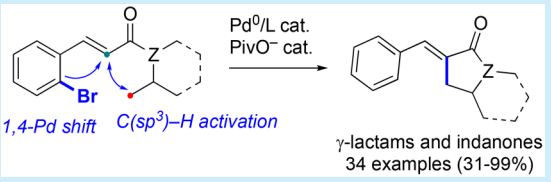
1,4-Palladium Shift/C(sp^3)–H Activation Strategy for the Remote Construction of Five-Membered Rings

Ronan Rocaboy and Olivier Baudoin*

University of Basel, Department of Chemistry, St. Johanns-Ring 19, CH-4056 Basel, Switzerland

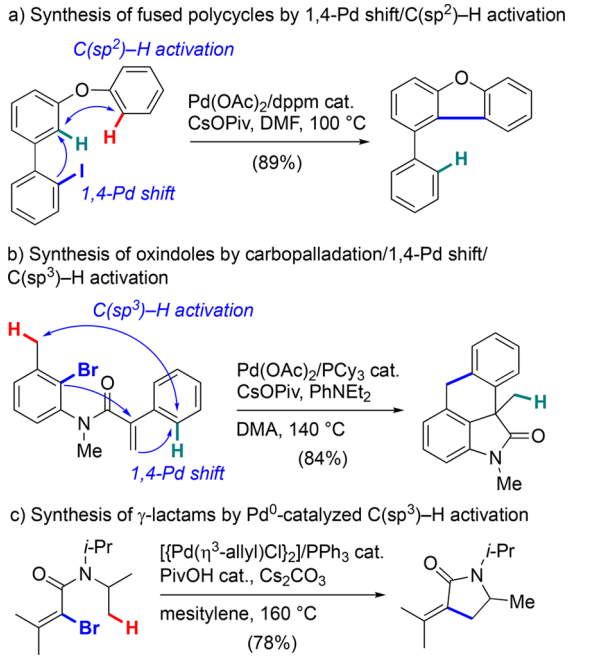
ABSTRACT: 1,*n*-Metal shift is an elegant alternative approach enabling the functionalization of remote C–H bonds from simple precursors. In this work, we report a novel and simple Pd^0-catalyzed domino reaction involving 1,4-palladium shift and C(sp^3)–H activation and leading to (fused) five-membered rings. This method allowed access to a broad range of valuable arylidene γ-lactams and indanones and was applied to the formal synthesis of (−)-pyrrolam.



The last two decades witnessed impressive developments in the formation of carbon–carbon and carbon–heteroatom bonds by transition-metal-catalyzed C–H activation, generally affording improved atom- and step-economy compared to traditional cross-coupling methods.[1] In addition to direct C–H functionalization methods, strategies based on 1,*n*-metal shift allow the functionalization of distal C–H bonds which may be otherwise difficult to access.[2] Since the initial observation of 1,4-palladium shift by Heck in 1972,[3] a number of 1,*n*-Pd migrations occurring between a wide range of C(sp^2)- or C(sp^3)-hybridized carbon atoms have been reported.[2] In 2003, Larock and co-workers showed the first example of Pd^0-catalyzed domino reaction[4] involving oxidative addition, 1,4-Pd shift, and C(sp^2)–H arylation, resulting in the construction of complex polycyclic molecules (Scheme 1a).[5] Later, they reported a domino reaction involving 1,4-Pd shift, carbopalladation, and C(sp^3)–H activation to form a fused cyclopropane.[6] A few years later, Zhu and co-workers described a general method to access fused oxindoles by combining carbopalladation, 1,4-Pd shift, and activation of benzylic C(sp^3)–H bonds (Scheme 1b).[7] However, to the best of our knowledge, there is no example of a method simply combining oxidative addition, 1,4-Pd shift, and C(sp^3)–H activation without an intermediate carbopalladation step. In the past years, our group has developed a set of Pd^0-catalyzed methods for the direct functionalization of C(sp^3)–H bonds from precursors containing a C(sp^2)–X bond (X = leaving group).[8] In particular, we reported the synthesis of (fused) γ-lactams from alkenyl bromides (Scheme 1c).[9] To extend the scope of this reaction, we hypothesized that the organopalladium intermediate arising from C–Br oxidative addition might be also generated by 1,4-Pd shift from a more remote C–X bond. Such an indirect strategy would allow the use of less congested, easily accessible substrates.

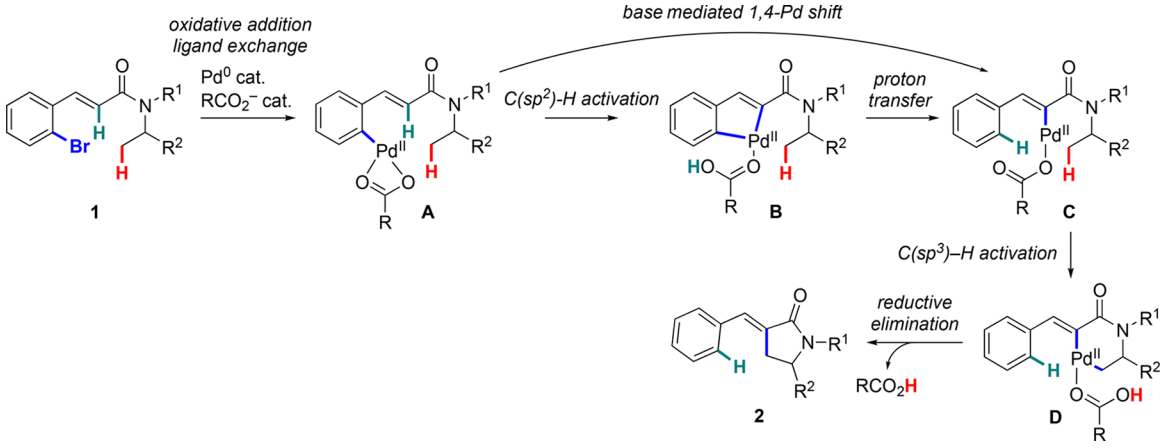
A mechanistic blueprint for this domino process is depicted in Scheme 2. Oxidative addition from aryl bromide **1** followed by bromide–carboxylate exchange leads to organopalladium intermediate **A**. Subsequent C(sp^2)–H activation through the carboxylate-mediated concerted metalation–deprotonation

Scheme 1. 1,4-Pd Shift/C–H Activation and Synthesis of γ-Lactams



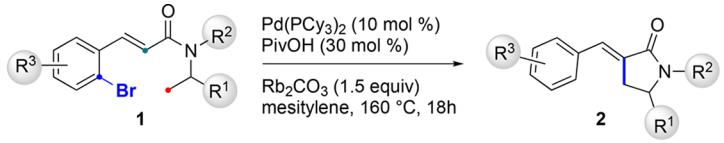
mechanism[10] affords the 5-membered palladacycle **B**. The latter is too strained to undergo reductive elimination and should readily open by proton transfer from the coordinated carboxylic acid, according to previous experimental observations[11] and mechanistic studies,[12] to give intermediate **C**. These two steps from **A** to **C** result in the net aryl to vinyl 1,4-Pd shift.[13,14] Organopalladium **C** is the same intermediate formed during the previous direct C(sp^3)–H activation reaction (see Scheme 1c).[9] Hence, base-mediated C(sp^3)–H activation from

Scheme 2. Mechanistic Hypothesis[a]

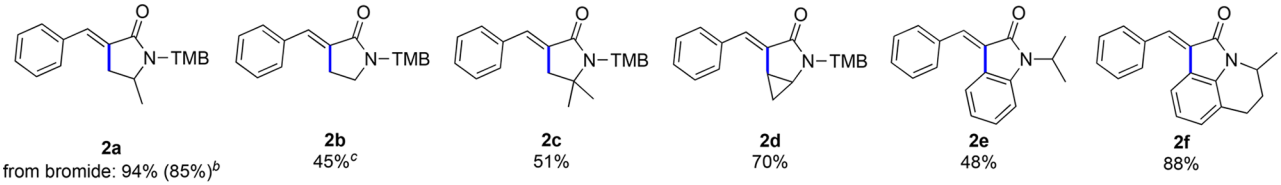


[a]The ligand has been omitted for clarity.

Scheme 3. Scope of the Synthesis of α-Arylidene γ-Lactams[a]

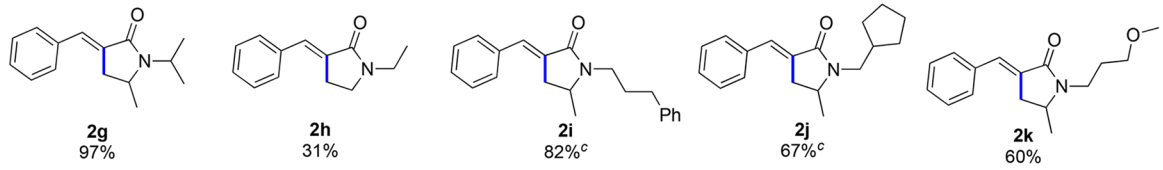


a) Variation of R^1

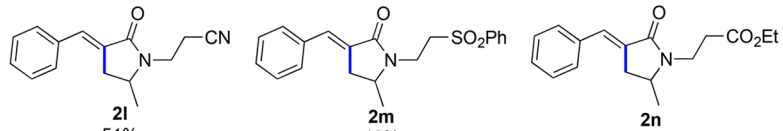


2a from bromide: 94% (85%)[b] from chloride: 55%; **2b** 45%[c]; **2c** 51%; **2d** 70%; **2e** 48%; **2f** 88%

b) Variation of R^2

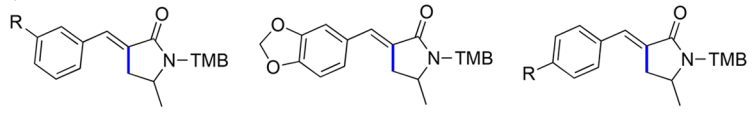


2g 97%; **2h** 31%; **2i** 82%[c]; **2j** 67%[c]; **2k** 60%



2l 51%; **2m** 40%; **2n** 62%

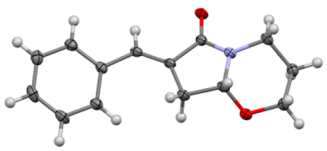
c) Variation of R^3



2o: R = F, 51%
2p: R = CF_3, 77%
2q: R = OMe, quant.
2r: R = OBn, 73%

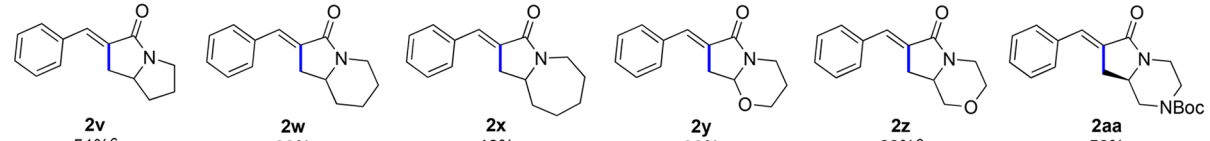
2s 71%

2t: R = F, 64%
2u: R = Me, 76%[c]



Xray structure of **2y**[d]

d) Bicyclic products



2v 51%[c]; **2w** 98%; **2x** 40%; **2y** 90%; **2z** 69%[c]; **2aa** 52%

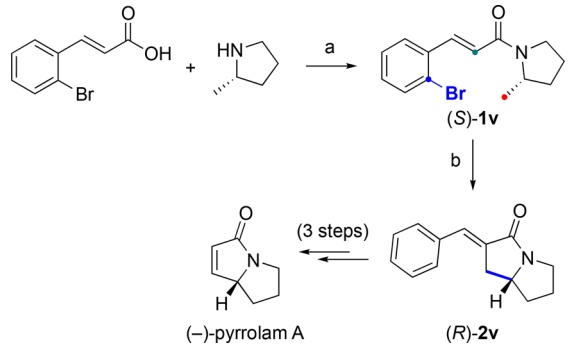
[a]All reactions were performed on a 0.1 mmol scale unless otherwise noted. [b]Performed on a 1 mmol scale. [c]Using additional PCy_3 (10 mol %). [d]Thermal ellipsoids shown at 50% probability. TMB = 2,4,6-trimethoxybenzyl.

C and reductive elimination from the resulting 6-membered palladacycle **D** would lead to γ-lactam **2**. At this point, we were aware of potential pitfalls resulting from the lack of precedence for (1) 1,4-Pd shift onto the α-position of an α,β-unsaturated system and (2) the combination of 1,4-Pd shift with the activation of nonactivated C(sp^3)−H bonds. Herein, we report the development of such a domino reaction to access a wide range of arylidene γ-lactams and indanones.

We started our investigations with the synthesis of γ-lactams **2** (Scheme 3). The optimization of reaction conditions was performed on the TMB-protected[15] isopropylamide **1a** derived from 2-bromocinnamic acid (Table S1). The desired product **2a** was obtained in 94% yield on a 0.1 mmol scale using the well-defined complex $Pd(PCy_3)_2$ as the catalyst,[16] co-catalytic pivalic acid, and Rb_2CO_3 as the stoichiometric base in mesitylene at 160 °C. This high temperature was required, similar to our previous study on the direct reaction,[9] to favor the formation of the strained α-arylidene γ-lactam and avoid the protodebromination side reaction. The reaction also proceeded satisfyingly on a 10-fold (1 mmol) scale, giving rise to **2a** in 85% yield. With the optimized conditions in hand, we studied the scope of the reaction. Addition of free PCy_3 (10 mol %) was found to be beneficial in some cases, presumably to avoid catalyst decomposition. Using the aryl chloride instead of the bromide also furnished **2a**, albeit in lower yield (55%). The influence of the alkyl group undergoing C−H activation was first studied on amides containing the TMB group (Scheme 3a). Average to good yields were achieved for ethyl (**2b**), *tert*-butyl (**2c**), as well as cyclopropyl (**2d**) groups. The former is a challenging case due to the lesser number of methyl groups and the lack of a Thorpe−Ingold effect favoring the C(sp^3)−H activation step. Expectedly, the competition between C(sp^2)−H and C(sp^3)−H activation was clearly in favor of the former, giving rise to the interesting (fused) oxindoles **2e**,**f**. Substrates bearing two potentially reactive substituents on the amide nitrogen were next examined (Scheme 3b). Average to very good yields were observed, together with a high site-selectivity for the primary positions of the isopropyl group vs equidistant secondary positions (**2i**, **2k**−**n**), including much more acidic ones adjacent to nitrile, sulfone, and ester groups (**2l**−**n**). It should be noted that the β-lactam arising from C−H activation at the α-position to the nitrogen atom[9,17] was never observed (e.g., **2b**, **2d**, **2h**). Next, the effect of substituents on the aromatic ring was studied (Scheme 3c). Electron-withdrawing or -donating groups at the *meta*- or *para*-position to the bromine atom were well tolerated, furnishing the corresponding products with good to excellent yields (**2o**−**u**). Interestingly, such α-arylidene γ-lactams have been shown to exhibit antifungal activities toward *Colletotrichum orbiculare*.[18] Finally, we turned our attention to the synthesis of bicyclic γ-lactams (Scheme 3d). The fused pyrrolidine **2v** and azepane **2x**, relevant to the synthesis of pyrrolizidine[19a] and *Stemona* alkaloids,[19b] respectively, were obtained from easily available precursors in 40−51% yield. In contrast, the fused piperidine **2w** was obtained in much higher yield (98%). This result was successfully extended to bicyclic 5,6-fused γ-lactams containing heteroatoms, such as oxazinanes **2y**−**z** and the enantiopure *N*-Boc-protected piperazine **2aa**. Of note, olefin isomerization of the reaction products was never observed.

Its application to the short formal synthesis of (−)-pyrrolam A, a pyrrolizidine alkaloid isolated from *Streptomyces olivaceus* strains,[20] illustrates the simplicity of the current method

Scheme 4. Formal Synthesis of (−)-Pyrrolam A[a]

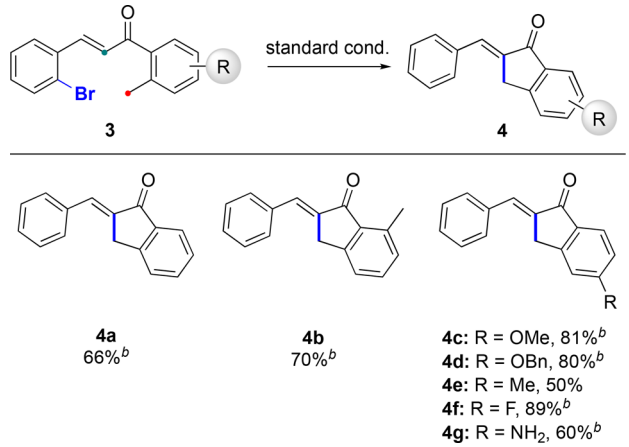


[a]Reaction conditions: (a) $(COCl)_2$ (1.5 equiv), Et_3N (2 equiv), CH_2Cl_2, 20 °C, quant; (b) $Pd(PCy_3)_2$ (10 mol %), PCy_3 (10 mol %), PivOH (30 mol %), Rb_2CO_3 (1.5 equiv), mesitylene (c = 0.025M), 160 °C, 18 h, 50%.

(Scheme 4). Standard amide formation from (*S*)-2-methylpyrrolidine and 2-bromocinnamic acid, both commercially available, gave the precursor for the key 1,4-Pd shift/C(sp^3)−H activation reaction (**1v**). The latter was reacted under standard conditions to afford the enantiopure γ-lactam **2v** in 50% yield. Compound **2v** was previously converted to (−)-pyrrolam A in three steps;[21] hence, the current approach allows for the synthesis of pyrrolam A in only five steps.

Next, we turned our attention toward the extension of the current method to other α,β-unsaturated carbonyl substrates for which the direct C(sp^3)−H activation reaction is not known. In particular, we examined the reactivity of readily available chalcones **3** containing benzylic C(sp^3)−H bonds (Scheme 5).[22] The reaction proceeded remarkably well under

Scheme 5. Synthesis of Arylidene Indanones[a]



[a]Reaction conditions: see Scheme 3. [b]Using additional PCy_3 (10 mol %).

the standard conditions, thereby furnishing a range of arylidene indanones **4**. The reaction was compatible with electron-rich and electron-deficient substituents (**4b**−**f**), and even with a free aniline (**4g**), giving rise to the corresponding products in average to excellent yields (50−89%).[23] Of note, such compounds possess a variety of interesting biological properties.[24]

To gain mechanistic insights, we performed experiments with fully and partially deuterated substrate **1a**, bearing deuterium atoms on the key C(sp^2) and C(sp^3) positions undergoing C−H activation (Scheme S1). We observed an

unexpectedly strong intermolecular D−H exchange,[12b] preventing us from analyzing the 1,4-Pd shift, but indicating that the C(sp^3)−H activation step (Scheme 2, **C** → **D**) is reversible and faster than the final reductive elimination leading to the strained α-arylidene γ-lactam ring.[9,16c]

In conclusion, we reported a simple, step-economical method to construct (fused) five-membered rings through a novel Pd^0-catalyzed domino reaction involving 1,4-palladium shift and C(sp^3)−H activation. The generality of this method was demonstrated on a broad range of arylidene γ-lactams and indanones, and its applicability was illustrated through the formal synthesis of (−)-pyrrolam. This work opens the way to the development of C(sp^3)−H functionalization reactions that are difficult to achieve through direct methods.

■ ASSOCIATED CONTENT

Accession Codes

CCDC 1884100 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: olivier.baudoin@unibas.ch.

ORCID

Olivier Baudoin: 0000-0002-0847-8493

Notes

The authors declare no competing financial interest.

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