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# Domino Synthesis of α,β-Unsaturated γ-Lactams via Stereo-selective Amination of α-Tertiary Allylic Alcohols

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Abstract: Tertiary allylic alcohols equipped with a carboxyl group can be smoothly aminated under ambient conditions via a conceptually new and stereoselective protocol under Pd catalysis. The *in situ* formed (*Z*)-configured γ-amino acid cyclizes to afford an α,β-unsaturated γ-lactam releasing water as the only by-product. This practical catalytic transformation highlights the use of a carboxyl group acting as a hydrogen donor, stereodirecting and functional group to provide a wide series of pharma-relevant building blocks. Various control reactions support the crucial role of a carboxyl group in the substrate to mediate these transformations.

Allylic substitution reactions mediated by transition metal catalysts are prominent in the area of synthetic chemistry providing convenient access to more complex target molecules via C−C and C−X (X = N, O, S) bond formation reactions.[1] More recent focus in this area features allylic alcohols as relatively unactivated and more ubiquitous substrates as to increase both the atom and step economy of the allylic substitution process.[2] Despite the attractiveness of using allylic alcohols as more environmentally benign substrates, the poor leaving group ability of the alcohol group renders the allylic substitution process more challenging. As such, often the use of a protic solvent such as MeOH or water, the presence of Lewis/Brøndsted additives and/or elevated temperatures are required for efficient turnover.[3]

In the realm of allylic substitution chemistry, allylic amination[4] has been intensively studied as the resultant amines are valuable synthons in natural product synthesis and bioactive molecules.[5] We have recently developed both stereo-[6] as well as enantioselective protocols[7] for challenging highly substituted allylic amines. Key to the success of these latter approaches was the presence of an activated allylic surrogate. We wondered whether direct amination of suitable allylic alcohol substrates would be feasible via a conceptually novel activation approach (Scheme 1) using a stereo-directing group. Inspired by previous work on allylic amination from Ozawa[8a-b] and Samec[8c] revealing a transient Pd hydride species, we hypothesized that an allylic alcohol substrate with a carboxyl group (Scheme 1) could generate a Pd hydride via oxidative addition to a suitable Pd(0) precursor.[9] This should allow for the formation of a palladacyclic intermediate that incorporates the requisite stereochemistry for efficient cyclization towards a γ-lactam product[10] via amination[11] of the terminal position of the Pd(allyl) species. These α,β-

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unsaturated γ-lactams are highly attractive scaffolds as they form part of a wide range of bioactive compounds (Scheme 1, below)[12] and are valuable precursors to pyrroles and γ-lactams.[13]
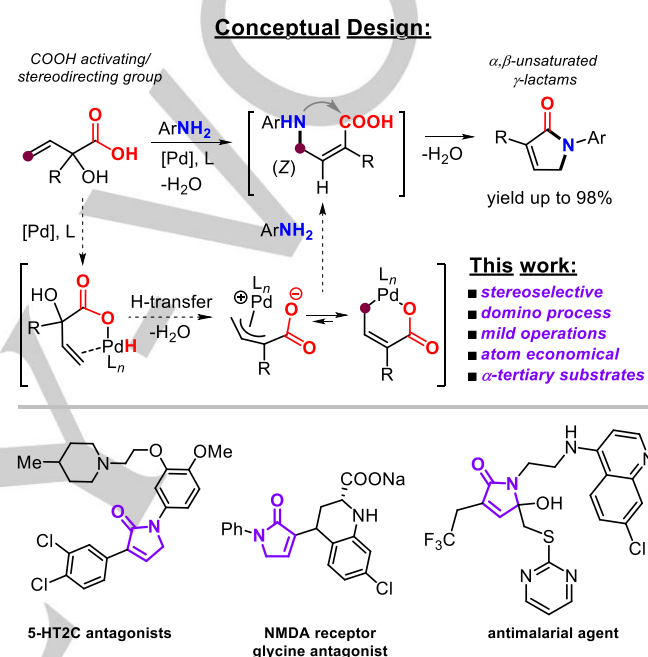
Scheme 1. Conceptual design towards a domino process converting α-tertiary allylic alcohols into α,β-unsaturated γ-lactams under Pd catalysis. Below selected examples of bioactive compounds with an unsaturated-γ-lactam core.

A few challenges in this envisioned manifold need to be addressed, including the rarely developed stereocontrolled conversion of α-tertiary allylic alcohols,[14] and the use of mild reaction conditions to reduce the intrinsic risk of parasitic decarboxylative pathways. Here we demonstrate that such a conceptual approach offers a novel and practical way for allylic alcohol conversion into valuable synthetic building blocks under ambient conditions.

First, the required substrates were designed and these could be readily prepared from α-keto acids and vinyl Grignard reagents affording in good yields the desired vinyl glycolic acids (see the Supporting Information, SI, for details). Allylic alcohol **A** was selected towards screening of appropriate reaction conditions and Pd/ligand combinations (Table 1) leading to the formation of γ-lactam **1a**. The use of a Pd(II) precursor (entries 1−2) proved to be rather unproductive.

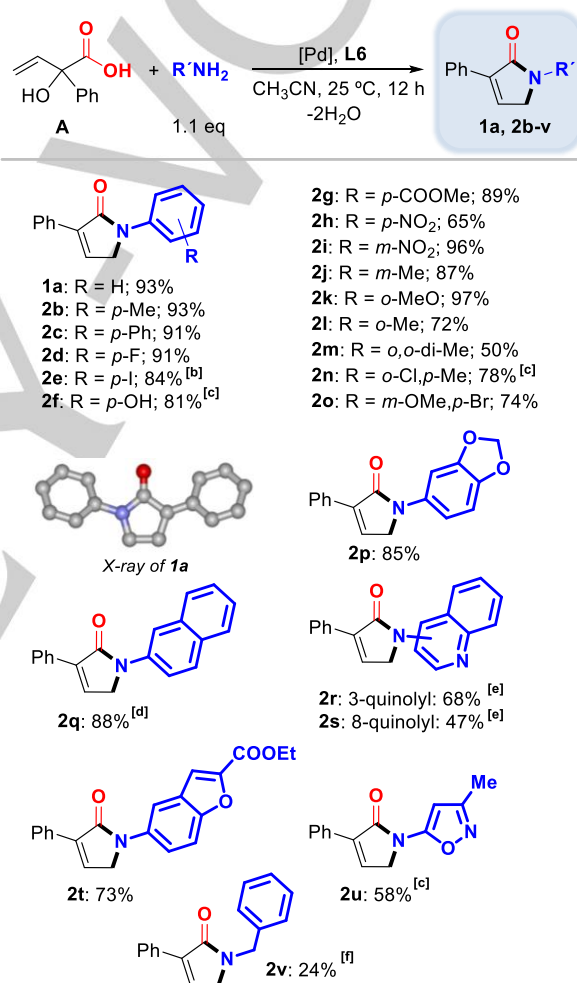**Table 1.** Pd-mediated conversion of COOH-substituted α-tertiary allylic alcohol **A** under various conditions.[a]

Entry	L	[Pd]	Solv. [1 M]	Yield of 1a[b]	Sel.[c] 1a:1b
1	**L1**	Pd(OAc)$_2$	CH$_3$CN	10	96/4
2	**L1**	[allylPdCl]$_2$	CH$_3$CN	0	–
3	**L1**	Pd$_2$(dba)$_3$·CHCl$_3$	CH$_3$CN	45	98/2
4	**L1**	Pd$_2$(dba)$_3$·CHCl$_3$	THF	14	76/24
5	**L1**	Pd$_2$(dba)$_3$·CHCl$_3$	DMF	21	100/0
6	**L1**	Pd$_2$(dba)$_3$·CHCl$_3$	DMSO	34	83/17
7	**L1**	Pd$_2$(dba)$_3$·CHCl$_3$	MeOH	25	93/7
8	**L1**	Pd$_2$(dba)$_3$·CHCl$_3$	CH$_2$Cl$_2$	30	99/1
9	**L1**	Pd$_2$(dba)$_3$·CHCl$_3$	EtOAc	12	98/2
10	**L1**	Pd$_2$(dba)$_3$·CHCl$_3$	Toluene	22	98/2
11	**L2**	Pd$_2$(dba)$_3$·CHCl$_3$	CH$_3$CN	5	–
12	**L3**	Pd$_2$(dba)$_3$·CHCl$_3$	CH$_3$CN	trace	–
13	**L4**	Pd$_2$(dba)$_3$·CHCl$_3$	CH$_3$CN	7	79/21
14	**L5**	Pd$_2$(dba)$_3$·CHCl$_3$	CH$_3$CN	18	87/13
15	**L6**	Pd$_2$(dba)$_3$·CHCl$_3$	CH$_3$CN	79	98/2
16	**L7**	Pd$_2$(dba)$_3$·CHCl$_3$	CH$_3$CN	trace	–
17	**L8**	Pd$_2$(dba)$_3$·CHCl$_3$	CH$_3$CN	trace	–
18	**L9**	Pd$_2$(dba)$_3$·CHCl$_3$	CH$_3$CN	8	–
19	**L10**	Pd$_2$(dba)$_3$·CHCl$_3$	CH$_3$CN	5	–
20[d]	**L6**	Pd$_2$(dba)$_3$·CHCl$_3$	CH$_3$CN	95	97:3
21[d,e]	**L6**	Pd$_2$(dba)$_3$·CHCl$_3$	CH$_3$CN	95	97:3
22	**L6**	–	CH$_3$CN	0	–

[a] Conditions: **1a** (0.15 mmol), aniline (0.23 mmol, 1.5 equiv), solvent (0.15 mL), Pd$_2$(dba)$_3$·CHCl$_3$ (0.003 g, 2.0 mol%), **L** (4.0 mol%), 25 °C. [b] By ^{1}H NMR (CDCl$_3$) using toluene as internal standard. [c] By ^{1}H NMR. [d] **L6** (5 mol %). [e] Aniline (1.1 equiv).

The use of a Pd(0) precursor (entries 3) showed a significant improvement in the yield of **1a** at only 25 °C, and the best solvent turned out to be acetonitrile (entry 3; 45% yield, **1a:1b** = 98:2). The use of other solvents showed in several cases significant formation of **1b** that is formed after decarboxylation following an aza-Michael addition (see SI for details). Other ligands (**L2–L10**, entries 11–19) were then probed, and the use of **L6** (dppf; entry 15) showed an encouraging increase in the yield of **1a** to 79%. The optimized conditions for the formation of **1a** were achieved by further increasing the amount of **L6** to 5 mol% and reducing the amount of aniline to 1.1 equiv (entry 21). The presence of a Pd catalyst was crucial as no conversion of substrate **A** was noted in its absence (entry 22). Under the optimized conditions, the synthesis of **1a** could be easily scaled up to gram quantities (see SI for details).


Figure 1. Scope in α,β-unsaturated γ-lactams using various (hetero)aromatic amines as coupling partners.

[a] Conditions: **A** (0.15 mmol), aniline (1.1 equiv), CH$_3$CN (0.15 mL), Pd$_2$(dba)$_3$·CHCl$_3$ (2.0 mol%), **L6** (5.0 mol%), 25 °C, 12 h; yields are of the isolated products. [b] 18 h. [c] By ^{1}H NMR. [d] CH$_3$CN (0.30 mL). [e] 50 °C, 24 h. [f] Using 50 mol% CF$_3$COOH as additive.

With the optimized conditions in hand, we then examined the scope in reaction partners and first varied the nature of the amine

substrate (Figure 1).[15] Various anilines with *para*-, *meta*, and *ortho*-substituents proved to be productive substrates giving clean access to the γ-lactam products (**1a**, **2b–2o**; **1a** characterized by X-ray analysis)[16] in typically appreciable to high isolated yields. The introduction of phenolic or aryl iodide groups in the lactam product is tolerated as exemplified by the successful isolation of product **2e** and **2f**, which have the potential for late stage modification towards the formation of biologically active compounds. Anilines with *para* electron-withdrawing groups or with a double *ortho*-substitution gave, as expected, somewhat lower yields (**2h**; 65% and **2m**; 50%). Interestingly, the developed protocol also tolerated the introduction of various other aromatic/heterocyclic fragments as illustrated by the synthesis of derivatives **2p–2u**, although in some of these latter cases a higher reaction temperature (50 ºC) and/or longer reaction time was required. Product **2s** incorporates a useful 8-quinolyl fragment, which is frequently utilized as a directing group in C-H functionalization. Finally we also attempted the use of alkyl amines, and while preliminary reactions showed that these easily become protonated and formation of the desired lactam is subsequently blocked,[15] addition of sub-stoichiometric amounts of a Brøndsted acid (CF₃COOH; **2v**, 24%) allows for some product formation.
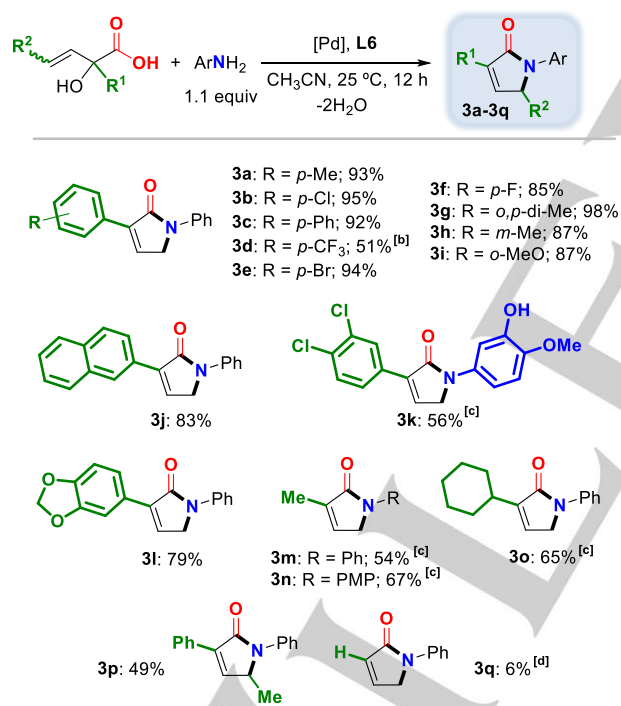

[a] Conditions unless stated otherwise: allylic alcohol (0.15 mmol), aniline (1.1 equiv), CH₃CN (0.15 mL), Pd₂(dba)₃·CHCl₃ (2.0 mol%), **L6** (5.0 mol%), 25 ºC, 12 h. Yields of the isolated products are reported. [b] 36 h. [c] Using DMF (0.15 mL) as solvent at 70 ºC. PMP = *p*-MeO-phenyl. [d] 70 ºC, 100% conversion, NMR yield of **3q**.

Figure 2. Scope in α,β-unsaturated γ-lactams using various allylic alcohols as coupling partners.

Upon variation of the substituent of the α-tertiary allylic alcohol, a further amplification of lactam products could be easily realized

(Figure 2; products **3a–3q**.[17] The installation of a bulky naphthyl group (**3j**) or a heterocycle (**3l**) in the lactam was feasible, while the conversion of the CF₃-substituted allylic alcohol (cf., synthesis of **3d**) required a longer reaction time. In the case of the alkyl-substituted substrate congeners (cf., preparation of **3m–3o**), the use of DMF at elevated temperature was required to maintain a homogeneous reaction medium. The use of a γ-substituted tertiary allylic alcohol also afforded the desired lactam product (R^1 = Ph, R^2 = Me; **3p**, 49%) though the use of a secondary allylic alcohol ($R^1 = R^2$ = H; **3q**) at rt showed no conversion. A higher reaction temperature was needed (70 ºC), though a complex mixture was obtained and the lactam derivative was formed in only 6% yield.
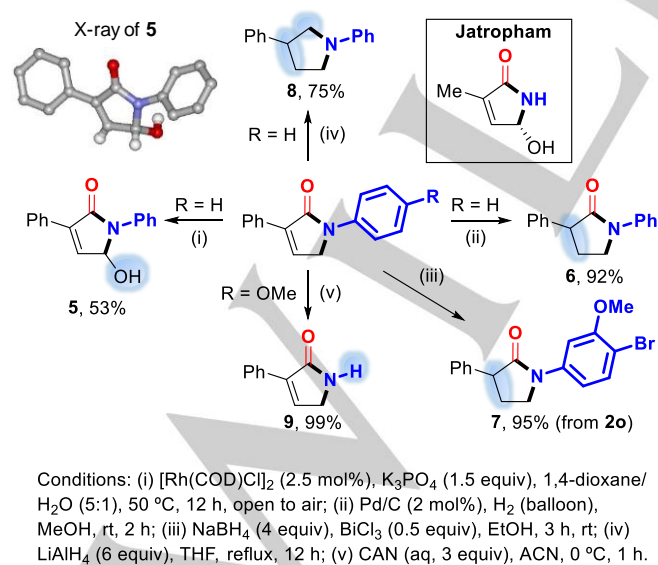
In order to support the mechanistic scenario displayed in Scheme 1, a number of control experiments were conducted (Scheme 2). First, various substitutions were examined in the allylic substrate (Scheme 2a), showing the crucial role of a carboxyl group in **A** (Figure 1) to accommodate the conversion of the allylic substrate under ambient conditions. The replacement of the COOH for an ester, amide, methyl, alcohol or strong electron-withdrawing CF₃ group did not lead to any observable conversion, whereas allylic alcohol protection still provided 60% yield of the lactam derivative **1a**. Further to this, in the presence of 1 equiv of base (Scheme 2b; Cs₂CO₃) also no conversion of **A** could be achieved, further affirming the key role of the free carboxyl group within the substrate.
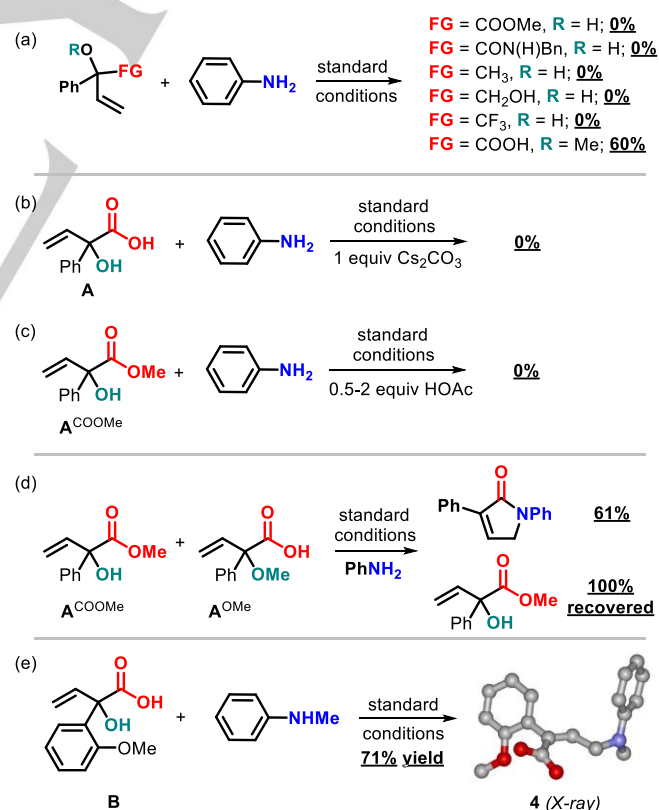
Scheme 2. Mechanistic control experiments to support the manifold proposed in Scheme 1. The standard conditions relate to entry 21 in Table 1.

The influence of the presence of (sub)stoichiometric amounts of a Brønsted acid (Scheme 2c) using methyl-ester **A**[COOMe] was also examined. However, no conversion was noted in the presence of 0.5–2 equiv HOAc as additive. An additional competition experiment involving a 1:1 mixture of the methyl-ester **A**[COOMe] and the alcohol-protected substrate **A**[OMe] showed only conversion of the latter: the ester derivative **A**[COOMe] was quantitatively recovered (Scheme 2d). Both reactions illustrate that intermolecular COOH⋯OH hydrogen-bond activation does not play any significant role in the conversion of the allylic substrate.[18] Crystallographic analysis[16] of allylic substrate **A** (see the SI for full details) revealed no productive H-bonding to account for intramolecular allylic alcohol activation. Various spectroscopic control experiments (see the SI) were conducted to investigate intramolecular solution phase hydrogen bonding but no conclusive confirmation of a requisite HO⋯HO-C(O) interaction could be established.[19] Finally, a secondary aniline (Scheme 2e) was tested in the allylic amination of **B** providing in 71% yield the unsaturated γ-amino acid (*Z*)-**4** in support of the proposed mechanism presented in Scheme 1.[20]

We further explored the synthetic utility of these lactam scaffolds through a series of site-selective post-modifications (Scheme 3). A Rh-mediated oxidative CH functionalization[21] of **1a** afforded **5** in 53% yield, and the identity of the product was unambiguously confirmed by X-ray analysis.[16] Hydrogenation of **1a** using Pd/C as catalyst gave clean access to **6** (92%), while the use of a different reducing medium (NaBH₄/BiCl₃) for more functional **2o** provided **7** in 95% yield. Pyrrolidine **8** could be prepared in 75% by reducing **1a** in the presence of LiAlH₄, and finally deprotection of the *N*-PMP protected lactam **3n** in the presence of cerium ammonium nitrate (CAN) gave the free lactam **9** in good yield. It should be further noted that products **3n**, **3k** and **7** are considered useful entries towards the formation of bioactive lactams Jatropham (Scheme 3),[21] the 5-HT2C-antagonist in Scheme 1,[22] and therapeutic agents for neurological disorders,[23] respectively.

Conditions: (i) [Rh(COD)Cl]₂ (2.5 mol%), K₃PO₄ (1.5 equiv), 1,4-dioxane/H₂O (5:1), 50 ºC, 12 h, open to air; (ii) Pd/C (2 mol%), H₂ (balloon), MeOH, rt, 2 h; (iii) NaBH₄ (4 equiv), BiCl₃ (0.5 equiv), EtOH, 3 h, rt; (iv) LiAlH₄ (6 equiv), THF, reflux, 12 h; (v) CAN (aq, 3 equiv), ACN, 0 ºC, 1 h.

Scheme 3. Post-synthetic potential of the α,β-unsaturated γ-lactam scaffolds.

In summary, we here disclose a user-friendly, mild and attractive protocol for direct and stereoselective amination of allylic alcohols to afford synthetically useful α,β-unsaturated γ-lactams using readily available substrates. Key to the observed and unique reactivity is the presence of a free, carboxyl group in the substrate that allows for Pd-mediated activation of the allylic alcohol under ambient conditions. This new activation mode therefore holds great promise for a wider range of stereoselective allylic substitutions reactions under sustainable reaction conditions.

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[15] Note that the use of aliphatic amines is not well-tolerated as mainly deprotonation (as observed) of the carboxyl group takes place. Other nucleophiles were also scrutinized (H_2O, PhOH, Ts-NH_2 and PhC(O)NH_2) but were ineffective towards lactam formation, see the SI for further details.

[16] See for details the SI, and CCDC 1858452–1858454, and 1865708.

[17] For the synthesis of the allylic alcohol substrates, see the SI.

[18] Benzoic acid was previously reported to act as an activator in the amination of allylic alcohols, see reference 3j.

[19] The occurrence of some degree of requisite HO···HOOC hydrogen bonding in solution cannot be fully ruled out, despite that such interactions are not observed in the solid state. See the X-ray analysis of **A** and related comments in the SI.

[20] Control experiments (see the SI) rule out that an (*E*)-configured product is first formed, following equilibration to its (*Z*) isomer. (Allyl)Pd complexes derived from α,β-unsaturated ketones and esters and their stoichiometric reactions with various nucleophiles were reported by Jackson et al., see: W. R. Jackson, J. U. Strauss, *Austr. J. Chem.* **1977**, *30*, 553-562. Under Pd-catalysis, the ester derivatives showed preference for the formation of (*E*)-configured products, in line with the crucial role of the carboxyl group in our tertiary allylic alcohol substrates.

[21] L.-W. Liu, Z.-Z. Wang, H.-H. Zhang, W.-S. Wang, J.-Z. Zhang, Y. Tang, *Chem. Comm.* **2015**, *51*, 9531-9534.

[22] N. J. Stam, P. Vanderheyden, C. van Alebeek, J. Klomp, T. de Boer, A. M. van Delft, W. Olijve, *Eur. J. Pharmacol.* **1994**, *269*, 339-348.

[23] B. Blass, *ACS Med. Chem. Lett.* **2015**, *6*, 1092-1094.

Entry for the Table of Contents:

COMMUNICATION

One, two, lactam! A domino synthesis of unsaturated γ-lactams is reported via a Pd-catalyzed amination of allylic alcohols. An intramolecular carboxyl group acts as a stereodirecting functional group, enabling the formation of (*Z*) configured γ-amino acids following cyclization towards the targeted lactam scaffolds. This protocol is atom-efficient and mild, and highlights a new way of allylic alcohol activation under ambient conditions.
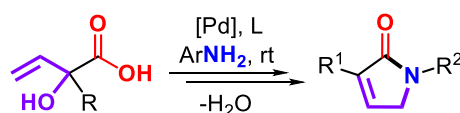
- *stereoselective*
- *>35 examples*
- *yield up to 98%*
- *domino process*
- *ambient conditions*

Jianing Xie, Sijing Xue, Eduardo C. Escudero-Adán and Arjan W. Kleij*

Domino Synthesis of α,β-Unsaturated γ-Lactams via Stereoselective Amination of α-Tertiary Allylic Alcohols