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Synthesis of γ-Lactams and γ-Lactones via Intramolecular Pd-Catalyzed Allylic Alkylations

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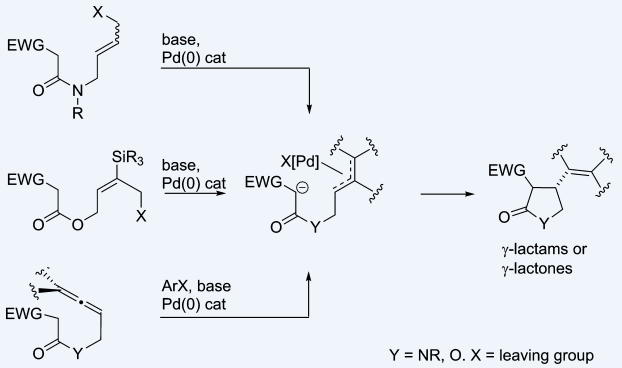
CONSPECTUS: Lactones and lactams are a well-known class of natural products and can be used as building blocks in organic synthesis. In addition, they can be found in many natural sources and synthetic drugs and have a broad range of biological or odorant properties. Chemists can create these useful compounds through palladium catalysis, which is a highly efficient tool for organic synthesis and is conveniently functional group tolerant. In this Account, we describe our work over the past 15 years in intramolecular Pd-catalyzed allylations where we have tethered the nucleophile and the electrophile by either an amide or an ester moiety, to produce γ-lactams and γ-lactones. We discuss in detail how the nature of the heteroatom tether influences the regioselectivity of the reaction. For example, a ketone [−C(O)-CH_2−] tether leads to mixtures of 5-*exo* and 7-*endo* cyclization products, while ester or amide [−C(O)X−] tethers afford sole 5-*exo* products. However, in the case of X = O, we were required to overcome two issues in the synthesis of γ-lactones. First of all, the tethering ester function can compete with the allylic leaving group in the oxidative addition to the Pd(0) center. Second, in this case, the proportion of the conformers that have a suitable geometry for cyclization is very low. When we insert a juxtaposed silyl group on the allyl fragment, the molecule can undergo oxidative addition and functionalization of the lactone via Hiyama cross-coupling.



We also performed DFT calculations on these systems, which allowed us to better understand the behavior of [−C(O)X−] and [−C(O)CH_2−] tethers. Computations also let us rationalize the different reactivities that we observed as a function of the geometry (*Z* or *E*) of the starting substrates. In addition, we were able to synthesize natural products or analogs (α-kainic acid, isoretronecanol, and picropodophyllin). We could turn these allylation reactions into asymmetric transformations and incorporate them into domino sequences. Thus, an allylation/Mizoroki−Heck sequence allowed us to straightforwardly access an aza-analog of picropodophyllin, as well as reach the lysergic acid backbone. Finally, we found that through carbopalladation of allenes, we could efficiently synthesize the key η^3-allylpalladium intermediates that were then ready for allylation reactions.

INTRODUCTION

Lactones and lactams are among the most well-known classes of natural products. Such structural motifs can be used as building blocks in organic synthesis and found in many natural sources as well as in synthetic drugs, displaying a broad range of biological or odorant properties.[1] Palladium catalysis has emerged as a highly competent and functional group tolerant tool for organic synthesis. We thus decided to start a long-term project aimed at studying the synthesis of γ-lactams and γ-lactones through the Pd-catalyzed allylation reaction.

γ-LACTAMS AND γ-LACTONES THROUGH METAL-CATALYZED C3−C4 RING CLOSURE

While the most obvious way of synthesizing γ-lactams and γ-lactones is represented by the intramolecular O- or N-acylation of γ-hydroxy- or γ-amino acid derivatives, an alternative, simple, and synthetically relevant way of obtaining such targets is through a metal-catalyzed C3−C4 ring closure. This less common disconnection has been extensively exploited by Lu and co-workers[2] using carbopalladation as the key ring closing step and by our group in the context of Pd-catalyzed allylations (Scheme 1).

We reasoned that targets such as **I** could be straightforwardly obtained provided that precursor **III** carries a soft nucleophile at position 3 and an appropriate allylic system at position 4 (target numbering), so as to allow an intramolecular Pd-catalyzed allylation reaction via intermediate **II** (Scheme 2).

TARGETING PYRROLIDONES

The starting point of our project was the cyclization of the unsaturated amide (*Z*)-**1a**, a transformation that was studied and improved over the years. The optimized conditions require [$Pd(C_3H_5)Cl]_2$/dppe] as the catalytic system, KOH, and *n*-Bu_4NBr under biphasic conditions (DCM/H_2O) at room

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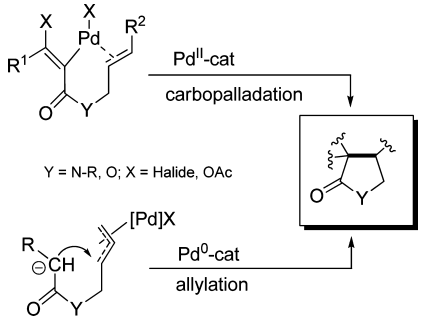
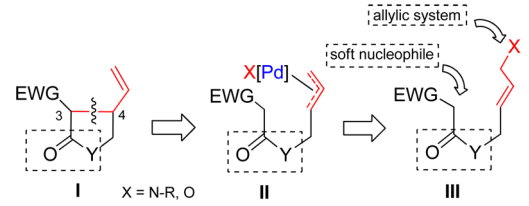
Scheme 1. Pd-Catalyzed Approaches to γ-Lactams and γ-Lactones Featuring C3−C4 Bond Formation

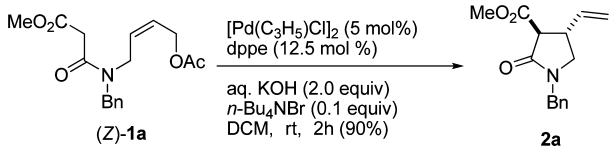


Scheme 2. Selected Ring-Closing Strategy for the Synthesis of Lactam- and Lactone-Based Heterocycles



temperature, affording **2a** in 90% yield as a single diastereoisomer (Scheme 3).[3]

Scheme 3. Optimized Conditions for the Cyclization of (Z)-1a to Pyrrolidone 2a



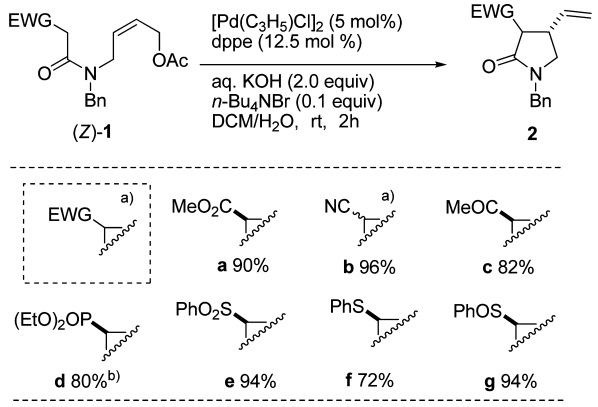
The scope of the intramolecular allylic alkylation reaction was examined by varying the nature of the acetamide-activating group. The cyclization of precursors **1b−g** took place smoothly, affording the corresponding 3,4-*trans*-γ-lactams **2b−g** in yields over 70% (Scheme 4).[4,5]

Although the pyrrolidone ring was the expected product, the total absence of a competitive 7-*endo* process could not be anticipated from the outset. In an attempt to bias such regioselectivity,[6] the silylated precursor **1h** was synthesized. However, treatment with $Pd(OAc)_2$/dppe and NaH in DMF yielded regio- and stereoselectively the pyrrolidone **2h**, which reveals the intrinsic preference of these N-tethered substrates to cyclize via 5-*exo* processes (Scheme 5).[7]

Chiral substrates with the allylic moiety incorporated into a cyclic structure were next examined.[8] Cyclization of the *cis*-precursors *cis*-**3a** and *cis*-**3b** at 50 °C afforded, respectively, the bicyclic products **4a** and **4b** in 90% yield. In both cases, the bicyclic pyrrolidone was obtained as a single diastereoisomer, displaying a *cis* ring junction and a 3,3a-*trans* relative configuration. Conversely, nitrile **3c** gave the corresponding bicyclic product **4c** as a 60:40 diastereoisomeric mixture (Scheme 6).

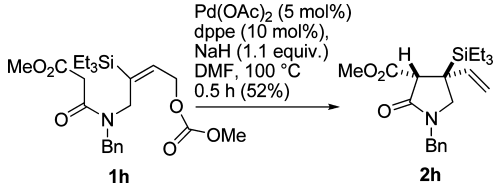
While the base-promoted postcyclization epimerization is expected to thermodynamically favor the diastereoisomer placing the bulky ester and sulfone groups on the less congested convex face of the molecule, location of the small, linear nitrile on either portion of space may be almost energetically equivalent.

Scheme 4. Scope of the Cyclization of Precursors (Z)-1 to the Corresponding Pyrrolidones

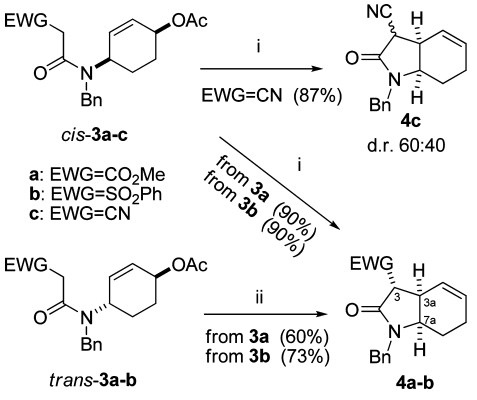


[a]Only or largely major 3,4-*trans* product except for **2b**. [b]Conditions: Pd_2dba_3 cat./PPh_3, BSA/AcOK cat., THF, reflux, 12 h.

Scheme 5. Cyclization of the Triethylsilyl-Substituted Precursor 1h



Scheme 6. Cyclization of the Alkyl-Bridged Precursors 3a−c[a]



[a]Conditions: (i) $Pd(OAc)_2$ (1 mol %), dppe (2 mol %), NaH (1.0 equiv), DMF, 50 °C, 0.5 h. (ii) $Pd(OAc)_2$ (5 mol %), dppe (10 mol %), NaH (1.0 equiv), DMF, 100 °C, 0.5 h.

Cyclization of the *trans*-precursor, *trans*-**3a**, required a harsher condition to proceed than that of the corresponding isomer *cis*-**3a** yet afforded the same product **4a**. This stereoconvergence may be rationalized as follows: the η^3-allylpalladium intermediate **V** derived from *cis*-**3a**, is well biased to afford the *cis*-fused product **4a**, according to a classical double inversion mechanism. On the other hand, the η^3-allylpalladium intermediate **VI** derived from *trans*-**3a** is not biased to intramolecularly react at the allylic terminus *anti* to the Pd atom (naturally required in this type of allylation), because generation of a 6/5 *trans* fusion is disfavored. Hence,

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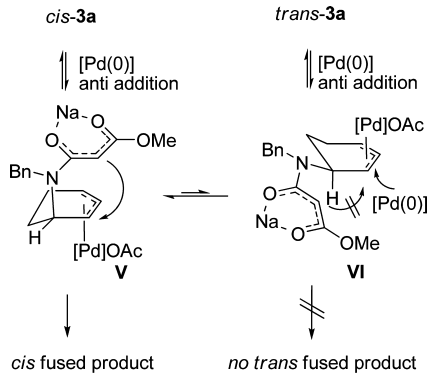
the only chance of evolution of complex **VI** is through slow isomerization to complex **V**, which (as previously seen) can easily react according to a regular *anti* stereochemistry. It should be noted that, due to the cyclic nature of the η^3-allylpalladium complexes, their equilibration can only take place through interaction with Pd(0), according to a bimolecular mechanism[9] (Scheme 7).

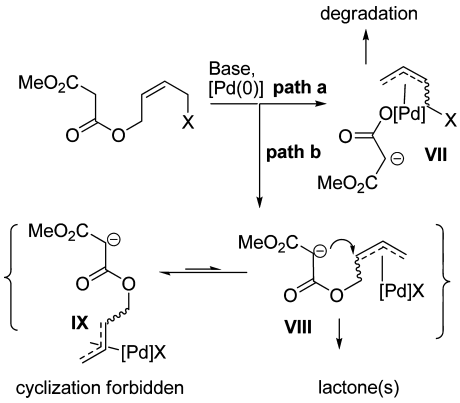
Scheme 7. Stereoconvergent Path of Allylamides *cis*-3a and *trans*-3a



TARGETING γ-LACTONES

Replacement of the amide in the cyclization precursor by an ester raised two new issues (Scheme 8).[10] Indeed, the ester

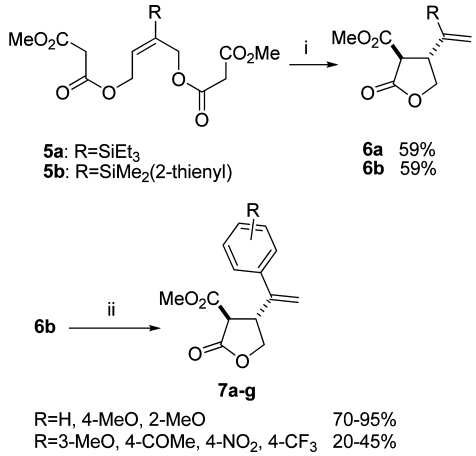
Scheme 8. Possible Paths of the Ester Precursor under Pd(0) Catalysis



tether may be competitively cleaved during the oxidative addition step, yielding an undesired η^3-allyl complex **VII** (path a). Moreover, switch from a tertiary amide to an ester may dramatically lower the amount of conformer possessing the required geometry for cyclization, such as **VIII** (path b).

Not unexpectedly, Pd-catalyzed cyclizations of simple ester analogs of **1a** met with failure. However, use of triethylsilyl-substituted precursors **5**, to force displacement of the acetoxy group vicinal to the silicon atom,[11] proved a successful strategy, giving a single *trans* diastereoisomer. Furthermore, lactone **6b** could be coupled with various aryl iodides to afford the expected 4-(α-styryl) γ-lactones **7a–g** in variable yields (Scheme 9).

Scheme 9. Cyclization of the Silyl Precursors 5a and 5b and Cross-Coupling of the Silyl Lactone 6b with Aryl Iodides[a]



[a]Conditions: (i) $Pd(OAc)_2$ (1 mol %), dppe (2 mol %), NaH (1.1 equiv), DMF, 60 °C, 1.5 h. (ii) ArI, $Pd_2(dba)_3$ (2.5 mol %), TBAF (2.4 equiv), THF, rt, 16 h.

COMPUTATIONAL STUDIES

In early studies, Tsuji[12] and later Pfaltz[13] reported that the Pd-catalyzed intramolecular allylation of unsaturated β-ketoesters yields a mixture of vinylcyclopentanones, cycloheptenones, and tetrahydrofurans in variable proportions, depending on the reaction conditions. Because these β-ketoesters represent the carbon analogs with respect to our nitrogen- and oxygen-based cyclization precursors, the total 5-*exo* selectivity of these latter appears particularly striking. A DFT study[14] was thus undertaken. Because the η^3-allyl palladium intermediates can exist as *syn* or *anti* isomers and each of them could theoretically react according to an *exo* or *endo* pathway, four cyclization transition states should be considered for each substrate, whereof the *syn*-7-*endo* ones can be neglected for geometric reasons. Also, only the most favorable enolate attack topology (involving the smallest steric interactions) was considered (Scheme 10).

The relative energies for the transition states located for the simplified C-, N-, and O-tethered models[15] (Table 1) indicate that the *anti*-7-*endo* cyclization is competitive with 5-*exo* cyclization in the case of C-tethered substrates (entries 1–3) yet highly disfavored for both N- and O-tethered precursors (entries 4–6 and 7–9), in perfect agreement with experimental data. The *anti*-5-*exo* path is less favored than the *syn*-5-*exo* path, and the larger the angle value between the forming and breaking bonds in the latter paths, the lower the activation barrier.

The above results suggest that the exclusive formation of five-membered rings with heteroatom tethers may result from the combination of a selective disfavoring of the *anti*-7-*endo* path and a selective favoring of the *syn*-5-*exo* path. Indeed, comparison of the *anti*-7-*endo* transition state structures reveals that the bond distances between the carbonyl and the two neighboring atoms are significantly shorter in the case of heteroatom-tethered substrates, giving rise to substantially more strained *anti*-7-*endo* transition states. On the other hand, the N- and O-tethered complexes attain very good approach vectors for the *syn*-5-*exo* path, as indicated by angles of 160° and 159°, respectively (entries 4 and 7), in contrast to

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Scheme 10. Cyclization Pathways, with Newman Projections along the Forming C−C Bonds

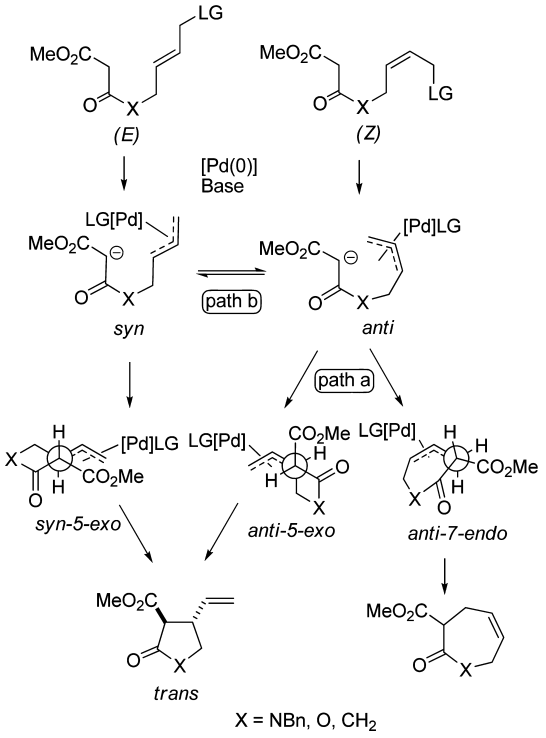
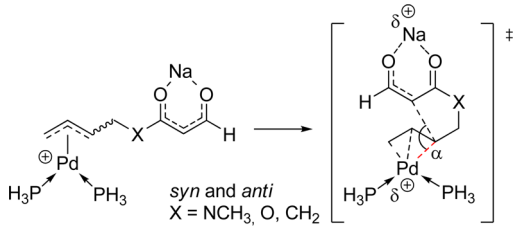


Table 1. Relative Energies of Transition State Conformations in the Presence of the Na^+ Counterion for Model Precursors



entry	X	pathway[a]	C···C[b]	Pd−C···C[c]	ΔE_{rl}[d]
1	CH_2	*syn*-5-*exo*	2.24	155	2
2	CH_2	*anti*-5-*exo*	2.22	147	7
3	**CH_2**	***anti*-7-*endo***	**2.38**	**140**	**0**
4	**NCH_3**	***syn*-5-*exo***	**2.44**	**160**	**0**
5	NCH_3	*anti*-5-*exo*	2.53	141	13
6	NCH_3	*anti*-7-*endo*	2.51	126	67
7	**O**	***syn*-5-*exo***	**2.27**	**159**	**0**
8	O	*anti*-5-*exo*	2.33	147	7
9	O	*anti*-7-*endo*	2.33	139	32

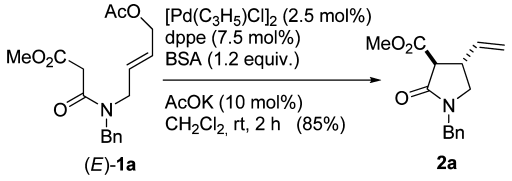
[a]Favored paths are represented in bold. [b]Length (Å) of the forming bond. [c]Angle α (deg) between forming and breaking bonds. [d]Energy (kJ mol^{-1}) relative to the lowest energy TS with the same tether X.

C-tethered substrates, which exhibit a more restricted rotation around the CH_2−CH_2 bond (entry 3).

Also, the higher activation energy required for the *endo*-cyclization of the N-tethered substrate (67 kJ mol^{-1}, entry 6), compared with the ester derivative (32 kJ mol^{-1}, entry 9), unveils the planar nature of the amide bond.

As mentioned earlier, the *syn*-5-*exo* path for the amide model is favored by 13 kJ mol^{-1} over the *anti*-5-*exo* path (entries 4 and 5). At the beginning of this study, we anticipated that the reaction of an (*E*)-configured substrate would directly cyclize according to a *syn*-5-*exo* path. Interestingly, the cyclization of the N-tethered precursor (*E*)-**1a** proceeded efficiently at room temperature, as opposed to the substrate (*Z*)-**1a** (Scheme 11).[16]

Scheme 11. Cyclization of the (*E*)-Precursor (*E*)-1a



Therefore, two distinct mechanisms for the formation of the 5-*exo* product **2a** starting from the precursor (*Z*)-**1a** could be envisioned: (a) the *anti*-η^3-allylpalladium complex reacts directly via an *anti*-5-*exo* pathway (Figure 1, path a), or (b)

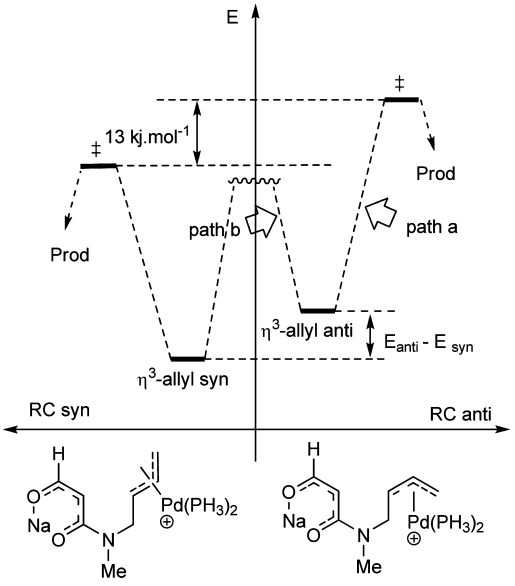


Figure 1. Possible paths in the cyclization of model amide (chelated).

initial isomerization affords the *syn*-η^3-allyl complex, which then undergoes a fast *syn*-5-*exo* cyclization, converging into the same path as the (*E*)-**1a** precursor (Figure 1, path b). Therefore, the path selected by the precursor (*Z*)-**1a** will depend on the difference between the energy barrier for *anti*-to-*syn* isomerization and that associated with path a.

We also anticipated that a naked enolate would cyclize under milder conditions than a metal-chelated one, even starting from a (*Z*)-precursor. Indeed, an ideal orbital overlap for the C−C bond formation would require a parallel disposition between the plane containing the enolate (α') and that containing the allyl fragment (β) (Figure 2, left). However, a resonance-stabilized Na-chelated enolate is conjugated with the amide function embedded in plane α (Figure 2, right). As a consequence, the transition state of the cyclization process might feature a significant loss of conjugation, resulting in a higher activation barrier to cyclization.

In line with the above reasoning, the cyclization of (*Z*)-**1a** in the presence of the Na-sequestering agent 15-C-5 took place at

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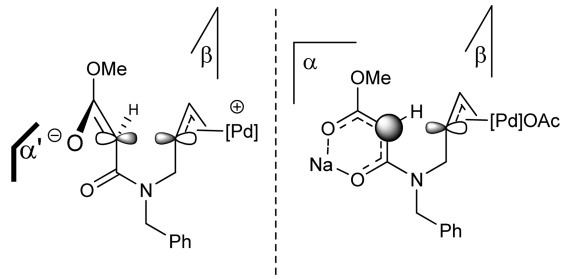
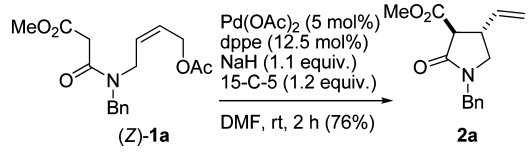


Figure 2. Influence of the enolate chelation in the TS of the cyclization.

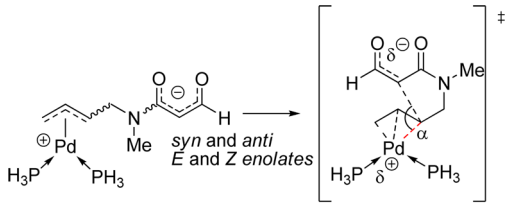
room temperature affording smoothly the expected product **2a** in 76% yield (Scheme 12).[3a]

Scheme 12. Cyclization of Precursor (*Z*)-1a in the Presence of a Na-Sequestering Agent



DFT calculations were performed again to locate the cyclizing transition states for both the (*Z*)- and (*E*)-enolates in the absence of Na^+ (Table 2).

Table 2. Relative Energies of the Transition States of the N-Tethered Counterion-Free Model Enolates



syn-5-exo, anti-5-exo, anti-7-endo

entry	pathway	*E*/*Z*	C···C[a]	Pd−C···C[b]	ΔE_{rel}[c]
1	*syn-5-exo*	*E*	2.62	160	0
2	*syn-5-exo*	*Z*	2.69	162	13
3	*anti-5-exo*	*E*	2.63	165	5
4	*anti-5-exo*	*Z*	2.71	155	21
5	*anti-7-endo*	*E*	2.58	134	54
6	*anti-7-endo*	*Z*	2.60	132	66

[a]Length of the forming bond (Å). [b]Angle (deg) between forming and breaking bonds. [c]Energy (kJ mol^{-1}) relative to the lowest energy TS.

Interestingly, under the counterion-free conditions, the transition states appear more reactant-like than those relative to the chelated system, and the ring closure from the *syn* intermediate is now favored by 5 kJ mol^{-1} over that from the alternative *anti* intermediate (Figure 3, Table 2, compare entries 1 and 3).

The above results suggest that under the "naked" conditions, an *anti*-to-*syn* isomerization barrier may become lower than that required for cyclization via the lower *anti*-5-*exo* (Figure 4; Table 2, entry 3). As a consequence, according to the Curtin−Hammett principle, the (*Z*)-**1a** isomer would cyclize via prior isomerization to the η^3-allyl palladium *syn* complex (path b). This scenario implies that the C−C bond formation transits

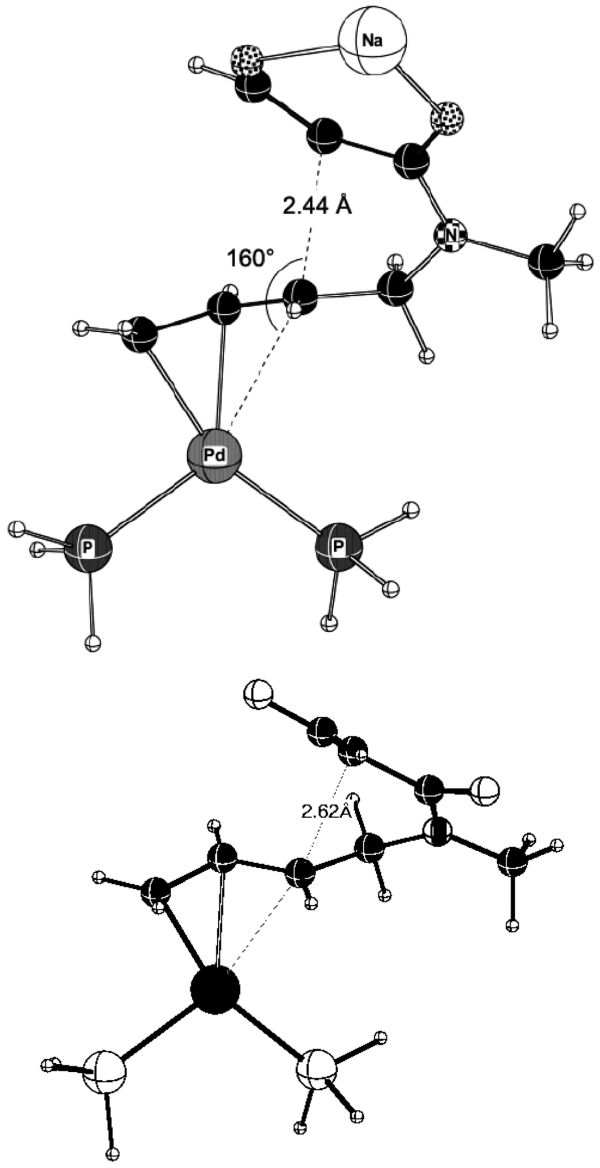


Figure 3. *Syn*-5-*exo* transition states of the N-tethered model substrates. Comparison between the Na^+-chelated enolate (top) and the (*E*)-configured counterion-free enolate (bottom).

exclusively through the most stable (*syn*) η^3-allyl palladium complex, independently of the geometry of the starting substrate.

■ SYNTHETIC APPLICATIONS

In the course of our studies, the synthetic potential of the Pd-catalyzed allylation of amides and esters was highlighted by the preparation of various natural products and analogs. The above strategy was successfully applied to the formal synthesis of (±)-α-kainic acid,[17] (Scheme 13). The cyclization of unsaturated phosphonoacetamide **8** quantitatively afforded the *trans* pyrrolidone **9**. Further functionalization including a Horner−Wadsworth−Emmons olefination followed by a diastereoselective conjugated hydride addition of the resulting electron-poor alkene yielded the advanced precursor **10** of kainic acid, previously reported by Xia and Ganem.[18]

Taking advantage of the availability of the bicyclic pyrrolidone **11**, the synthesis of racemic isoretronecanol was also accomplished (Scheme 14).[8] Installation of the pyrrolizi-

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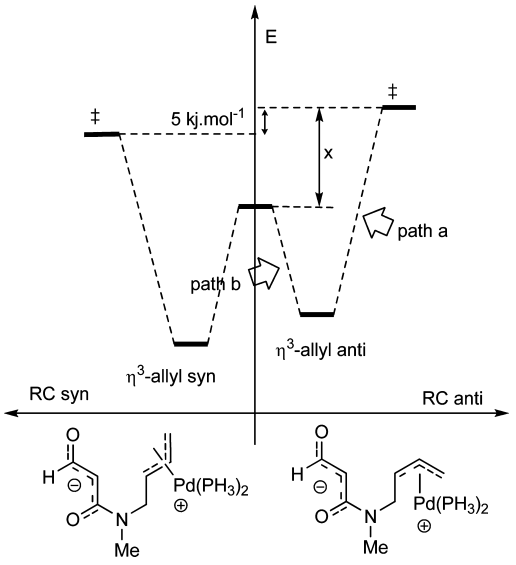
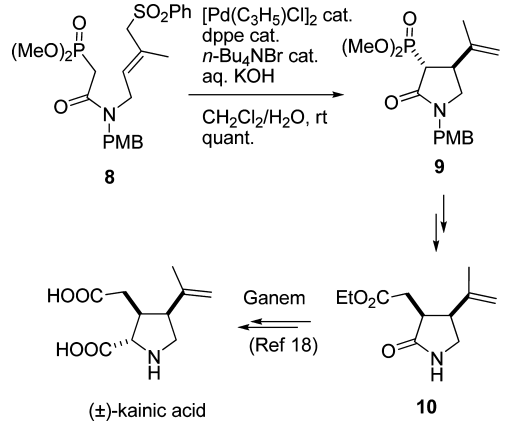
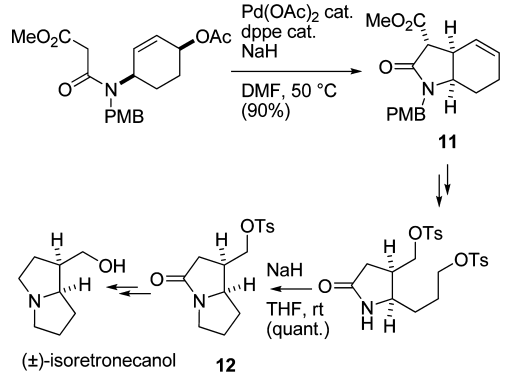


Figure 4. *Syn* and *anti* cyclizing transition states from model amide (naked).

Scheme 13. Formal Synthesis of (±)-Kainic Acid



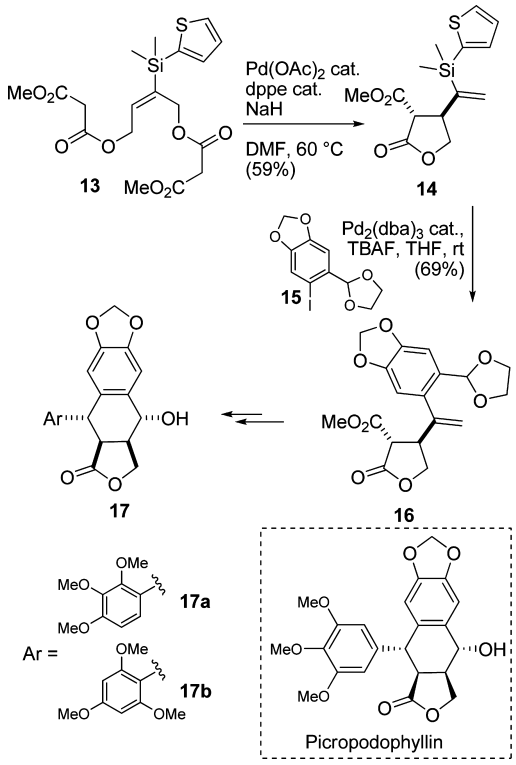
Scheme 14. Synthesis of (±)-Isoretronecanol



dine structure required the oxidative opening of the cyclohexene moiety, followed by a regioselective 5-*exo* cyclization affording the key intermediate **12**. The desired alkaloid was finally obtained after a short functional group make up.

Having successfully transposed our cyclization strategy from unsaturated amides to esters, targets featuring a γ-lactone moiety became accessible, as was the case for picropodophyllin (Scheme 15).[10b] The palladium-catalyzed two-step allylation/

Scheme 15. Synthesis of Picropodophyllin Analogs



Hiyama coupling sequence involving precursor **13** and iodide **15** gave the expected styryl γ-lactone **16**. Further functionalization including a key aldolization and an electrophilic aromatic substitution, afforded the two picropodophyllin analogs, **17a** and **17b**.

γ-LACTAMS AND γ-LACTONES THROUGH CATALYTIC DOMINO SEQUENCES

In the current effort toward an ever more sustainable chemistry, transition metal-catalyzed domino reactions, in their *pure* as well as type I and type II *pseudo* variants,[19] are a major asset, because they allow building up complexity in an atom- and step-economical way.

In this context, we recently developed a phosphine-free Pd-catalyzed carbopalladation/allylation pure-domino sequence starting from a linear allenyl amide precursor **18**[20] and aryl halides to afford 4-(α-styryl)-γ-lactams **19**.[21] The above pure-domino sequence was successfully applied to the synthesis of pyrrolidone **20**, a racemic aza-analog of the naturally occurring lignan (+)-oxo-parabenzlactone **21**.[21]

An analogous strategy allowed conversion of anthranilic allenamides into 2-(α-styryl)-quinazolinones.[22] This same type of domino sequence was also extended to *O*-α-allenyl malonate **22**, to afford the corresponding γ-lactone **23** (Scheme 16).[23]

In the context of pseudodomino type I sequences,[24] we anticipated that the alkenyl substituent generated during the cyclization of the unsaturated amides could be a suitable partner for Pd-catalyzed Mizoroki–Heck couplings. Accordingly, treatment of precursor (*Z*)-**1a** with various aryl bromides in the presence of the Herrmann–Beller catalyst, NaH, and AcONa gave regio- and stereoselectively the (*E*)-4-(β-styryl) pyrrolidones **24** (Scheme 17).[25]

Switch of the molecularity from an "*intra–inter*" to an "*intra–intra*" type offered an original access to lactam analogs

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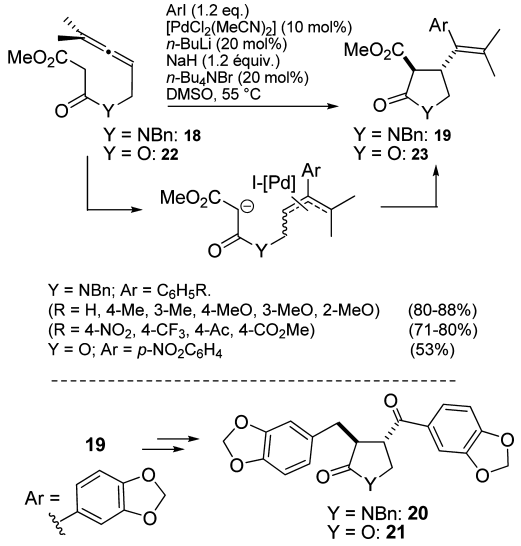
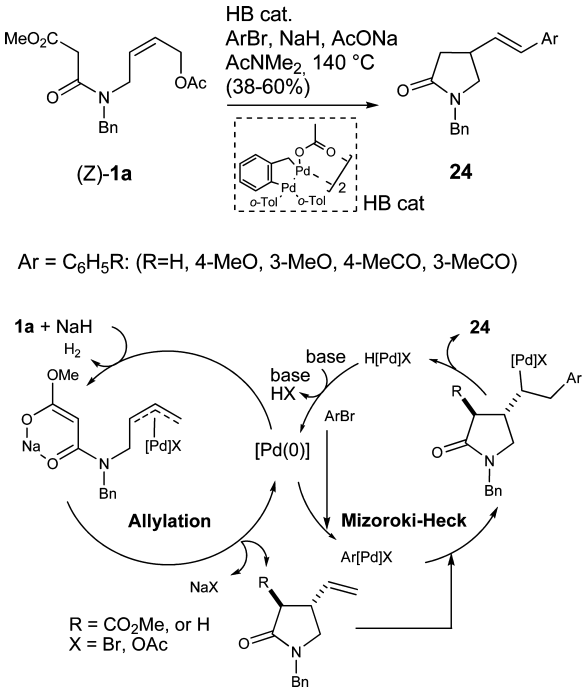
Scheme 16. Pd-Catalyzed Carbopalladation/Allylation Pure Domino Sequences toward 4-(α-Styryl)-γ-lactams and γ-Lactones



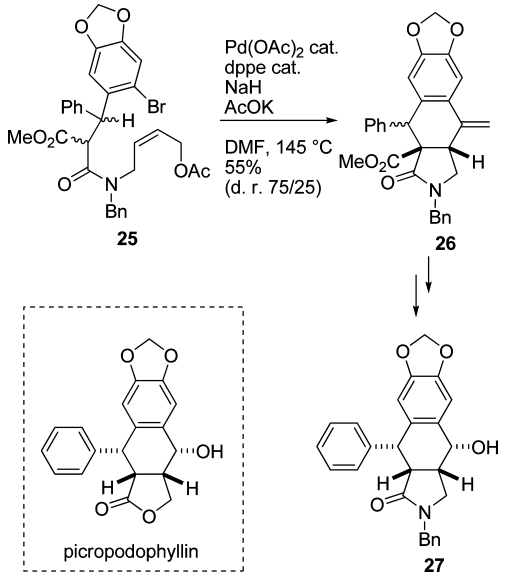
Scheme 17. Pd-Catalyzed Allylic Alkylation/Mizoroki−Heck Coupling Pseudodomino Sequence



of the podophyllotoxin family. Thus, optimized reaction conditions allowed conversion of the benzhydryl-substituted precursor **25** into the fused tetracyclic γ-lactam **26**. Further standard transformations allowed us to attain the desired picropodophyllin aza analog **27** (Scheme 18).[19]

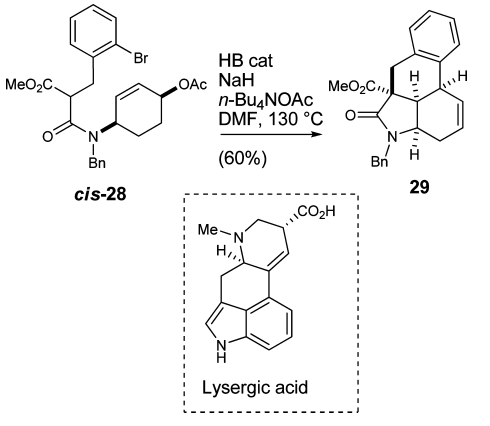
These domino cyclizations were also extended to precursors having an allylic moiety incorporated into a cyclic structure, so as to obtain polycondensed structures. Specifically, 1,4-aminoacetoxycyclohexene derivative *cis*-**28** underwent the expected pseudodomino process affording the tetracycle **29**, featuring three fused bonds connected to a common carbon atom. Noteworthy, this single synthetic operation provides the backbone of lysergic acid through the generation of two new

Scheme 18. Doubly Intramolecular Pseudodomino Sequence Applied to the Synthesis of the Picropodophyllin Aza Analog 27



C−C bonds and three new stereocenters in a totally diastereoselective way (Scheme 19).[3c]

Scheme 19. Doubly Intramolecular Pseudodomino Sequence To Afford the Lysergic Acid Backbone



■ ALLYLATION OF AMIDES VIA ASYMMETRIC CATALYSIS

The catalytic asymmetric cyclization between malonamide anions and η^3-allylpalladium complexes was also tackled. Treatment of (*E*)-**1a** and (*Z*)-**1a** under phase-transfer catalysis conditions and in the presence of ligand **L1**, gave the *trans* pyrrolidone **2a** in er's up to 92:8 (Scheme 20). The er's predicted via DFT studies were found to be in good agreement with the observed experimental values. Experiments performed using different allylic leaving groups or catalyst loading suggest that the C−C bond formation is the enantiodiscriminating step, while the preceding generation of the η^3-allylpalladium intermediate is a reversible pre-equilibrium step.[5]

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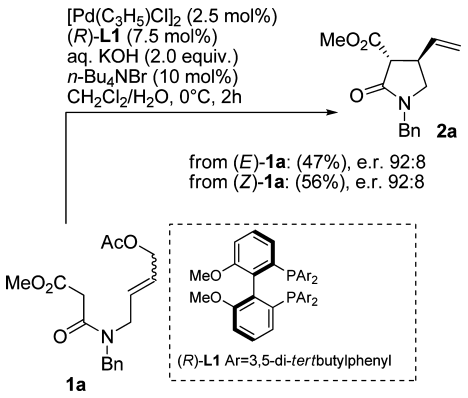
Scheme 20. Palladium-Catalyzed Intramolecular Asymmetric Allylic Alkylation of Allylamides



CONCLUSION AND PERSPECTIVES

Pd-catalyzed intramolecular allylation reactions wherein the nucleophilic and the electrophilic partners are tethered by an amide or an ester moiety proved to be a powerful strategy to generate heterocycles such as γ-lactams and γ-lactones, alternative to the classical lactonization and lactamization reaction. The selectivities of these cyclizations are different with respect to those observed with a carbonyl tether, and this feature has been rationalized by computational studies. This intramolecular allylation strategy has been successfully applied to the synthesis of various biologically relevant heterocycles, some of them in enantioselective fashion. Finally, domino processes generating the key η^3-allyl palladium intermediate via allene carbopalladation or triggering two consecutive mechanistically unrelated Pd-catalyzed steps have also been successfully developed. Future research on this topic will focus on the development of improved enantioselective versions as well as of new oxidative protocols featuring C−H functionalization.

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Notes

The authors declare no competing financial interest.

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