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Asymmetric Synthesis of α-Quaternary γ-Lactams through Palladium-Catalyzed Asymmetric Allylic Alkylation

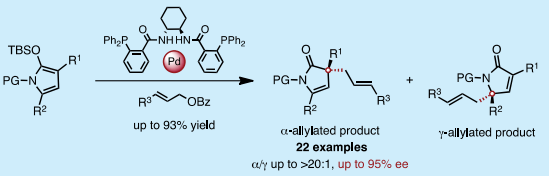
Tao Song,[†] Stellios Arseniyadis,*[,†,‡] and Janine Cossy*[,†]

[†]Laboratoire de Chimie Organique, Institute of Chemistry, Biology and Innovation (CBI), ESPCI Paris/CNRS/PSL Research University, 10 rue Vauquelin, 75231 Paris Cedex 05, France

[‡]Queen Mary University of London, School of Biological and Chemical Sciences, Mile End Road, London, E1 4NS, U.K.

Supporting Information

ABSTRACT: The synthesis of chiral unsaturated γ-lactams is reported featuring a highly enantioselective palladium-catalyzed asymmetric allylic alkylation of α,γ-disubstituted 2-silyloxypyrroles. This method allows a straightforward access to optically active γ-lactams bearing an α-quaternary stereogenic center in high yields (up to 93%), high regioselectivities (up to >20:1), and excellent enantioselectivities (up to 95% *ee*). To further demonstrate the synthetic utility of the method, the resulting allylated products were converted to various versatile chiral building blocks, such as pyrrolidines and pyrrolidinones.



Nitrogen-containing heterocycles are very important structural units in nature. Among them, γ-lactams are arguably among the most prevalent, as they are ubiquitous in many biologically active natural products and pharmaceuticals[1,2] such as (−)-pramanicin,[2a,b] azaspirene,[2c−f] (+)-lactacystin,[2g−k] and (−)-salinosporamide[2l] just to name a few (Figure 1).

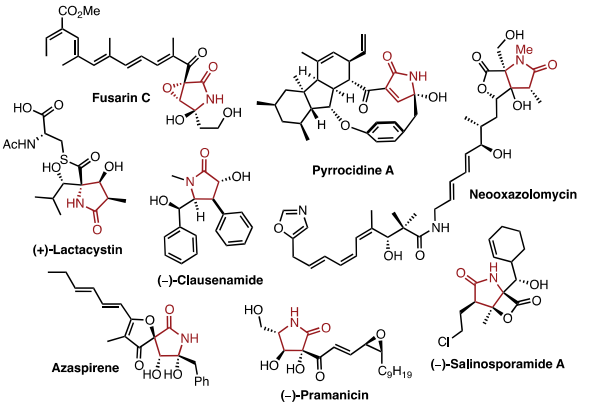


Figure 1. Typical examples of γ-lactam-containing natural products and pharmaceuticals.

In view of the plethora of compounds that bear this intriguing chiral motif and the interesting biological activities displayed, a tremendous amount of effort has been dedicated to the development of efficient and highly selective methods to construct diversely substituted γ-lactams.[1−3] These methods include for example the cyclization of chiral γ-amino acids, the ring expansion of substituted β-lactams, and the transition-metal-catalyzed intramolecular carbenoid C−H insertion.

The functionalization of γ-butyrolactams is another important strategy to access chiral lactam derivatives. This approach usually involves the use of *N*-protected α,β-unsaturated γ-butyrolactams[4] or 2-silyloxypyrroles[5,6] as precursors. In view of the literature in the field, a number of methods have been developed to access optically active lactams bearing a tertiary stereogenic center at the α- or γ-position; these include asymmetric vinylogous Michael additions,[7] Mukaiyama Mannich-type additions,[8] or aldol reactions.[9] In contrast, asymmetric construction of γ-lactams bearing a quaternary stereogenic center is rather scarce.[10−12] Moreover, there are only a few asymmetric methods which allow a straightforward and highly enantioselective access to γ-lactams bearing a quaternary stereogenic center at either the α- or γ-position. One of them is the direct enantioselective vinylogous Michael addition on α,β-unsaturated γ-lactam using phase-transfer catalysis, which allows γ,γ′-disubstituted γ-lactams to be accessed in high yields and excellent enantioselectivities (Scheme 1A).[13]

Another approach involves the use of dimeric cinchona alkaloids to catalyze the enantioselective sulfenylation of β,γ-unsaturated γ-lactams, which affords highly functionalized γ-lactams bearing a quaternary stereogenic center in high yields and excellent enantioselectivities (Scheme 1B).[14]

Optically active γ-lactams can also be prepared through a Ni-catalyzed enantioselective *C*-acylation of an α-substituted γ-lactam. The process, which is formally a three-component coupling reaction involving a lithium enolate, a benzonitrile, and an aryl halide, allows the formation of the corresponding β-keto γ-lactams in high yields and excellent enantioselectivities (up to 94% *ee*) (Scheme 1C).[15]

Finally, a decarboxylative Pd-AAA strategy was reported by Stoltz et al. for the synthesis of not only five- but also six- and seven-membered ring lactams bearing a quaternary stereogenic center (Scheme 1D).[16]

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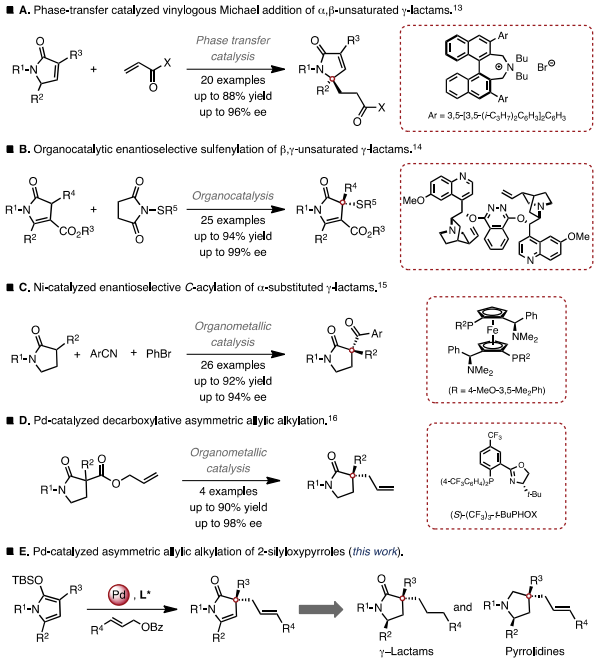
Scheme 1. Selected Strategies for the Asymmetric Synthesis of Chiral γ-Lactams Bearing a Quaternary Stereogenic Center



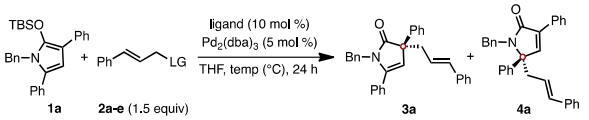
Based on our previous results on the asymmetric synthesis of optically active heterocyclic scaffolds through palladium-catalyzed asymmetric allylic alkylation (Pd-AAA),[17] and precedents in the field,[18] we envisioned that optically active γ-lactams could potentially be accessed using a similar strategy starting from α,γ-disubstituted 2-silyloxypyrroles (Scheme 1E). Indeed, if this approach was successful, it would allow a straightforward and potentially highly enantioselective access to this important scaffold.

We chose to initiate our study using *N*-benzyl-3,5-diphenyl-2-silyloxypyrrole **1a** as a model substrate. The latter was prepared in four steps and 50% overall yield starting from chalcone (see Supporting Information for more details). With this compound in hand, we started by exploring the influence of each reaction parameter on the reactivity, regioselectivity, and enantioselectivity of the reaction; the results are depicted in Table 1.

The first parameter to be evaluated was the leaving group on the allyl donor, as it had previously been shown to influence both the reactivity and enantioselectivity in Pd-[18] and Ir-catalyzed[19] asymmetric allylic alkylations. The original reaction was run in THF at rt using cinnamyl acetate, and the catalytic system was comprised of $Pd_2(dba)_3$ (5 mol %) and Trost's ligand (*R*,*R*)-**L$_1$** (10 mol %), which gave the best results in all of the Pd-AAA reactions we attempted.[16] Unfortunately, under these conditions, no product was observed even after 36 h (Table 1, entry 1). In order to improve the reactivity, we decided to run the reaction at 60 °C under otherwise identical conditions, and luckily we were able to isolate **3a** albeit in only 17% yield and 33% *ee* (Table 1, entry 2). To improve the selectivity, we ran the same reaction using 1.0 equiv of NaOAc. After 22 h, all of the starting material had been converted to the corresponding α- and γ-allylated products **3a** and **4a** in a 3.8:1 ratio in favor of **3a**. Unfortunately, the α-allylated product was obtained in only 20% *ee* (Table 1, entry 3). This erosion of the selectivity can potentially be attributed to a higher concentration of the lactam enolate. Four additional allyl donor derivatives including the methyl carbonate **2b** (Table 1, entry 4), the diethylphosphonate **2c** (Table 1, entry 5), the *tert*-butyl carbonate **2d** (Table 1, entry 6), and the benzoate **2e** (Table 1, entry 7) were tried under the aforementioned conditions. The latter afforded the desired α-allylated product **3a** in an improved 76% yield and 58% *ee*. Most importantly, the reaction could be run at rt with roughly the same outcome in terms of both yield and enantioselectivity (Table 1, entry 8). Interestingly, the reaction with $[Pd(allyl)Cl]_2$ instead of $Pd_2(dba)_3$ was more sluggish and far less selective (Table 1, entry 9).

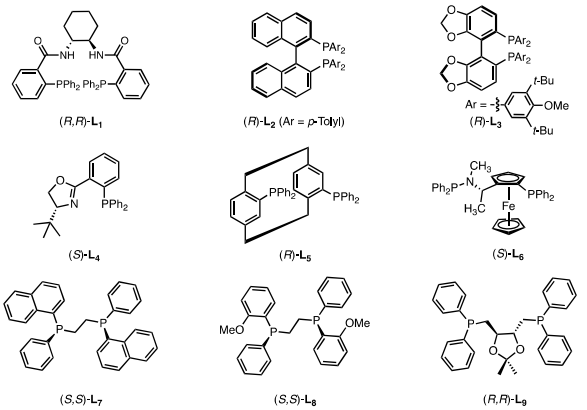
The influence of the solvent was next evaluated (results not shown in Table 1). As a general trend, ethers such as THF

Table 1. Systematic Study[a]



entry	ligand	LG	temp (°C)	3a/4a[b]	3a, Yield[c] (%)	3a, *ee*[d] (%)
1	(*R*,*R*)-**L1**	OAc	rt	-	-	-
2	(*R*,*R*)-**L1**	OAc	60	13:1	17	33
3[e]	(*R*,*R*)-**L1**	OAc	60	3.8:1	76	20
4	(*R*,*R*)-**L1**	OCO_2Me	60	2.6:1	40	25
5	(*R*,*R*)-**L1**	$OPO(OEt)_2$	60	2:1	24	20
6	(*R*,*R*)-**L1**	OBoc	60	5.5:1	58	–3
7	(*R*,*R*)-**L1**	OBz	60	3.5:1	76	58
8	(*R*,*R*)-**L1**	OBz	rt	3.4:1	75	58
9[f]	(*R*,*R*)-**L1**	OBz	rt	3:1	46	35
10	(*R*)-**L2**	OBz	rt	3.9:1	62	17
11	(*R*)-**L3**	OBz	rt	>20:1	23	19
12	(*S*)-**L4**	OBz	rt	>20:1	99	–16
13	(*R*)-**L5**	OBz	rt	1.4:1	57	–3
14	(*S*)-**L6**	OBz	rt	>20:1	99	19
15	(*S*,*S*)-**L7**	OBz	rt	>20:1	85	26
16	(*S*,*S*)-**L8**	OBz	rt	>20:1	99	6
17	(*R*,*R*)-**L9**	OBz	rt	5.6:1	84	5
18	(*R*,*R*)-**L1**	OBz	0	4.5:1	68	74
19	(*R*,*R*)-**L1**	OBz	–20	12:1	73	82
20[g]	(*R*,*R*)-**L1**	OBz	–30	12:1	89	84
21[h,i]	(*R*,*R*)-**L1**	OBz	–30	6:1	59	84
22[h,j]	(*R*,*R*)-**L1**	OBz	–30	6:1	27	74

[a]All reactions were run on a 0.2 mmol scale. [b]Determined by ^1H NMR on the crude reaction mixture. [c]Isolated yield. [d]Determined by supercritical fluid chromatography (SFC) analysis. [e]Reaction run with 1.0 equiv of NaOAc. [f]Reaction run with $[Pd(allyl)Cl]_2$ instead of $Pd_2(dba)_3$. [g]Reaction run for 45 h. [h]Reaction run for 65 h. [i]Reaction run with 2.5 mol % of $Pd_2(dba)_3$ and 5 mol % of (*R*,*R*)-**L1**. [j]Reaction run with 1 mol % of $Pd_2(dba)_3$ and 3 mol % of (*R*,*R*)-**L1**.



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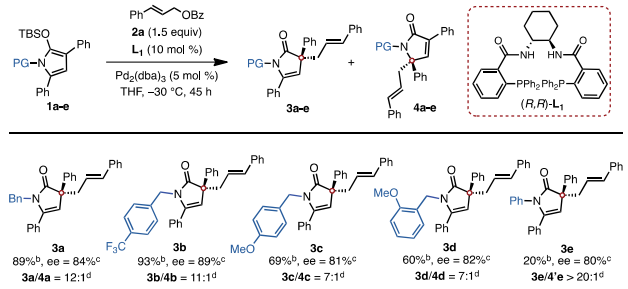
Scheme 2. Scope of the Reaction: Variation of the *N*-Protecting Group[a]



[a]All reactions were run on a 0.2 mmol scale. [b]Isolated yield. [c]Determined by ^{1}H NMR on the crude reaction mixture. [d]Determined by supercritical fluid chromatography (SFC) analysis.

(>99%, **3a**/**4a** = 3.4:1, 58% *ee*), Et_2O (81%, **3a**/**4a** = 4.3:1, 59% *ee*), and 2-Me-THF (85%, **3a**/**4a** = 11.6:1, 51% *ee*) led to similar enantioselectivities, with **3a** obtained with *ee*'s ranging from 51% to 59%. CH_3CN (89%, **3a**/**4a** = 3.3:1, 54% *ee*) afforded roughly the same selectivity, while the reactions run in CH_2Cl_2 (38%, **3a**/**4a** = 2.6:1, 47% *ee*), toluene (23%, **3a**/**4a** = 3.8:1, 43% *ee*), or a more polar solvent such as DMF (89%, **3a**/**4a** = 2.3:1, 35% *ee*) resulted in lower yields and lower enantioselectivities (see Supporting Information for more details).

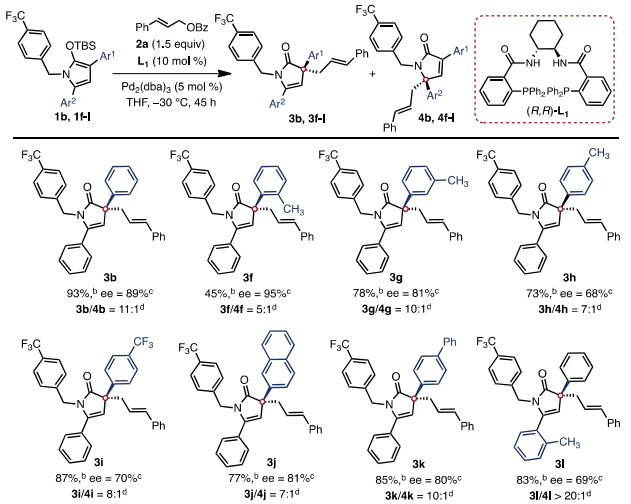
Encouraged by these results, we next evaluated the influence of the ligand. The investigation revealed that C2-symmetric diphosphine ligands such as **L1** afforded a higher level of selectivity (58% *ee*) (Table 1, entry 8) than the axially chiral diphosphines **L2** and **L3** (17% and 19% *ee*) (Table 1, entries 10 and 11), the phosphine oxazoline **L4** (16% *ee*) (Table 1, entry 12), the atropisomeric Phanephos **L5** (3% *ee*) (Table 1, entry 13), the ferrocenephosphine **L6** (19% *ee*) (Table 1, entry 14), the DIPAMP-type ligands **L7** and **L8** (26% and 6% *ee*) (Table 1, entries 15 and 16), and the C2-symmetric diphosphine ligand developed by Kagan and co-workers (5% *ee*) (Table 1, entry 17).

The higher reactivity of cinnamyl benzoate prompted us to run the reactions at lower temperatures. Luckily, we were able to improve the enantioselectivity without losing any reactivity by simply running the reaction at 0 °C (Table 1, entry 18). This result could be further improved by running the reaction at −20 °C (73% yield, 82% *ee*) (Table 1, entry 19). The best result was however obtained when running the reaction in THF at −30 °C, conditions under which the desired α-allylated product **3a** was obtained in high yield (89%), with great regioselectivity (12:1) and excellent enantioselectivity (*ee* up to 84%) (Table 1, entry 20). Various additives such as tetrabutylammonium benzoate and sodium benzoate were also tested, but no improvement was observed in terms of enantioselectivity despite an improved regioselectivity (**3a**/**4a** > 20:1; results not shown in the Table 1).

Before evaluating the substrate scope, we decided to lower the catalyst loading to verify whether it had an impact on the selectivity. The amount of $Pd_2(dba)_3$ was therefore reduced from 5 mol % (Table 1, entry 19) to 2.5 mol % (Table 1, entry 21). Interestingly, this did not change the enantioselectivity (84% *ee*); however, it had a detrimental effect on both the yield and regioselectivity, which went from 89% to 59% and from 12:1 down to 6:1, respectively. Logically, further lowering the catalyst loading to 1 mol % had a detrimental effect on the overall process (27%, **3a**/**4a** = 6:1, 74% *ee*) (Table 1, entry 22).

With our optimized conditions in hand [$Pd_2(dba)_3$ (5 mol %), (*R*,*R*)-$\mathbf{L_1}$ (10 mol %), THF, −30 °C], we next examined the

Scheme 3. Scope of the Reaction: Variation of the Aryl Substituents[a]



[a]All reactions were run on a 0.2 mmol scale. [b]Isolated yield. [c]Determined by supercritical fluid chromatography (SFC) analysis. [d]Determined by ^{1}H NMR on the crude reaction mixture.

substrate scope by applying these conditions to various α,γ-diphenyl 2-silyloxypyrrole derivatives **1a**−**e** bearing different *N*-protecting groups (Scheme 2). As depicted in Scheme 2, the best results were obtained with **1b** bearing a *para*-(trifluoromethyl)benzyl *N*-protecting group. Substrates **1c** and **1d**, respectively bearing a *para*- and an *ortho*-(methoxy)benzyl group, were converted to the corresponding allylated products **3c** and **3d** in good yields (60−69%), good enantioselectivities (81−82% *ee*), and an interesting 7:1 regioselectivity in favor of the α-allylated product. In contrast, when the *N*-benzyl protecting group was replaced by a *N*-phenyl group, the allylated product **3e** was obtained with a similar enantioselectivity (80% *ee*) and an excellent regioselectivity (>20:1) but with a low yield of 20%.

As the *N*-*para*(trifluoromethyl)benzyl derivative induced the highest enantioselectivity, a variety of 2-silyloxypyrroles incorporating this moiety (**1f**−**l**) were synthesized and evaluated under our optimized conditions. The results are summarized in Scheme 3.

We first started by evaluating the influence on the selectivity of the aromatic substituent at the C2 position of the pyrrole ring (Ar^1). The first results showed that a higher enantioselectivity was obtained with **1f**, bearing an *ortho*-methyl-substituted phenyl ring (**3f**/**4f** = 5:1, 95% *ee*), than with **1g** and **1h**, which have a *meta*- (**3g**/**4g** = 10:1, 81% *ee*) and a *para*-methyl-substituted (**3h**/**4h** = 7:1, 68% *ee*) aromatic ring, respectively, indicating that the steric hindrance may be an important parameter that accounts for the enantioselectivity.

Replacing the *para*-methyl group by an electron-withdrawing *para*-trifluoromethyl gave the α-allylated product **3i** in 87% yield however with a slightly lower 70% *ee*.

Finally, the substrates bearing a naphthyl (**1j**) or biphenyl (**1k**) also appeared to be suitable precursors, as the corresponding α-allylated products **3j** and **3k** were both obtained in roughly 81% *ee*. Finally, we evaluated the influence of the aromatic substituent at the C4 position of the pyrrole ring (Ar^2) on the selectivity. Substrate **1l** bearing a methyl substituent at the *ortho*-position of the phenyl ring was thus synthesized and subjected to our optimized Pd-AAA conditions.

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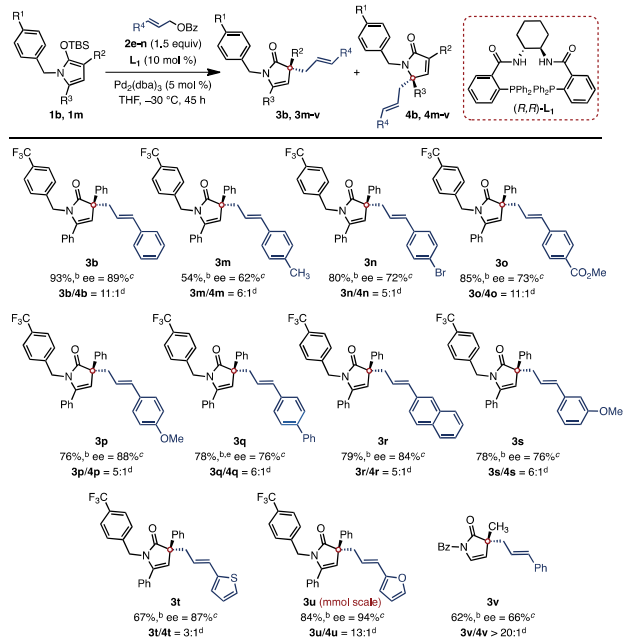
Scheme 4. Scope of the Reaction: Variation of the Allyl Donor[a]



[a]All reactions were run on a 0.2 mmol scale. [b]Isolated yield. [c]Determined by supercitical fluid chromatography (SFC) analysis. [d]Determined by ^{1}H NMR on the crude reaction mixture. [e]The two regioisomers **3q** + **4q** could not be separated; overall yield.

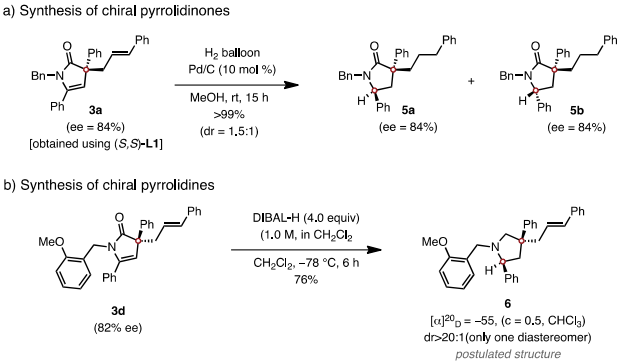
Pleasingly, the regioselectivity improved from 11:1 (**3b**) to >20:1 in favor of the α-allylated product **3l**, but the enantioselectivity dropped dramatically from 89% (**3b**) to 69% ee (**3l**).

After evaluating the substrate scope, we decided to vary the allyl donor in order to gain structural diversity. A variety of 3-substituted allyl benzoates (**2e–n**) were thus prepared and engaged in the Pd-AAA of 2-silyloxypyrroles **1b** and **1m**; the results are depicted in Scheme 4.

We first evaluated various *para*-substituted cinnamyl benzoate derivatives (**2f–j**), which all afforded good to high levels of enantioselectivity ranging from 62% to 88% *ee*. The cinnamyl benzoate bearing either a methoxy substituent at the *meta* position or a naphthalene in place of the phenyl ring also afforded high enantioselectivities ranging from 76% *ee* (**3s**) to 84% *ee* (**3r**). Most importantly, the 3-substituted allylbenzoates bearing a heterocylic substituent such as a thiophene (**3t**, 87% *ee*) or a furan (**3u**, 94% *ee*) afforded the best selectivities. Unfortunately, when applying our optimized Pd-AAA conditions to the monosubstituted 2-silyloxypyrrole **1m**, the corresponding α-allylated product **3v** was obtained in a moderate 66% *ee* albeit with excellent regioselectivity (>20:1).

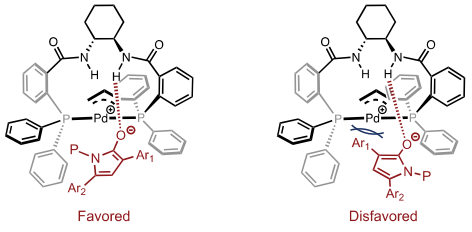
To further demonstrate the synthetic utility of our method, the reaction was run on a 1 mmol scale using 2-silyloxypyrrole **1b** and 3-substituted allyl benzoate **2n**. The corresponding allylated product **3u** was obtained in 84% yield and 94% *ee*. In addition, the allylated product **3a** was quantitatively converted to the corresponding optically active pyrrolidinones **5a** and **5b** through a hydrogenation over Pd/C (Scheme 5). Compound **3d**, on the other hand, was easily converted to the corresponding pyrrolidine **6**, which was obtained in 76% yield as a single diastereoisomer through a DIBAL-H-mediated reduction.

Scheme 5. Post-functionalization: Synthesis of Chiral Pyrrolidinones and Pyrrolidines



The absolute configuration of the newly formed quaternary center resulting from the Pd-AAA could not be confirmed by single crystal X-ray analysis. However, by analogy with the selectivities previously observed on similar systems[17,18] and in accordance with the prediction model proposed by Lloyd-Jones, Norrby and co-workers,[20] where the amide proton of the cationic [allyl-Pd-DACH] complex directs the enolate carbon to the allyl through H-bonding, we believe the enolate approaches the palladium π-allyl-(*R*,*R*)-**L$_1$** complex by its *Re*-face; this avoids the steric clash between the bulky aryl group Ar$_1$ and the ligand framework (Scheme 6).

Scheme 6. Proposed Stereochemical Pathway



In summary, we have successfully developed a highly regio- and enantioselective palladium-catalyzed allylic alkylation of α,γ-disubstituted 2-silyloxypyrroles to access optically active γ-lactam derivatives bearing a quaternary stereogenic center. Overall, the process is operationally trivial and scalable and allows the corresponding α-allylated β,γ-unsaturated γ-lactams to be obtained in usually high yields, good to excellent regioselectivities ranging between 3:1 and >20:1, and up to 95% *ee*. Most importantly, the allylated γ-lactams could be easily converted to various useful building blocks, including chiral pyrrolidinones and pyrrolidines, through simple synthetic transformations.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03613.

Details of experimental procedures, ^{1}H and ^{13}C NMR spectra, Supercritical Fluid Chromatography (SFC) chromatograms (PDF)

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AUTHOR INFORMATION

Corresponding Authors

*E-mail: janine.cossy@espci.fr.
*E-mail: s.arseniyadis@qmul.ac.uk.

ORCID

Stellios Arseniyadis: 0000-0001-6831-2631
Janine Cossy: 0000-0001-8746-9239

Notes

The authors declare no competing financial interest.

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