C–H Activation

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Synthesis of Strained γ-Lactams by Palladium(0)-Catalyzed C(sp^3)–H Alkenylation and Application to Alkaloid Synthesis

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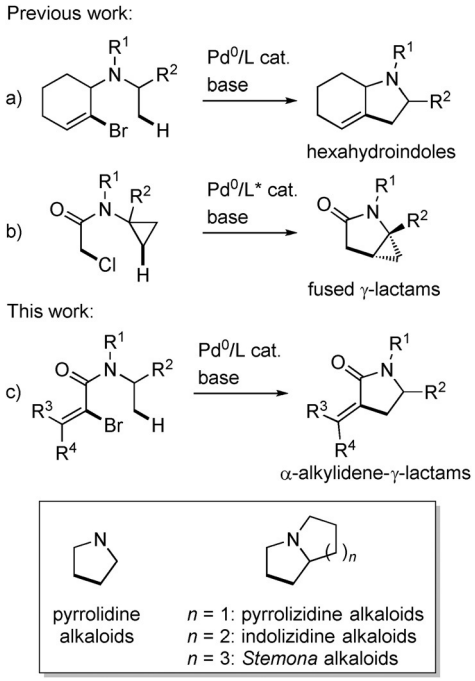
Abstract: *A variety of strained α-alkylidene-γ-lactams were synthesized by palladium(0)-catalyzed intramolecular C(sp^3)–H alkenylation from easily accessible acyclic and monocyclic bromoalkene precursors. These lactams are valuable intermediates for accessing various classes of mono- and bicylic alkaloids containing a pyrrolidine ring, as illustrated with the synthesis of an advanced model of the marine natural product plakoridine A and of the indolizidine alkaloid δ-coniceine.*

The intramolecular palladium(0)-catalyzed activation of non-acidic C(sp^3)–H bonds is a powerful tool for accessing a vast array of bicyclic and polycyclic systems.[1–3] Recent efforts in this field have focused on the use of non-aromatic halogenated substrates, and allows synthesis of C(sp^3)-rich nitrogen heterocycles, which are of high interest for the synthesis of active ingredients and natural products. In particular, our group reported the construction of hexahydroindoles by intramolecular C(sp^3)–H alkenylation (Scheme 1a),[4a] and its application to the total synthesis of aeruginosins.[4b,c] While the current work was in progress, Cramer and co-workers disclosed the asymmetric synthesis of β-lactams[5a] and cyclopropane-fused γ-lactams (Scheme 1b)[5b] from α-chloroamides by intramolecular alkylation of benzylic and cyclopropyl C(sp^3)–H bonds, respectively, in the presence of a chiral ligand. Herein, we report a unique example of an intramolecular alkenylation of unactivated primary C(sp^3)–H bonds using acyclic bromoalkenes, thus giving rise to mono- and bicyclic α-alkylidene-γ-lactams (Scheme 1c). This new method is relevant to the synthesis of five-membered nitrogen heterocycles, which are present as substructures in numerous bioactive natural products such as pyrrolidine,[6a] pyrrolizidine,[6b] indolizidine,[6c] and *Stemona*[6d] alkaloids.



Scheme 1. Palladium(0)-catalyzed intramolecular C(sp^3)–H alkenylation and alkylation to synthesize bicyclic and monocyclic N-heterocycles.

We set out to optimize the cyclization of the SEM-protected bromoamide **1a**, which was readily synthesized in three steps from 3,3-dimethylacrylic acid (Table 1). The main problem was the formation of significant quantities of the protodebrominated compound **3a**, which is diagnostic of the high ring strain created in such reactions.[2c,e,4a] The first interesting results were obtained with PPh_2Et as the ligand, by using reaction conditions similar to those initially developed by Fagnou and co-workers (entry 1).[3f] Among the various palladium sources tested, the allylpalladium(II) chloride dimer turned out to be the best choice (entries 2 and 3). Then, a number of trialkylphosphines and diphenylmonoalkylphosphines were screened (entries 4–9), and triphenylphosphine emerged as the optimal ligand (entry 7). In addition, cesium carbonate (1.5 equiv, optimized quantity) was found to be the optimal stoichiometric base in combination with pivalic acid (entries 10 and 11). Furthermore, a high reaction temperature of 160 °C was found to be necessary, since lower temperatures gave higher amounts of **3a** (entry 12). This result further illustrates the high activation energy required to form the strained α-alkylidene-γ-lactam **2a**. Finally, the catalyst loading could be reduced to 5 mol% palladium and 10 mol% ligand (entry 13), but the yield of **2a**

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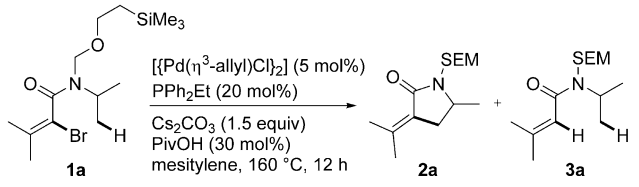
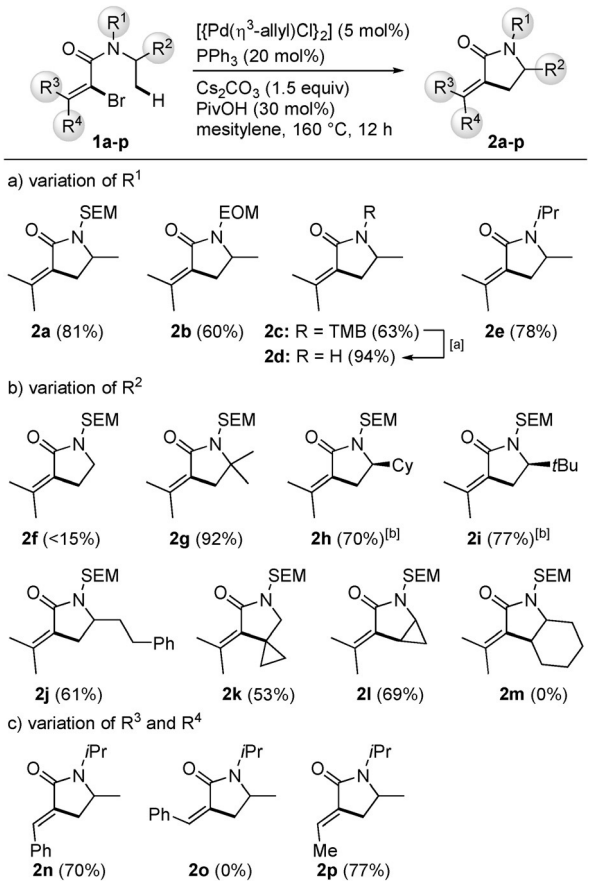
Table 1: Optimization of reaction conditions.



Entry	Deviation from standard conditions	**2a**/**3a**[a]	Yield **2a** [%][a,b]
1	–	91:9	83
2	$Pd(OAc)_2$ (10 mol%) instead of $[\{Pd(\eta^3\text{-allyl})Cl\}_2]$	76:24	65
3	Pd_2dba_3 (5 mol%) instead of $[\{Pd(\eta^3\text{-allyl})Cl\}_2]$	91:9	81
4	PCy_3 instead of PPh_2Et	47:53	22
5	PEt_3 instead of PPh_2Et	41:59	35
6	PPh_2Me instead of PPh_2Et	84:16	78
7	PPh_3 instead of PPh_2Et	91:9	83 (81)
8	$P(p\text{-}NMe_2C_6H_4)_3$ instead of PPh_2Et	86:14	49
9	$P(p\text{-}CF_3C_6H_4)_3$ instead of PPh_2Et	–	0
10	K_2CO_3 instead of Cs_2CO_3	83:17	64
11	Rb_2CO_3 instead of Cs_2CO_3	86:14	76
12	140 °C instead of 160 °C	46:54	20
13	2.5 mol% $[\{Pd(\eta^3\text{-allyl})Cl\}_2]$/10 mol% PPh_3	92:8	91 (83)
14	1.25 mol% $[\{Pd(\eta^3\text{-allyl})Cl\}_2]$/5 mol% PPh_3	84:16	79

[a] Determined by GCMS analysis of the crude reaction mixture. [b] Determined by GCMS analysis using tetradecane as an internal standard. Yield of isolated product **2a** is given within parentheses. SEM = [2-(trimethylsilyl)ethoxy]methyl, Piv = pivaloyl.



Scheme 2. Scope, limitations, and selectivity pattern of the intramolecular C(sp^3)–H alkenylation reaction. [a] Reaction conditions: CF_3CO_2H, anisole, 20 °C. [b] Obtained from enantiomerically pure substrates. EOM = ethoxymethyl, TMB = 2,4,6-trimethoxybenzyl.

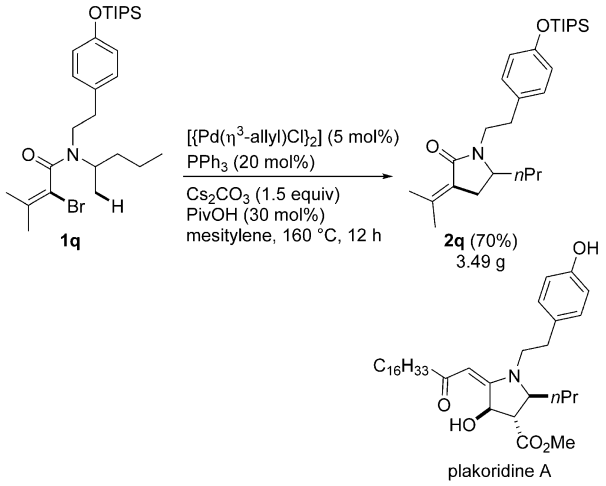
decreased with lower catalyst loadings (entry 14). Under the optimized reaction conditions, **2a** was obtained in 83% yield upon isolation, and the amount of **3a** was less than 10% of the mass balance (entry 13).

The scope and limitations of this intramolecular C(sp^3)–H alkenylation reaction are shown in Scheme 2. First, the nitrogen substituent was varied (Scheme 2a), and the reaction was found to tolerate an aminal (**2a**,**b**) and trimethoxybenzyl (**2c**) group,[5b] in addition to an alkyl (**2e**) group. Other amide-protecting groups could either not be introduced or were found to be unstable (for example, the Boc group; Boc = *tert*-butyloxycarbonyl) to the current reaction conditions. Importantly, the TMB group in **2c** could be cleaved under acidic conditions to provide the NH-lactam **2d**.[7]

The nature of the alkyl group (R^2) undergoing C–H activation was varied (Scheme 2b) with R^1 = SEM.[8] First, the compound **1f**, containing a N-ethyl group (R^2 = H) provided only small amounts of the γ-lactam **2f** along with the corresponding protodebrominated product **3f** (**2f**/**3f** 14:86), thereby demonstrating poor reactivity of linear alkyl groups. In contrast, the reaction of the compound **1g**, bearing a *tert*-butyl substituent, was highly favored and gave rise to the γ-lactam **2g** in 92% yield. The reactivity trend **1f** < **1a** < **1g** is consistent with previous observations, and can be attributed to Thorpe–Ingold effects, which have an important impact in this class of reactions.[2f] Other substrates successfully underwent selective activation/cyclization at primary (**1h–j**) and cyclopropyl (**1k**) C–H bonds to give the corresponding monocyclic (**2h–j**) and spirocyclic (**2k**) γ-lactams in the presence of less reactive methylene and methine C–H bonds. Indeed, the activation/cyclization of secondary C–H bonds was unsuccessful, even in the absence of primary C–H bonds (**2m**), except for more activated cyclopropyl C–H bonds (**2l**).[9] The reaction of bromoalkenes bearing a trisubstituted double bond was also analyzed (Scheme 2c). Gratifyingly, phenyl- (**1n**) and methyl-substituted (**1p**) *Z*-configured bromoalkenes furnished the corresponding γ-lactams with similar efficiency. In contrast, the *E* isomer of **1n** (**1o**) was found to undergo rapid base-promoted elimination to give the corresponding alkyne even in the absence of palladium catalyst, thereby precluding the C–H alkenylation process.

The remarkable site-selectivity observed in the above examples was further demonstrated with the reaction of the compound **1q** (Scheme 3), which provided the γ-lactam **2q** in 70% yield on a multigram scale. Among all potentially reactive C–H bonds in **1q**, the primary C–H bonds highlighted in Scheme 3 underwent cyclization selectively. The lactam **2q** can be viewed as an advanced intermediate for the synthesis of the marine natural product plakoridine A,[10] which is currently under study.

We next examined the selectivity of the activation of non-equivalent primary C–H bonds on the reactants **1r–u**, which may either give rise to the γ-lactams **2r–u**, or possibly to the

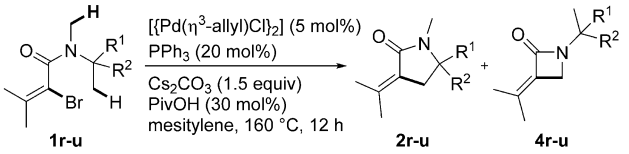


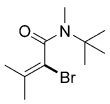
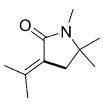
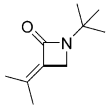
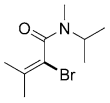
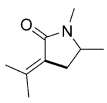
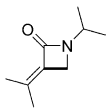
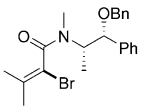
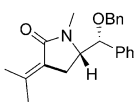
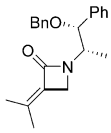
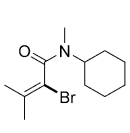
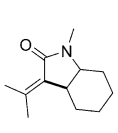
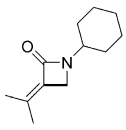
Scheme 3. Gram-scale access to an advanced intermediate for the synthesis of the marine product plakoridine A. TIPS = triisopropylsilyl.

more strained β-lactams **4r–u** (Table 2). The compound **1r**, bearing N-methyl and N-*tert*-butyl substituents, underwent selective reaction at the *tert*-butyl group to give **2r** in high yield (entry 1). Replacing the *tert*-butyl group with an isopropyl group (**1s**) generated a separable mixture of both lactam products (entry 2). In contrast, the substrate **1t**, derived from (−)-ephedrine and containing one methyl group less than **1s**, underwent selective reaction to form the β-lactam **4t** in moderate yield, and was accompanied by significant amounts of the protodebrominated product **3t** (entry 3).

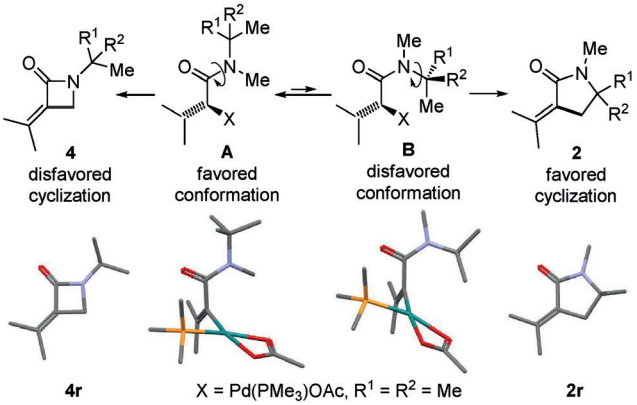
These results can be rationalized by considering the opposing conformational and strain effects in the current system (Scheme 4). The most stable conformation of the palladium intermediate undergoing C–H activation[2c,3f,h] is **A**, where the smallest N-methyl substituent turns toward the palladium center [see the computed model structure with X = $Pd(PMe_3)OAc$]. However, C–H activation at this methyl group and/or C–C reductive elimination to form the β-lactam **4** should be disfavored because of the generation of ring strain. In contrast, the formation of the less strained γ-lactam **2** should be easier, but has to occur from the higher-energy conformer **B**. Increasing the number of methyl groups at R^1, R^2 should increase the population of this reactive conformer **B** and should thus favor the γ-lactam product (Table 2, entries 3–1). Finally, the reactant **1u**, bearing N-methyl and N-cyclohexyl groups provided a separable mixture of **4u** and **3u**, together with traces of **2u**, as expected from the lack of reactivity of secondary C–H bonds under the current reaction conditions (Table 2, entry 4; also see **2m** in Scheme 2). These results show that the formation of highly strained α-alkylidene-β-lactams is also feasible upon careful choice of amide substituents, but with reduced efficiency compared to γ-lactams.[11]

Table 2: Selectivity of the activation of primary C–H bonds.



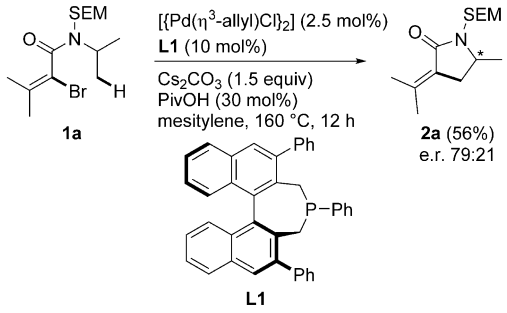
Entry	Reactant	Product(s)[a]		2/4[b]
1				
	1r	**2r** (92%)	**4r** (0%)	>98:2
2				
	1s	**2s** (38%)	**4s** (11%)	71:29[c]
3				
	1t	**2t** (<5%)	**4t** (47%)	7:93[c]
4				
	1u	**2u** (<5%)	**4u** (40%)	<2:98[c]

[a] Yield of isolated product is given within parentheses. [b] Determined by GCMS analysis of the crude reaction mixture. [c] The corresponding protodebrominated products **3s–u** were also formed in the following ratios (GC): **2s/4s/3s** 53:22:25; **2t/4t/3t** 5:63:32; **4u/3u** 48:52.



Scheme 4. Contradictory effects on reaction selectivity. Bottom: DFT-optimized structures (M06/6-31G**), H atoms omitted for clarity. With these substituents, **A** was computed to be more stable than **B** by 4.8 kcal mol^{-1} and **2r** more stable than **4r** by 19.5 kcal mol^{-1}.

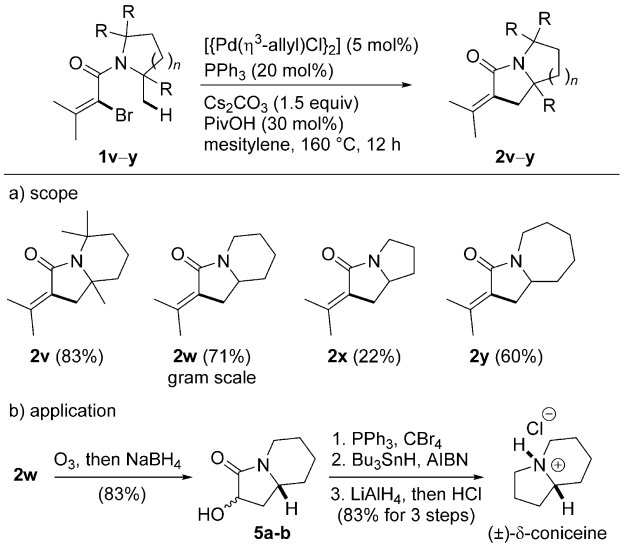
The asymmetric C–H alkenylation of **1a** in the presence of a chiral ligand instead of PPh_3 was also studied. In particular, we tested P-arylbinepines, chiral surrogates of PPh_3,[12b] as they were reported to provide high enantioselectivities in intramolecular C(sp^3)–H arylations leading to (fused) indanes.[12,13] We found that the ligand **L1**, which was initially introduced by Fu and co-workers,[14] led to γ-



Scheme 5. Proof-of-concept enantioselective C(sp^3)–H alkenylation.

lactam **2a** with moderate enantioselectivity (Scheme 5). Although there is admittedly room for improvement, this result constitutes a proof of concept for enantioselective γ-lactam synthesis through this C(sp^3)–H alkenylation method.

Next, the reactivity of monocyclic precursors, relevant to the synthesis of bicyclic alkaloids, was examined (Scheme 6a).



Scheme 6. Construction of bicyclic γ-lactams and application to the synthesis of δ-coniceine. AIBN = 2,2′-azobis(2-methylpropionitrile).

As expected, the reaction of methyl-rich bromoalkene **1v**, derived from 2,2,6,6-tetramethylpiperidine, gave **2v** in high yield. More strikingly, a piperidine precursor (**1w**) containing a single exocyclic methyl group underwent selective C–H alkenylation, to give the fused γ-lactam **2w** in 71% yield on a gram scale. No trace of product arising from activation at the methylene C–H bonds α to the nitrogen atom was observed in the crude reaction mixture, which is consistent with the preceding results. The compound **2w** can be employed as a platform for the synthesis of various indolizidine alkaloids.[6c] For instance, reductive ozonolysis of **2w** furnished a diastereomeric mixture of alcohols (**5a**,**b**), which should provide an entry into hydroxylated indolizidine alkaloids such as lentiginosine (Scheme 6b).[15] Alternatively, **5a**,**b** underwent deoxybromination and reduction of the C–Br bond under classical conditions (Scheme 6b). Reduction of the resulting saturated lactam with $LiAlH_4$ and protonation afforded racemic δ-coniceine hydrochloride in good overall yield.[16]

Finally, fused pyrrolidine **2x** and azepane **2y**, relevant to the synthesis of pyrrolizidine[6b] and *Stemona*[6d] alkaloids, respectively, were obtained in a similar fashion from easily accessible precursors **1x**,**y** by intramolecular C–H alkenylation (Scheme 6a). However, compound **2x** was obtained in low yield due to competitive protodebromination (**2x**/**3x** 1:1) which likely results from excessive ring strain in the formation of the 5,5 ring system.[2e]

In conclusion, a variety of α-alkylidene-γ-lactams were obtained by palladium(0)-catalyzed intramolecular C(sp^3)–H alkenylation of easily accessible acyclic bromoalkene precursors. These lactams can be employed to access various classes of mono- and bicylic alkaloids containing a pyrrolidine ring.

Acknowledgments

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Keywords: C–C coupling · C–H activation · natural products · nitrogen heterocycles · palladium

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