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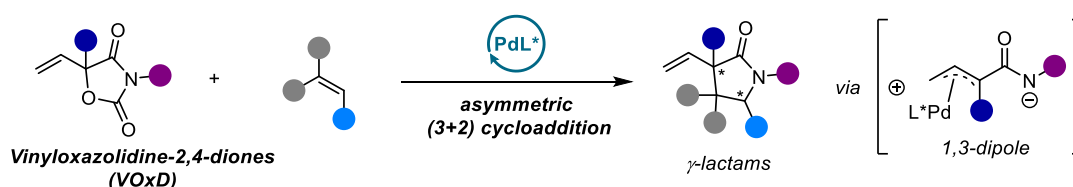
Diastereo- and Enantioselective (3+2) Cycloaddition of a New Palladium-Aza-Oxyallyl Intermediate

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Supporting Information Placeholder



ABSTRACT: Cycloaddition of azaoxyallyl cations or other C–(C=O)–N synthon precursors is a well-established route towards lactams and other *N*-heterocycles but, despite the wide synthetic scope of this approach, enantioselective versions remain scarce. We herein report 5-vinylloxazolidine-2,4-diones (VOxD) as a suitable precursor of chiral palladium-aza-oxyallyl intermediates. In the presence of electrophilic alkenes, (3+2) γ -lactam cycloadducts could be formed with high level of diastereo- and enantioselectivity.

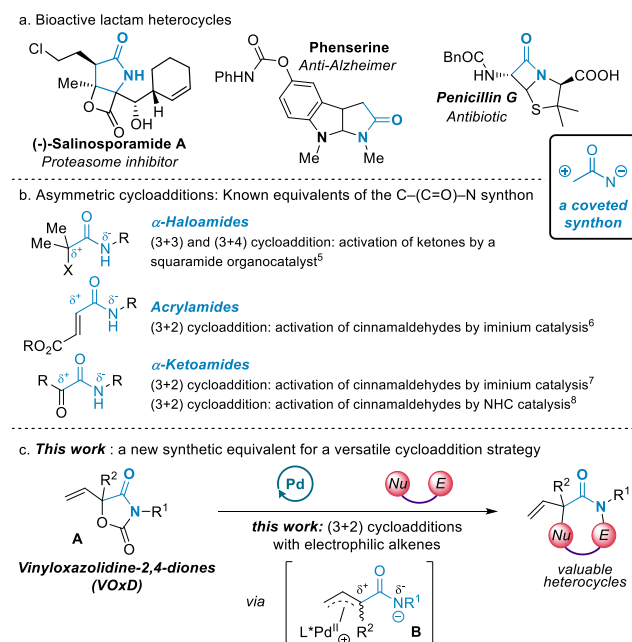
Nitrogen heterocycles are ubiquitous scaffolds in bioactive compounds and can display a wide range of activities.¹ Among them, lactams are a unique class of heterocycles which continue to draw the interest of medicinal chemists and pharmaceutical industries (Scheme 1a).²

A plethora of methods are available to the synthetic chemist who desires to access these heterocyclic structures and cycloadditions, allowing the formation of two σ -bonds in one step,³ naturally emerge as an advantageous strategy. Dipolar cycloadditions of synthetic equivalents of the crucial C–(C=O)–N synthon have therefore attracted considerable interest. While the reactivity of α -haloamides has been widely documented,⁴ only two enantioselective dipolar cycloadditions have been reported and rely on the activation of the electrophilic cycloaddition partner by a squaramide organocatalyst.⁵ The group of Hamada exploited the dipolar properties of acrylamides to design an enantioselective (3+2) cycloaddition based on a chiral iminium activation method.⁶ α -Ketoamides have also been involved as a synthetic equivalent of the same synthon and can act as a nucleophilic cycloaddition partner through the same iminium catalysis approach⁷ or as the electrophilic partner with cinnamaldehydes activated by a chiral NHC catalyst (Scheme 2b).⁸

It is worth pointing out that all these strategies do not rely on the catalytic activation of the C–(C=O)–N synthon's equivalent but rather of the other cycloaddition partner, hampering their generalization to the preparation of other *N*-heterocycles. To answer this shortfall, we envisioned to build on the research interest of group⁹ and develop a cycloaddition involving a π -allyl-Pd^{II} zwitterionic dipolar intermediate. This strategy has drawn considerable interest over the last decade¹⁰ and Pd-stabilized

aza-dipoles have notably been utilized to access various enantioenriched nitrogenated heterocycles in the presence of a chiral palladium ligand.¹¹⁻¹³

Scheme 1. Asymmetric cycloadditions of the C–(C=O)–N synthon.



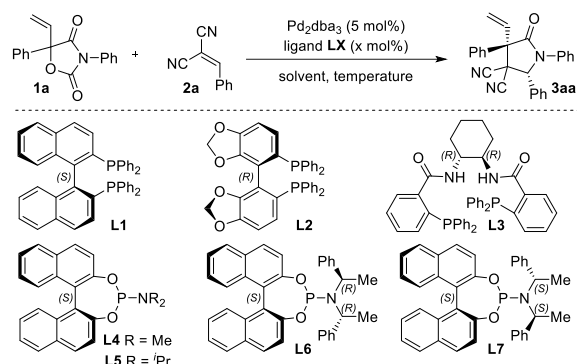
We identified the original vinylloxazolidine-2,4-diones **A** (VOxD, Scheme 1c) as promising new synthetic equivalents of the desired C–(C=O)–N synthon. Under catalysis with a PdL^{*}

complex, an oxidative addition would furnish, after decarboxylation, the putative dipolar intermediate **B** bearing a nucleophilic nitrogen and an electrophilic π -allyl-Pd^{II} moiety. In this manuscript, we report the first use of a VOxD precursors to access relevant γ -lactam heterocycles with high diastereo- and enantioselectivities (Scheme 1c).

After designing a straightforward multi-gram scale preparation of these original starting materials,¹⁴ the feasibility of an asymmetric palladium-catalyzed cycloaddition was explored with vinyloxazolidin-2,4-dione **1a** and 2-benzylidenemalononitrile **2a** as test substrates. During the finalization of this manuscript, the group of Guo also reported the use of VOxD for Pd-catalyzed asymmetric (5+4) and (3+2) cycloadditions.¹⁵

A first screening of chiral ligands was performed (THF, rt) but no reactivity was observed with common diphosphine ligands (Table 1, entries 1-3). Gratifyingly, we then identified phosphoramidites as adequate ligands for this original transformation and (*S*)-**L4** furnished **3aa** in moderate yield and good diastereoselectivity albeit with low enantioselectivity (Table 1, entry 4). The enantioselectivity could be drastically improved using sterically hindered phosphoramidite ligand (*S*)-**L5** derived from diisopropylamine (Table 1, entry 5). After a first screening (Table 1, entries 5-7), toluene was identified as a promising solvent and the enantioselectivity could then be enhanced using the bulkier phosphoramidite (*S,R,R*)-**L6** (Table 1, entry 9, 96:4 *er*) albeit with a sluggish reactivity (41%).

Table 1. Optimization of reaction conditions.^a



Entry	Ligand (x mol%)	Solvent	T (°C)	Yield ^b	<i>dr</i> ^c	<i>er</i> ^d
1	L1 (10 mol%)	THF	rt	0	-	-
2	L2 (10 mol%)	THF	rt	0	-	-
3	L3 (10 mol%)	THF	rt	0	-	-
4	L4 (20 mol%)	THF	rt	54	87:13	51:49
5	L5 (20 mol%)	THF	rt	76	89:11	93:7
6	L5 (20 mol%)	CH ₂ Cl ₂	rt	75	85:15	92:8
7	L5 (20 mol%)	toluene	rt	81	90:10	93:7
8	L5 (20 mol%)	toluene	60	88	88:12	93:7
9	L6 (20 mol%)	toluene	60	41	90:10	96:4
10	L7 (20 mol%)	toluene	60	0	-	-
11	L6 (20 mol%)	<i>o</i> -xylene	60	68	87:13	98:2
12	L6 (24 mol%)	<i>o</i> -xylene	60	95	90:10	96:4
13	L6 (24 mol%)	<i>o</i> -xylene	70	99	90:10	98:2

^aReaction conditions: **1a** (0.075 mmol), **2a** (0.050 mmol), Pd₂dba₃ (5 mol%), ligand **LX** (x mol%) in solvent (0.5 mL, 0.1M) ^b Isolated yield. ^cDetermined by ¹H NMR analysis of the crude product. ^dDetermined by chiral HPLC analysis.

It is worth noting that the diastereomer (*S,S,S*)-**L7** only led to the recovery of starting materials (Table 1, entry 10). Finally, a second screening of solvents furnished **3aa** with better enantioselectivity when the reaction was performed in *o*-xylene (Table 1, entry 11) and a better reactivity was restored by increasing slightly the amount of ligand while working at 70 °C (Table 1, entries 12 and 13).

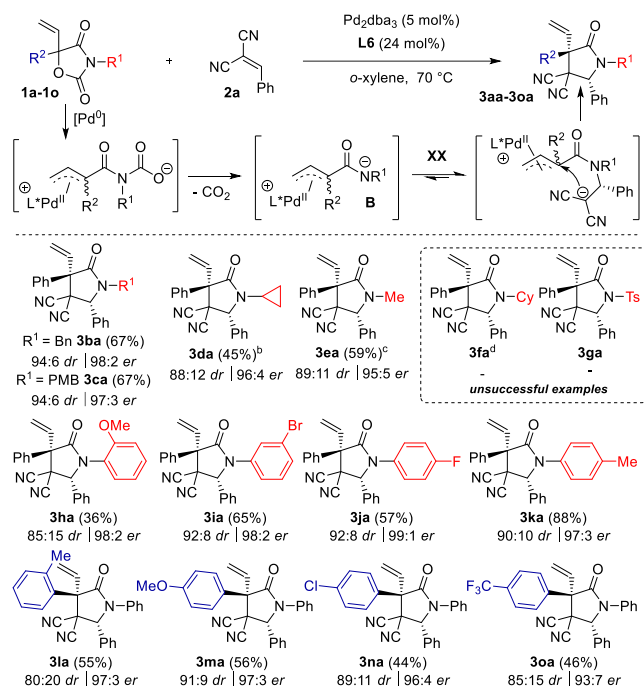
Having these optimized conditions in hand, we first explored the reactivity of VOxD bearing different substituents on the nitrogen atom (R¹ group) as the putative transformation mechanism highlights the critical influence of its electronic properties (Scheme 2). Indeed, an electron withdrawing group will result in a more stabilized zwitterionic intermediate **B**, favoring the decarboxylation step but also diminishing its nucleophilicity. On the other hand, a more nucleophilic intermediate could be formed by installing a more electron-donating R¹ group but its formation would require a more energy demanding decarboxylation process.

When compared to our initial optimization study using **1a** (R¹ = Ph), VOxD **1b** (R¹ = Bn) and **1c** (R¹ = PMB) possess more electron-donating R¹ groups but the corresponding (3+2) cycloadducts **3ba** and **3ca**, respectively, were generated with excellent enantioselectivities under the same reaction conditions. However, no reactivity was observed with VOxD **1d** (R¹ = C₃H₅) and **1e** (R¹ = Me) and increasing the temperature to 90 °C and 110 °C, respectively, was necessary to obtain γ -lactams **3da** (45%) and **3ea** (59%) while retaining a similar stereoselectivity. VOxD **1f** bearing a more electron-donating cyclohexyl group was not found to be a suitable substrate as the decarboxylation step might be hampered even at higher temperatures (*o*-xylene, 130 °C). On the other hand, the decarboxylation step would be favored with VOxD **1g** substituted by an electron-withdrawing tosyl group but the nucleophilicity of the resulting zwitterionic intermediate might be insufficient for the cycloaddition to proceed as cycloadduct **3ga** was not observed.

Vinyloxazolidin-2,4-diones **1h-1k** derived from various anilines (R¹ = Ar) were applicable and similar yields and stereoselectivity were observed. A steric hindrance at this position resulted in a lower yield for the preparation of γ -lactam **3ha** (2-O-MeC₆H₄) while maintaining high level of enantioselectivity (98:2 *er*). To further explore the tolerance of this methodology, different aryl groups were installed at the allylic position. Steric hindrance slightly decreased the diastereoselectivity as γ -lactam **3la** (2-Me) was obtained with a 80:20 diastereoisomeric ratio but we were pleased to observe the enantioselective formation of cycloadducts **3ma** (4-OMe), **3na** (4-Cl) and **3oa** (4-CF₃) bearing electron-withdrawing or donating groups at the *para* position (Scheme 2).

We then began to explore the scope of the electrophilic cycloaddition partner, starting with a variety of benzylidenemalononitrile derivatives. Electron-rich phenyl groups were well tolerated and **3ab**, **3ac** and **3ad** bearing a methoxy group at the *ortho*, *meta* and *para* position, respectively, could be readily obtained from the corresponding activated alkenes with very good enantioselectivities. The presence of electron-withdrawing groups on the aryl group resulted in a slight loss of diastereoselectivity, but excellent enantioselectivities (98:2 *er*) were obtained for the cycloaddition of VOxD **1a** with alkenes **2e** (3-CNC₆H₄) and **2f** (4-CF₃C₆H₄).

Scheme 2. Scope of vinyloxazolidine-2,4-diones.^a

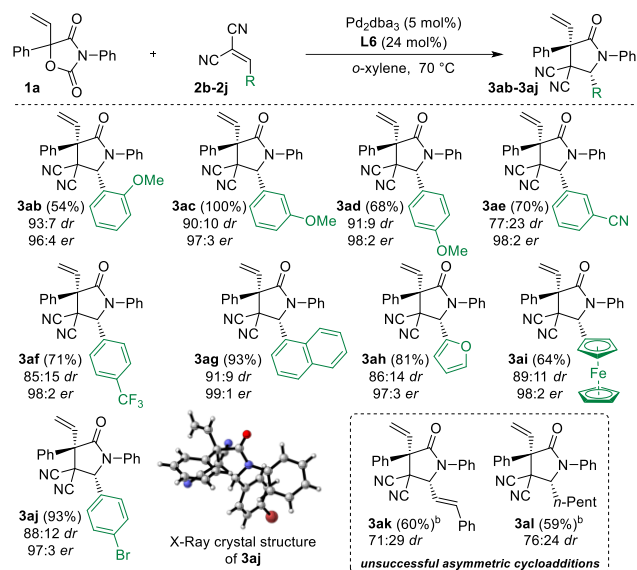


^aReaction conditions: **1a-1o** (0.30 mmol), **2a** (0.20 mmol), Pd₂dba₃ (5 mol%), **L6** (24 mol%), *o*-xylene (2 mL, 0.1M), 70 °C. ^bReaction run at 90 °C. ^cReaction run at 110 °C. ^dReaction run at 130 °C.

The cycloaddition of sterically demanding substrate **2g** was also carried out without loss of stereoselectivity (99:1 *er*) and γ -lactam **3ag** (93%), bearing a 1-naphthyl group, could be easily prepared. This methodology further accommodates the presence of a 2-furyl and a ferrocenyl group as the two corresponding cycloadducts **3ah** (81%, 97:3 *er*) and **3ai** (64%, 98:2 *er*) were isolated with excellent enantioselectivities. Finally, (3+2) cycloadduct **3aj** (93%), bearing a *para*-bromo-phenyl moiety, was prepared (97:3 *er*) and its absolute configuration was determined by single-crystal X-ray analysis.¹⁵ Throughout our study, we also examined the reactivity of cinnamylidene and alkylidene malononitriles **2k** and **2l**, respectively. In both cases, we were able to prepare the corresponding racemic cycloadducts, but a complex mixture was unfortunately obtained under the optimized conditions with chiral phosphoramidite ligands **L6** or **L4** (Scheme 3).

To continue our investigation for other suitable electrophiles, we involved benzylidene **4a** derived from indane-1,3-dione and benzaldehyde. Under the same optimized conditions (**L6**, *o*-xylene, 70 °C), the expected spiro- γ -lactam **7aa** (65%, 91:9 *dr*) was isolated with high enantioselectivity (98:2 *er*) and a variety of other benzylidenes were successfully engaged under these conditions. Electron-rich and electron-poor substituents were well-tolerated at the *para* position and spirocycloadducts **7ab** (4-OMe) and **7ac** (4-CF₃) were generated with excellent enantioselective ratios.

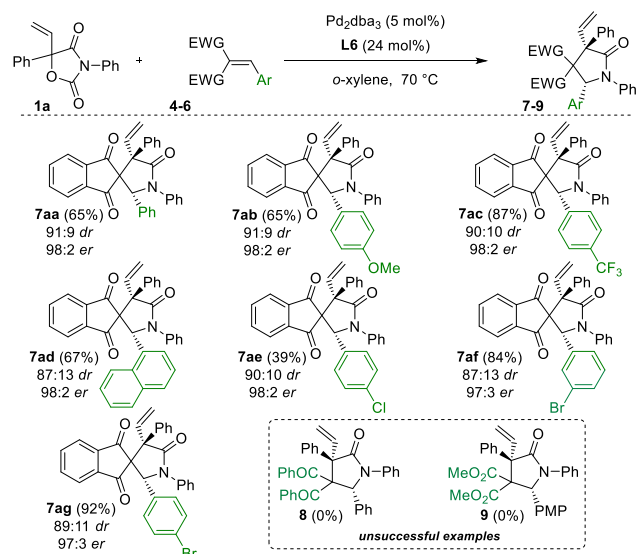
Scheme 3. Cycloadditions of benzylidenemalononitriles.^a



^aReaction conditions: **1a** (0.30 mmol), **2b-2j** (0.20 mmol), Pd₂dba₃ (5 mol%), **L6** (24 mol%), *o*-xylene (2 mL, 0.1M), 70 °C. ^bPPh₃ was used as the ligand.

This strategy also allowed the preparation of sterically hindered lactam **7ad** bearing a 1-naphthyl group. Halogen atoms are susceptible to tempering the course of the transformation as a competitive oxidative addition of the palladium(0) catalyst can occur but benzylidenes **4e** (4-Cl), **4f** (3-Br) and **4g** (4-Br) were converted in moderate to good yields to the corresponding (3+2) γ -lactams cycloadducts. The reactivity of less activated alkenes **5** (EWG = C₆H₅) and **6** (EWG = CO₂Me) was also examined but these substrates have proven to be unreactive under the optimized conditions (Scheme 4).

Scheme 4. Scope of other C=C acceptors.^a

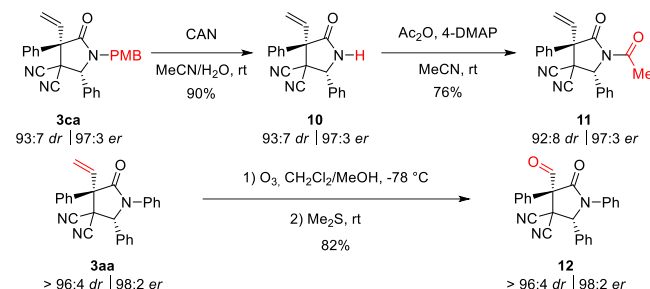


^aReaction conditions: **1a** (0.30 mmol), **4-6** (0.20 mmol), Pd₂dba₃ (5 mol%), **L6** (24 mol%), *o*-xylene (2 mL, 0.1M), 70 °C.

Finally, we demonstrated the utility of our method by performing further synthetic transformations. After its preparation on a

mmol scale, the deprotection of γ -lactam **3ca**, bearing a *para*-methoxybenzyl group (CAN, MeCN/H₂O) afforded the free amide **10** (90%) with an unaltered enantiomeric ratio of 97:3. Under usual conditions (Ac₂O, 4-DMAP), this latter can subsequently lead to the enantioenriched acetylated product **11** which could not be directly attained with our strategy. Finally, the ozonolysis of γ -lactam **3aa** afforded efficiently aldehyde **12** without deterioration of the enantiomeric ratio. (Scheme 5).

Scheme 5. Further synthetic transformations.



In summary, we have developed a straightforward synthesis of original vinyloxazolidine-2,4-diones (VOxD) which have been engaged in enantioselective (3+2) cycloadditions towards γ -lactams under palladium catalysis. This study establishes VOxD as versatile synthetic equivalents of the ubiquitous C-(C=O)-N synthon in asymmetric cycloaddition reactions and further studies are ongoing in our laboratory to better understand and exploit their reactivity with other cycloaddition partners.

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(16) XRD analysis of **1a**: 2243998; XRD analysis of **3aj**: 2243999; XRD analysis of *rac*-**(7aa)**: 2244000.