acrylate (Scheme 6).



Scheme 6 Pd(II)-catalyzed alkenylation

In summary, we have developed a palladium(II)-catalysed sp^3 C–H carbonylation of N,O-ketal-masked ketones. This transformation, which represents a formal β-functionalization of ketones, demonstrates a broad substrate scope and good functional group tolerance. The products obtained undergo facile hydrolysis to reveal the γ-keto carboxylic acids in excellent yields. Finally, the transformation is not limited to carbonylation as demonstrated through a palladium-catalysed C–H alkenylation process.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1611664.

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(13) **General Experimental Procedure for a Representative C–H Carbonylation to 5l**

To a flame-dried round-bottom flask, equipped with a stir bar, was charged the oxazolidine (0.20 mmol), palladium(II) acetate (0.02 mmol, 0.1 equiv), silver(I) acetate (0.40 mmol, 2.0 equiv), and toluene (0.05 M). The reaction flask was evacuated and back-filled with carbon monoxide (3 times, balloon). A balloon filled with carbon monoxide was fitted, and then the flask was placed in a pre-heated oil bath at 120 °C and heated at this temperature for 16 h under vigorous stirring. The reaction mixture was then cooled to room temperature and filtered through a small pad of Celite®. The filtrate was concentrated in vacuo and purified by flash chromatography (eluting with 0–20% ethyl acetate in petroleum ether) provided the desired lactam **5l** (54 mg, 79%). R_f (ethyl acetate in petroleum ether, 25%): 0.23. IR (film): ν_{max} = 2976, 2952, 1773, 1704, 1466, 1396, 1366, 1273, 1124, 1058, 1002, 882, 721, 667 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.85 (dd, *J* = 5.5, 3.0 Hz, 2 H), 7.73 (dd, *J* = 5.5, 3.0 Hz, 2 H), 4.00 (d, *J* = 9.2 Hz, 1 H), 3.94 (d, *J* = 8.9 Hz, 1 H), 3.81–3.64 (m, 2 H), 2.63 (ddd, *J* = 17.0, 12.3, 8.0 Hz, 1 H), 2.56–2.40 (m, 1 H), 2.20 (ddd, *J* = 12.3, 8.0, 0.8 Hz, 1 H), 2.02–1.66 (m, 5 H), 1.55 (s, 3 H), 1.40 (s, 3 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 173.5, 168.3, 134.1, 132.0, 123.3, 102.6, 81.6, 58.1, 37.9, 35.4, 33.0, 32.5, 26.7, 24.5, 23.5. HRMS (ESI): *m/z* calcd for $C_{19}H_{23}N_2O_4$: 343.1652; found $[M + H]^+$: 343.1656.

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