Palladium-Catalyzed Asymmetric Allylic Alkylation of 4-Substituted Isoxazolidin-5-ones: A Straightforward Access to $\beta^{2,2}$-Amino Acids
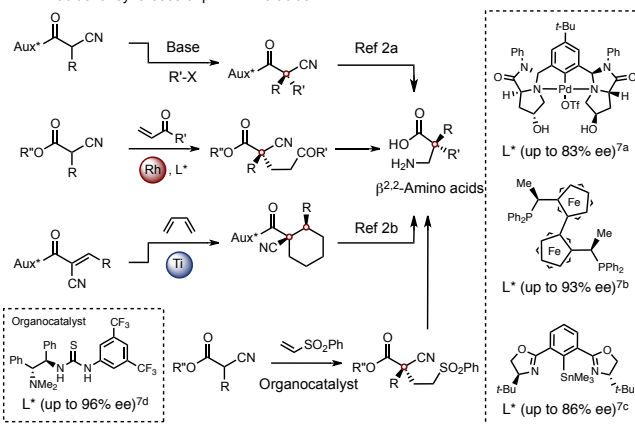
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Abstract: *We report here an unprecedented and highly enantioselective palladium-catalyzed allylic alkylation applied to 4-substituted isoxazolidin-5-ones. Ultimately, the process provides a straightforward access to $\beta^{2,2}$-amino acids bearing an all-carbon quaternary stereogenic center in great yields and a high degree of enantioselectivity.*

Asymmetric methods allowing a straightforward access to β-amino acids have been the focus of tremendous efforts ever since this structural motif was shown to offer interesting prospects in medicinal chemistry. Indeed, compounds bearing a β-amino acid moiety tend to exhibit remarkable biological activities along with increased biological stability, particularly towards common peptidases.[1] They have thus emerged as potent protease resistant peptidomimetics as well as potential precursors to β- or α/β-peptides and β-lactams.[2-4] Another important aspect of β-amino acids is their ability to fold into different secondary structures often with a reversed orientation of their α-amino acid counterparts. Interestingly however, despite all the methods that have been reported to access enantioenriched β^2- and β^3-amino acids,[5,6] the asymmetric synthesis of $\beta^{2,2}$-amino acids remains a challenge,[7-8] in particular for compounds bearing a stereodefined all-carbon quaternary stereogenic centers (Figure 1A).[9]

For the past several years, our group has focused on the development of new synthetic tools and strategically implementing them in the total synthesis of various biologically relevant natural products.[10] In this context, we recently applied the palladium-catalyzed asymmetric allylic alkylation[11] to two new classes of pro-chiral substrates, namely allyl dienol[12,13] and allyl enol[14] carbonates. This method provided a highly enantioselective access to a wide variety of chiral butenolides and butyrolactones bearing an all carbon α-quaternary stereogenic center. It was also used as a key step in the total synthesis of (−)-nephrosteranic acid and (−)-roccellaric acid, two members of the paraconic acid family of natural products,[15] which exhibit interesting antibiotic properties. In view of these

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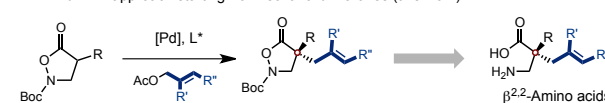
Figure 1. A) Traditional synthetic routes to $\beta^{2,2}$-amino acids. B) Palladium-catalyzed asymmetric allylic alkylation of α-substituted isoxazolidin-5-ones.

results, we envisioned that a Pd-AAA could potentially be applied to 4-substituted isoxazolidin-5-ones to afford the corresponding α,α-disubstituted products which could in turn be readily converted to $\beta^{2,2}$-amino acids after subsequent reductive N−O bond cleavage (Figure 1B). This method appeared all the more appealing that the only example reported in the literature featuring the use of α-substituted isoxazolidin-5-ones was limited to the synthesis of α-sulfanyl-$\beta^{2,2}$-amino acid derivatives *via* an enantioselective organocatalytic phase-transfer α-sulfanylation.[16]
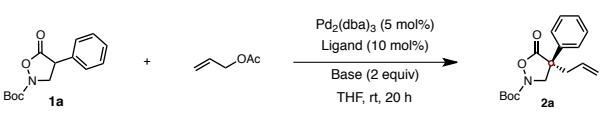
We thus initiated our study using 4-phenylisoxazolidin-5-one **1a** as a model substrate. The latter was prepared in four steps starting from diethyl malonate *via* a palladium-catalyzed arylation, a saponification, the formation of the corresponding C5-substituted Meldrum's acids and a formal [3+2] cycloaddition.[17] This substrate was eventually engaged in a reactivity and enantioselectivity screen across an array of conditions; the results are summarized in Table 1.

For the first set of conditions, we decided to evaluate the influence of the ligand by running the reactions in THF at room temperature using allyl acetate (1.0 equiv.), Na$_2$CO$_3$ (2.0 equiv.), Pd$_2$(dba)$_3$ (5 mol%) and a variety of chiral ligands (10 mol%). As a general trend, all the reactions afforded the corresponding α,α-disubstituted isoxazolidin-5-one in good yields ranging from 85% to 95% independently of the ligand used. Interestingly however, the nature of the ligand had a tremendous impact on

Table 1. Systematic study.[a]

Pd$_2$(dba)$_3$ (5 mol%), Ligand (10 mol%), Base (2 equiv), THF, rt, 20 h. 1a + allyl acetate (OAc) → 2a

entry	solvent	ligand	base	yield[b] (%)	ee[c] (%)
1	THF	(R,R)-L1	Na$_2$CO$_3$	95	90
2	THF	(R,R)-L2	Na$_2$CO$_3$	81	82
3	THF	(R,R)-L3	Na$_2$CO$_3$	93	26
4	THF	(S)-L4	Na$_2$CO$_3$	92	4
5	THF	(R)-L5	Na$_2$CO$_3$	94	22
6	THF	(S,R,R)-L6[d]	Na$_2$CO$_3$	85	8
7	THF	(R)-L7	Na$_2$CO$_3$	90	3
8	THF	(R,R)-L1	Li$_2$CO$_3$	90	87
9	THF	(R,R)-L1	Cs$_2$CO$_3$	83	82
10	THF	(R,R)-L1	NaH	96	87
11	THF	(R,R)-L1	DBU	14	86
12	MTBE	(R,R)-L1	Na$_2$CO$_3$	99	89
13	1,4-dioxane	(R,R)-L1	Na$_2$CO$_3$	85	83
14	PhMe	(R,R)-L1	Na$_2$CO$_3$	99	66
15	MeCN	(R,R)-L1	Na$_2$CO$_3$	92	42
16	NMP	(R,R)-L1	Na$_2$CO$_3$	78	82
17	THF (0 °C)	(R,R)-L1	Na$_2$CO$_3$	95	91
18	THF (−10 °C)	(R,R)-L1	Na$_2$CO$_3$	94	92
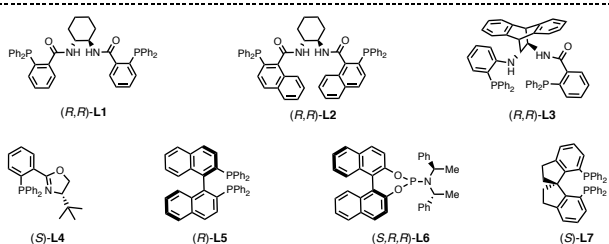
(R,R)-L1   (R,R)-L2   (R,R)-L3

(S)-L4   (R)-L5   (S,R,R)-L6   (S)-L7

[a]Unless otherwise noted, all reactions were run on a 0.19 mmol scale using 5 mol% of Pd$_2$(dba)$_3$ and 10 mol% of ligand. [b]Isolated yield. [c]Determined by Supercritical Fluid Chromatography (SFC) analysis. [d]5 mol% of Pd$_2$(dba)$_3$ and 20 mol% of (S,R,R)-L6 were used.

the selectivity. Indeed, the investigation revealed that phosphine oxazoline type ligands such as PHOX, (S)-L4, axially chiral diphosphines, such as BINAP, (R)-L5, spirocyclic diphosphines, such as (R)-SDP (L7), and the phosphoramidite-type ligands such as (S,R,R)-L6 induced low levels of enantioselectivity (Table 1, entries 4-7), while the C2-symmetric diphosphines developed by Trost et al. (L1, L2 and L3) afforded much higher ees ranging from 26% to 90%; the best results being obtained with L1 (Table 1, entry 1).

With this result in hand, we next evaluated the influence of the base, which appeared to have a limited impact on the selectivity as exemplified by the ees obtained with Na$_2$CO$_3$ (90% ee, Table 1, entry 1), Li$_2$CO$_3$ (87% ee, Table 1, entry 8), Cs$_2$CO$_3$ (82% ee, Table 1, entry 9), NaH (87% ee, Table 1 entry 10) and DBU (86% ee, Table 1, entry 11). However, while most bases afforded the allylated product in good to excellent yields (82-95%), the use of DBU was detrimental as the yield drastically decreased to 14%.
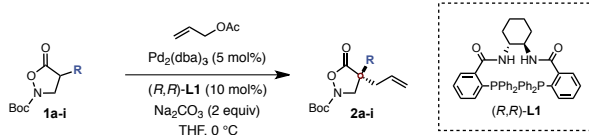
To optimize this Pd-AAA reaction further, we also evaluated the influence of the palladium catalyst precursor and found Pd$_2$(dba)$_3$ (95% yield, 90% ee) to be superior to [Pd(allyl)Cl]$_2$ (43% yield, 70% ee), [Pd(cinnammyl)(Cl)]$_2$ (40% yield, 80% ee) and Pd(OAc)$_2$ (10% yield, 78% ee) (not shown in Table; see Supporting Information for more details). In addition,

decreasing the amount of Pd$_2$(dba)$_3$ from 5 to 1.25 mol% led to a considerable erosion of the ee from 90% to 79% and this option was therefore discarded.

We next wondered whether a change in the enantioselectivity would be observed if running the Pd-AAA process along with some additives under otherwise identical conditions. However, a complete shutdown of the reaction was observed when stoichiometric amounts of LiCl were used, while the use of 15-crown-5 provided comparable enantioselectivities albeit lower yields.

We eventually investigated the effect of the solvent on the selectivity outcome. As a general trend, ethers such as THF (Table 1, entry 1), MTBE (Table 1, entry 12) and dioxane (Table 1, entry 13), and more polar solvents such as NMP (Table 1, entry 16) provided the best selectivities with ees ranging from 82 to 90%. Curiously, the use of solvents such as toluene (Table 1, entry 14) and MeCN (Table 1, entry 15) afforded the alkylated product in quasi-quantitative yield, however in a much lower enantioselectivity (66% and 42% ee respectively). Finally, the ees could be slightly improved by running the reaction at a lower temperature such as 0 °C or −10 °C (Table 1, entries 17 and 18), however, for practical purposes we decided to set the reaction temperature at 0 °C.

After having identified the best set of reaction conditions [Pd$_2$(dba)$_3$ (5 mol%), (R,R)-L1 (10 mol%), Na$_2$CO$_3$ (2 equiv), THF, 0 °C], we next examined the substrate scope by applying these conditions to various 4-substituted isoxazolidin-5-ones. The results are summarized in Table 2.

Table 2. Scope of the Pd-AAA of 4-substituted isoxazolidin-5-ones.[a]

allyl acetate (OAc), Pd$_2$(dba)$_3$ (5 mol%), (R,R)-L1 (10 mol%), Na$_2$CO$_3$ (2 equiv), THF, 0 °C. 1a-i → 2a-i. (R,R)-L1

2a (95%,[b] ee = 91%[c]) [ee > 99%][d]

2b (91%,[b] ee = 90%[c])

2c (86%,[b] ee = 87%[c])

2d (97%,[b] ee = 92%[c])

2e (95%,[b] ee = 86%[c])

2f (92%,[b] ee = 91%[c])

2g (91%,[b] ee = 89%[c])

2h (93%,[b] ee = 85%[c])

2i (97%,[b] ee = 89%[c])

Favored   Disfavored

[a]Unless otherwise noted, all reactions were run on a 0.19 mmol scale using 5 mol% of Pd$_2$(dba)$_3$ and 10 mol% of ligand. [b]Isolated yield. [c]Determined by Supercritical Fluid Chromatography (SFC) analysis. [d]After recrystallization.

As a general trend, this method proved to be applicable to a wide range of 4-aryl/heteroaryl isoxazolin-5-ones as illustrated by the high yields (86-97%) and the excellent enantioselectivities (85-92%) obtained. Hence, substrates bearing an electron-

donating substituent on the arene ring, such as a *p*-methoxy (86% yield, 87% ee) or a *p*-methyl (91% yield, 90% ee), as well as compounds bearing an electron-withdrawing substituent on the arene ring, such as a *p*-chloro (92% yield, 91% ee), a *p*-bromo (91% yield, 89% ee), a *p*-fluoro (97% yield, 92% ee) or a *p*-trifluoromethyl (92% yield, 91% ee), appeared to be suitable. In addition, the optical purity of the products could be further improved after recrystallization from a pentane/ether mixture. This was the case for the crystalline product **2a** which was isolated in a quasi enantiopure form (>99% ee).

As for the absolute configuration of the newly formed all-carbon quaternary stereogenic center, it could be predicted using the model proposed by Trost *et al*. where the enolate approaches the π-allylpalladium-(*R,R*)-**L1** complex by its *Re* face to avoid any disfavored steric interaction between the "wall" of the ligand and the Boc group of the substrate. This selectivity was later confirmed by single crystal X-Ray analysis (see structure in Table 2).

In an effort to broaden the scope of the reaction, we subsequently turned our attention to introduce more structural diversity using substituted allyl acetates, in particular 2-substituted allyl acetates. The results are depicted in Table 3.

Table 3. Scope of the Pd-AAA with 2-substituted allyl acetates.[a]
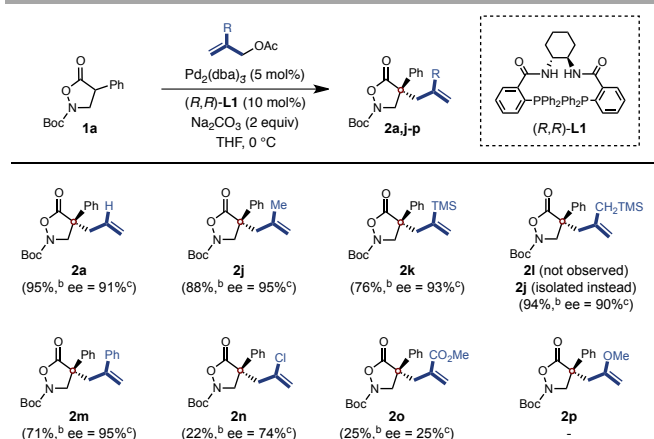
[a]Unless otherwise noted, all reactions were run on a 0.19 mmol scale using 5 mol% of Pd$_2$(dba)$_3$ and 10 mol% of ligand. [b]Isolated yield. [c]Determined by Supercritical Fluid Chromatography (SFC) analysis.

Interestingly, when subjecting isoxazolidin-5-one **1a** to an array of allyl acetates under the aforementioned conditions we were able to isolate the corresponding α-allylated products in generally excellent enantioselectivities (up to 95% ee). Overall, electronic effects appeared to have a much more pronounced impact on the enantioselectivity than steric effects. Indeed, increasing the bulk of the substituent at the C2 position by replacing the hydrogen atom (**2a**, 91% ee) with a methyl (**2i**, 95% ee), a trimethylsilyl (**2j**, 93% ee) or a phenyl (**2m**, 95% ee) led to a slight improvement of the enantioselectivity albeit along with a small loss of reactivity. In contrast, replacing the hydrogen with a chlorine atom (**2m**, 74% ee) or a methylester (**2n**, 25% ee) had a detrimental effect on both the enantioselectivity and the yield. Interestingly, the use of 2-[(trimethylsilyl)methyl] allyl acetate yielded the methallyl derivative **2j** in 94% yield and 90% ee. Finally, a complete shut down of the reaction was even observed when using a 2-methoxy-substituted allyl acetate (**2o**).

Finally, after having established a practical and highly enantioselective route to enantioenriched α,α-disubstituted isoxazolidin-5-ones **2**, we decided to demonstrate the synthetic utility of the method by developing a straightforward sequence which would allow to convert the latter to the corresponding β^{2,2}-amino acids **3** and β-lactams **4** (Scheme 1).
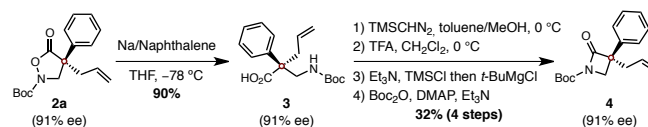
Scheme 1. Synthesis of β^{2,2}-amino acids and β-lactams.

To effect the N-O bond cleavage, we screened various reaction conditions (Na$_2$S$_2$O$_4$/EtOH/H$_2$O, SmI$_2$/THF, Zn/AcOH),[18] however none of them led the desired amino acid. Luckily, the use of sodium naphthalenide in THF at –78 °C afforded the title product **3** in 90% isolated yield. Subsequent methylation of the carboxylic acid using TMSCHN$_2$, Boc-deprotection using TFA and lactam formation using Et$_3$N, TMSCl followed by *t*-BuMgCl resulted in the formation of the corresponding cyclized product **4**, which was *N*-Boc protected for purification purposes.[19]

In summary, we have developed a novel, robust and highly enantioselective catalytic protocol for the synthesis of α,α-disubstituted isoxazolidin-5-ones bearing an all-carbon α-quaternary stereogenic center.[20] The method relies on a key palladium-catalyzed asymmetric allylic alkylation and affords the desired products in both high yields and excellent enantioselectivities (ees up to 95%). Besides the high level of efficiency and stereocontrol achieved, this method allows a straightforward entry into the valuable β^{2,2}-amino acids and β-lactams.

Experimental Section

General procedure for the Pd-AAA with allyl acetate: To a solution of Pd$_2$(dba)$_3$ (0.01 mmol, 0.05 equiv) in THF (1 mL) at rt was added (*R,R*)-**L1** (0.02 mmol, 0.1 equiv) and the mixture was stirred for 30 min. This solution was then cooled to 0 °C and transferred *via* cannula to a flask containing a cooled solution (0 °C) of 4-substituted isoxazolidin-5-one (0.19 mmol, 1.0 equiv) and Na$_2$CO$_3$ (0.38 mmol, 2.0 equiv) in THF (1 mL). Once the addition was complete, allyl acetate (0.19 mmol, 1.0 equiv) was added and the reaction mixture was stirred at the same temperature until complete consumption of the starting material (reaction monitored by TLC). The reaction mixture was eventually filtered through a plug of Celite© and concentrated under reduced pressure to afford a crude residue, which was purified by flash column chromatography over silica gel.

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[20] During the preparation of this paper a closely related work was released by Shibasaki, Noda *et al.* Their method relies on a very complementary palladium-catalyzed decarboxylative allylic alkylation approach and allows a straightforward access to alkyl-substituted $\beta^{2,2}$-amino acids starting from 4-allyl ester-substituted isoxazolin-5-ones, see: J.-S. Yu, H. Noda, M. Shibasaki, *Angew. Chem. Int. Ed.* (DOI: 10.1002/anie.201711143); *Angew. Chem.* (DOI: 10.1002/ange.201711143).

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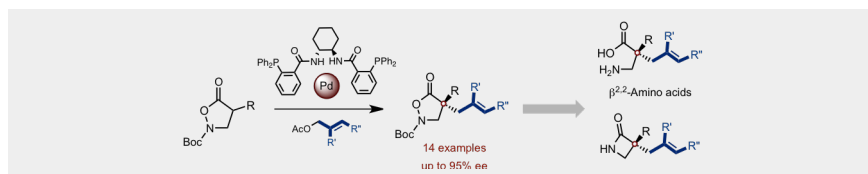
AAA for AA. An unprecedented and highly enantioselective palladium-catalyzed allylic alkylation of 4-substituted isoxazolidin-5-ones is reported. The method is both high yielding and highly enantioselective, and allows a straightforward access to β²,²-amino acids and β-lactams bearing an all-carbon α-quaternary stereogenic center.

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Palladium-Catalyzed Asymmetric Allylic Alkylation of α-Substituted Isoxazolidin-5-ones: A straightforward access to β²,²-Amino Acids