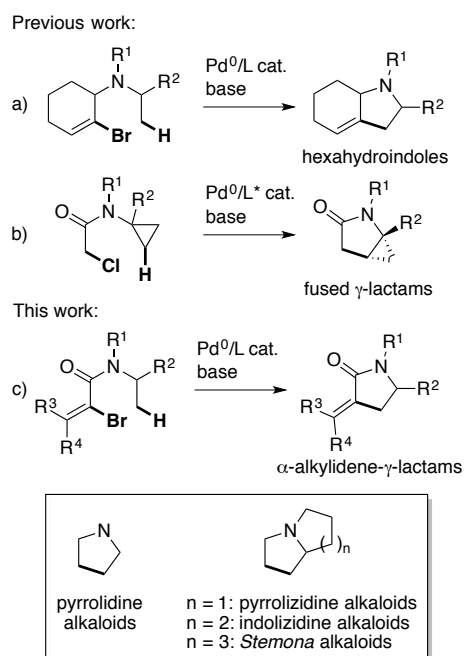


Synthesis of Strained γ -Lactams by Palladium(0)-Catalyzed C(sp³)-H Alkenylation and Application to Alkaloid Synthesis**

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Abstract: A variety of strained α -alkylidene- γ -lactams were synthesized by Pd⁰-catalyzed intramolecular C(sp³)-H alkenylation from easily accessible acyclic and monocyclic bromoalkene precursors. These lactams are valuable intermediates to access various classes of mono- and bicyclic 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.



Scheme 1. Pd⁰-catalyzed intramolecular C(sp³)-H alkenylation and alkylation to build bicyclic and monocyclic *N*-heterocycles.

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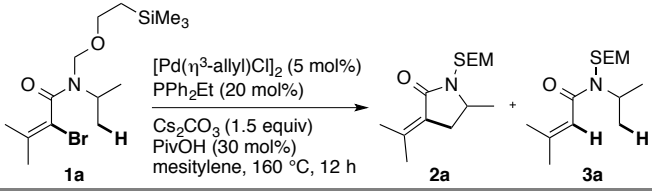
The intramolecular palladium(0)-catalyzed activation of nonacidic C(sp³)-H bonds has recently proven to be a powerful tool to access a vast array of bicyclic and polycyclic systems.^[1-3] Recent efforts in this field have focused on the use of nonaromatic halogenated substrates, which allow to synthesize sp³-rich nitrogen heterocycles of high interest for the synthesis of active ingredients and natural products. In particular, our group reported the construction of hexahydroindoles by intramolecular C(sp³)-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(sp³)-H bonds, respectively, in the presence of a chiral ligand. Herein, we report a unique example of intramolecular alkenylation of unactivated primary C(sp³)-H bonds from acyclic bromoalkenes, 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.

We set out to optimize the cyclization of SEM-protected bromoamide **1a**, which was readily synthesized in three steps from 3,3-dimethylacrylic acid (Table 1). The main issue was the formation of significant quantities of protodebrominated compound **3a**, which is diagnostic of the high ring strain built in such reactions.^[2c,e,4a] The first interesting results were obtained with PPh₂Et as the ligand, under conditions similar to those initially developed by Fagnou and co-workers (entry 1).^[3] Among various Pd sources tested, allylpalladium(II) chloride dimer turned out to be the best choice (entries 2-3). Then, a number of trialkylphosphines and diphenylmonoalkylphosphines were screened (entries 4-9), among which simple 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 10-11). Furthermore, a high reaction temperature of 160 °C was found to be necessary, since lower temperatures gave higher amounts of by-product **3a** (entry 12). This 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% Pd and 10 mol% ligand (entry 13), but the yield of **2a** decreased under lower catalyst loadings (entry 14). Under optimized conditions, γ -lactam **2a** was obtained in 83% isolated yield, and the amount of protodebrominated product **3a** was less than 10% of the mass balance (entry 13).

The scope and limitations of this intramolecular C(sp³)-H alkenylation reaction are shown in Scheme 2. The nitrogen substituent was first varied (Scheme 2a), and the reaction was found to tolerate aminal (**2a-b**) and trimethoxybenzyl (**2c**)^[5b] in addition to

alkyl (**2e**) groups. Other amide protecting groups could not be introduced or were found to be unstable [e. g. 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 NH-lactam **2d**.^[7]

Table 1. Optimization of reaction conditions.

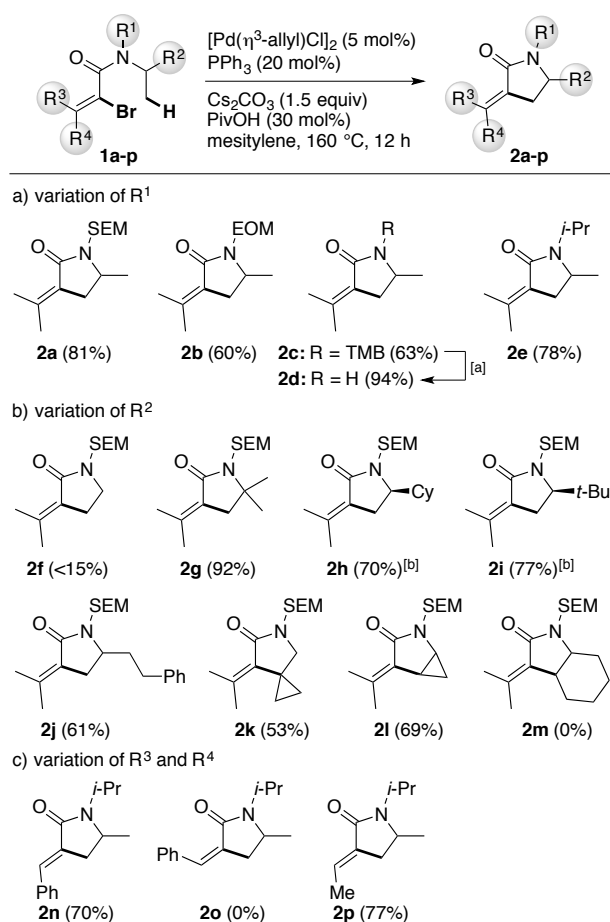


Entry	Deviation from standard conditions	2a/3a ^[a]	Yield of 2a (%) ^[a,b]
1	–	91:9	83
2	Pd(OAc) ₂ (10 mol%) instead of [Pd(η ³ -allyl)Cl] ₂	76:24	65
3	Pd ₂ dba ₃ (5 mol%) instead of [Pd(η ³ -allyl)Cl] ₂	91:9	81
4	PCy ₃ instead of PPh ₂ Et	47:53	22
5	PEt ₃ instead of PPh ₂ Et	41:59	35
6	PPh ₂ Me instead of PPh ₂ Et	84:16	78
7	PPh ₃ instead of PPh ₂ Et	91:9	83 (81)
8	P(<i>p</i> -NMe ₂ -Ph) ₃ instead of PPh ₂ Et	86:14	49
9	P(<i>p</i> -CF ₃ -Ph) ₃ instead of PPh ₂ Et	–	0
10	K ₂ CO ₃ instead of Cs ₂ CO ₃	83:17	64
11	Rb ₂ CO ₃ instead of Cs ₂ CO ₃	86:14	76
12	140 °C instead of 160 °C	46:54	20
13	2.5 mol% [Pd(η ³ -allyl)Cl] ₂ /10 mol% PPh ₃	92:8	91 (83)
14	1.25 mol% [Pd(η ³ -allyl)Cl] ₂ /5 mol% PPh ₃	84:16	79

[a] Determined by GCMS analysis of the crude mixture. [b] Determined by GCMS analysis using tetradecane as standard. Yield of isolated product **2a** in parentheses. SEM = [2-(trimethylsilyl)ethoxy]methyl.

The nature of the alkyl group undergoing C–H activation was next varied (Scheme 2b), while keeping the nonreactive SEM group as R¹.^[8] First, compound **1f** containing a *N*-ethyl group (R² = H) provided only low amounts of γ -lactam **2f**, to the profit of the corresponding protodebrominated product **3f** (**2f/3f** 14:86), thereby showing the lack of reactivity of linear alkyl groups in the current system. In contrast, the reaction of compound **1g** bearing a *tert*-butyl substituent was highly favored, and gave rise to γ -lactam **2g** in 92% yield. The reactivity trend **1f** < **1a** < **1g** is consistent with previous observations, and can be imputed to Thorpe-Ingold effects, which have an important impact in this class of reactions.^[2] Other substrates successfully underwent selective activation/cyclization at primary (**1h–j**) or cyclopropyl (**1k**) C–H bonds to give the corresponding monocyclic (**2h–j**) or spirocyclic (**2k**) γ -lactams, in the presence of less reactive methylene and methine C–H bonds. Indeed, the activation/cyclization of 2° C–H bonds was unsuccessful, even in the absence of 1° 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- and methyl-substituted *Z*-bromoalkenes **1n** and **1p** furnished the corresponding γ -lactams with similar efficiency. In contrast, compound **1o**, the *E*-isomer of

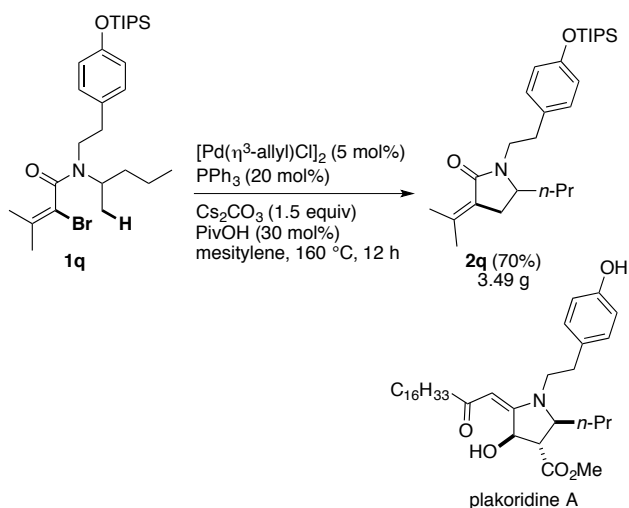
1n, was found to undergo rapid base-promoted elimination to give the corresponding alkyne even in the absence of Pd catalyst, thereby precluding the C–H alkenylation process.



Scheme 2. Scope, limitations and selectivity pattern of the intramolecular C(sp³)–H alkenylation reaction. [a] Reaction conditions: CF₃CO₂H, anisole, 20 °C. [b] Obtained from enantiomerically pure substrates. EOM = ethoxymethyl; TMB = 2,4,6-trimethoxybenzyl.

The remarkable site-selectivity observed in the above examples was further demonstrated with the reaction of compound **1q** (Scheme 3), which provided γ -lactam **2q** in 70% yield on multigram scale. Among all potentially reactive C–H bonds in **1q**, the 1° C–H bonds highlighted in Scheme 3 underwent cyclization selectively. 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 nonequivalent 1° C–H bonds on reactants **1r–u**, which may either give rise to γ -lactams **2r–u** as shown above, or possibly to the more strained β -lactams **4r–u** (Table 2). Compound **1r** bearing *N*-methyl and *N*-*tert*-butyl substituents underwent selective reaction on the *t*-Bu group to give γ -lactam **2r** in high yield (entry 1). Replacing the *t*-Bu group with an *i*-Pr group (**1s**) generated a separable mixture of both lactam products (entry 2). In contrast, substrate **1t** derived from (–)-ephedrine and containing one Me group less than **1s** underwent selective reaction to form β -lactam **4t** in moderate yield, accompanied by significant amounts of protodebrominated product **3t** (entry 3).



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

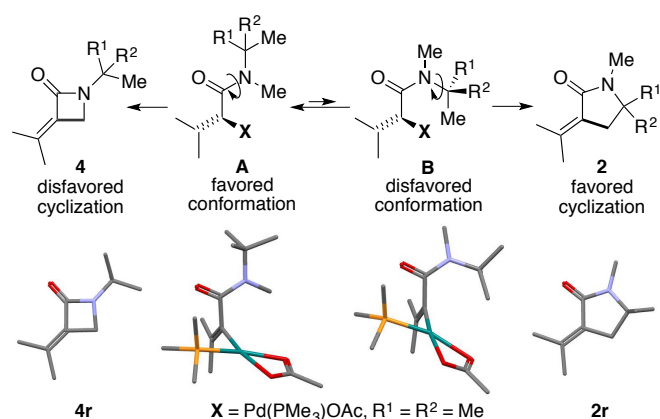
Table 2. Selectivity of the activation of 1° C–H bonds.

Entry	Reactant	Product(s) ^[a]	2/4 ^[b]
1		 	>98:2
2		 	71:29 ^[c]
3		 	7:93 ^[c]
4		 	<2:98 ^[c]

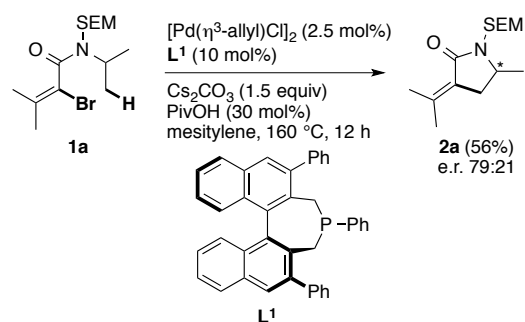
[a] Yield of isolated product in parentheses. [b] Determined by GCMS analysis of the crude mixture. [c] The corresponding protodebrominated products **3s–u** were also formed in the following GC ratios: **2s/4s/3s** 53:22:25; **2t/4t/3t** 5:63:32; **4u/3u** 48:52.

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 Pd intermediate undergoing C–H activation^[2c,3f,h] is **A**, where the smallest *N*-Me substituent turns

toward the Pd center [see the computed model structure with X = Pd(PMe₃)OAc]. However, C–H activation at this Me group and/or C–C reductive elimination to form β-lactam **4** should be disfavored due to the building of strong ring strain. On the other hand, 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 Me groups as R¹, R² should increase the population of this reactive conformer **B** and should thus favor the γ-lactam product (Table 2, entries 3→1). Finally, reactant **1u** bearing *N*-Me and *N*-Cy groups provided a separable mixture of β-lactam **4u** and protodebrominated product **3u**, together with traces of γ-lactam **2u**, as expected from the lack of reactivity of 2° C–H bonds under the current conditions (entry 4, see also Scheme 2, compound **2m**). 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]



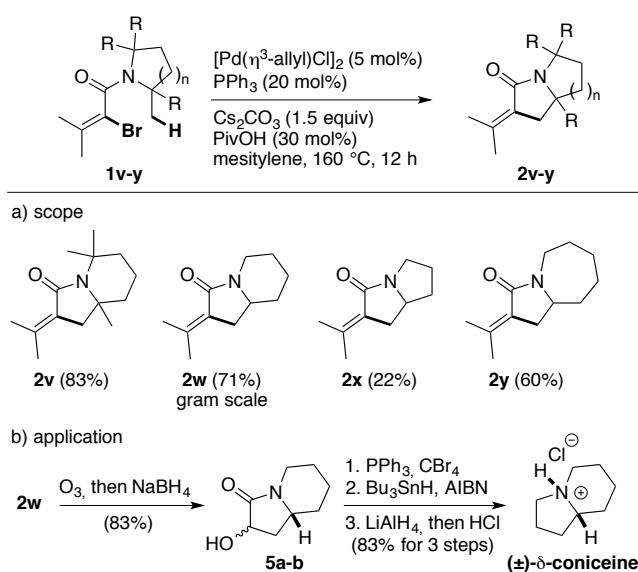
Scheme 4. Contradictory effects on reaction selectivity. Bottom: DFT-optimized structures (M06/6-31G**), H atoms omitted for clarity. With these substituents, **A** was computed to be more stable than **B** by 4.8 kcal mol⁻¹ and **2r** more stable than **4r** by 19.5 kcal mol⁻¹.



Scheme 5. Proof-of-concept enantioselective C(sp³)-H alkenylation.

The asymmetric C–H alkenylation of substrate **1a** in the presence of a chiral ligand instead of PPh₃ was also studied. In particular, we tested P-arylbinaphthyls, which can be regarded as chiral surrogates of PPh₃,^[12b] and which provided us with high enantioselectivities in intramolecular C(sp³)-H arylations leading to (fused) indanes.^[12-13] We found that ligand **L¹**, which was initially introduced by Fu and co-workers,^[14] allowed to obtain γ-lactam **2a** with moderate (e.r. 79:21) 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(sp³)-H alkenylation method.

Next, the reactivity of monocyclic precursors relevant to the synthesis of bicyclic alkaloids was examined (Scheme 6a). As expected, the reaction of Me group-rich bromoalkene **1v** derived from 2,2,6,6-tetramethylpiperidine occurred in high yield (**2v**). More strikingly, piperidine precursor (**1w**) containing a single exocyclic methyl group underwent selective C–H alkenylation at the latter, to give fused γ -lactam **2w** in 71% yield on gram scale. No trace of product arising from activation at the methylene C–H bonds α to the nitrogen atom was observed on the crude mixture, consistent with the preceding results. 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.^[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 LiAlH₄ and protonation afforded racemic δ -coniceine hydrochloride in good overall yield.^[16]



Scheme 6. Construction of bicyclic γ -lactams and application to the synthesis of δ -coniceine.

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 Pd⁰-catalyzed intramolecular C(sp³)–H alkenylation of easily accessible acyclic bromoalkene precursors. These lactams can be further employed to access various classes of mono- and bicyclic alkaloids containing a pyrrolidine ring.

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C–H Activation

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Alkenylation and Application to Alkaloid
Synthesis

