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PALLADIUM-CATALYZED FORMATION AND STEREOSELECTIVE ISOMERIZATION OF 5-VINYLOXAZOLINES. APPLICATION TO THE FORMAL SYNTHESIS OF (S,S)-4-AMINO-3-HYDROXY-5-PHENYLPENTANOIC ACID

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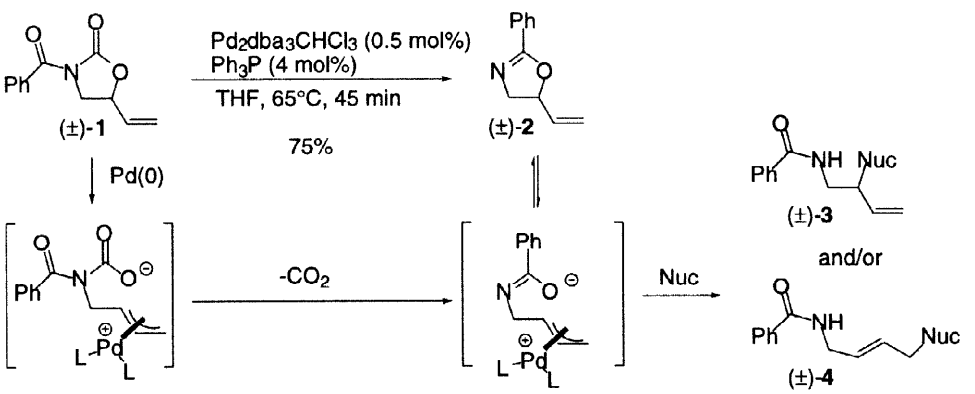
Abstract: Vinyloxazolidinones have been found to undergo Pd(0)-catalyzed ionization followed by loss of carbon dioxide and subsequent cyclization to form vinyloxazolines. The reaction occurred under mild conditions, and enhancement of diastereomeric ratios with chiral substrates was obtained. 4-Benzyl-5-vinyloxazoline prepared by this method has been utilized in the stereoselective synthesis of (S,S)-4-amino-3-hydroxy-5-phenylpentanoic acid (AHPPA).

The utility of oxazoline ring systems as carboxyl protecting groups, templates for organic synthesis, and chiral ligands has been well demonstrated.[1] As a result of the vast synthetic applications, many methods for their preparation have been reported. Most of these preparations rely on the condensation of a 1,2-aminoalcohol with a carboxylic acid (or equivalent), and typically require relatively high temperatures (>100 °C) and/or strongly acidic or basic reagents.[1b] Milder methods have been reported. Among these are cyclization of hydroxyamides by activation of the hydroxyl group,[2] and cyclization of enamides or enimidates by activation of the olefin with electrophiles.[3] During the course of our studies on transition metal-catalyzed allylations of 5-vinyloxazolidinones, we have encountered a mild palladium-mediated oxazoline formation reaction. In addition, chiral 4-substituted oxazoline systems derived from α-amino acids were found to undergo Pd-catalyzed isomerization to the thermodynamically favored *trans*-oxazolines. Thus, the utility of oxazolines has been extended to the facile stereoselective preparation of vinyl 1,2-aminoalcohols, important precursors to antibiotics and enzyme inhibitors. This is particularly noteworthy as the stereoselective addition of vinyl or allyl nucleophiles to α-amino aldehydes has been problematic.[4,5] We report herein the results of our initial investigation of this cyclization/isomerization, and its application to the synthesis of (S,S)-4-amino-3-hydroxy-5-phenylpentanoic acid (AHPPA).

Scheme 1



The treatment of *N*-benzoyl-5-vinyloxazolidinone **1**[6] with a Pd(0) catalyst in THF at 65 °C resulted in the formation of vinyloxazoline **2**[7] in 75% isolated yield (scheme 1). The reaction is thought to proceed via an initial oxidative addition to afford a zwitterionic π-allyl intermediate, followed by loss of CO_2, and subsequent

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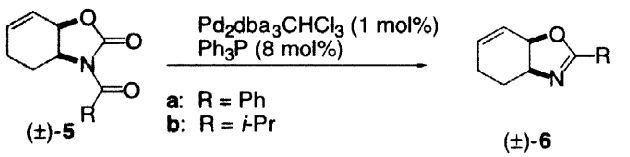
cyclization of the amide oxygen.[8] This last step was found to be reversible, as the π-allyl intermediate could be trapped with external nucleophiles ($BnNH_2$, diethyl malonate) to give **3** and/or **4** under the catalytic conditions starting from either **1** or **2**. The reaction would proceed at room temperature as well. Complete conversion of **1** to **2** was obtained in two hours with 2.5 mol% of the Pd(0) catalyst at ambient temperature. The bicyclic oxazolidinone **5**[9] behaved similarly (eq 1, table 1). Treatment of **5a** with 1 mol% of the dipalladium catalyst in THF at 60 °C for 30 min, afforded **6a**[7] in 98% yield (entry 1), while only a 50% conversion of **5a** to **6a** was observed after 1 hour at 25 °C (entry 2). The utilization of other solvents led to complete conversion within 1 hour at room temperature (entries 3-5). The compatibility of this process with protic solvents is particularly noteworthy. The reaction worked equally well when carried out in ethanol (entry 5), and a high yield of **6a** was obtained. Substitution of the *N*-acyl moiety with alkyl amide groups[10] also afforded a high yield of the oxazoline product **6b**[7] (entry 6). This process was not restricted to the formation of oxazolines. Thus, the six-membered ring analog, 6-vinyl-tetrahydro-1,3-oxazin-2-one[6] (**7**), reacted smoothly with the Pd(0) catalyst to give **8**[7] in 72% isolated yield (eq 2).

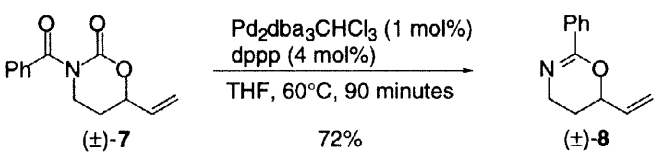


(eq 1)

Table 1. Oxazoline **6** from Oxazolidinone **5**

Entry	5	Solvent	T (°C)	time (h)	Yield of 4[a]
1	**a**	THF	60	0.5	98%
2	**a**	THF	25	1	50%[b]
3	**a**	CH_3CN	25	1	98%
4	**a**	CH_2Cl_2	25	1	88%
5	**a**	EtOH	25	1	88%
6[c]	**b**	THF	60	3	90%[d]

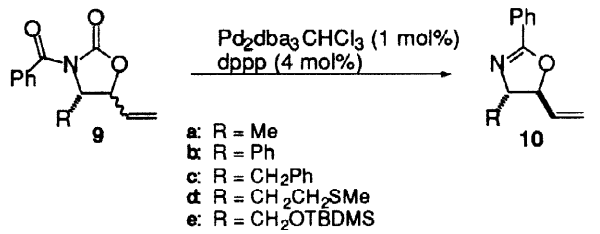
[a]Isolated yields. [b]Conversion. [c]dppp (4 mol%) was used as the ligand. [d]Crude yield. Contains ~4% of an elimination product, *N*-2,4-cyclohexadienylisobutyramide.



(eq 2)

The reaction of chiral oxazolidinones derived from α-amino acids[6] afforded chiral oxazolines (eq 3), and the results are summarized in table 2. Oxazolidinone **9a**, derived from L-alanine, gave oxazoline **10a**[7] in nearly quantitative yield (entry 1). The diastereomeric ratio of the product was different from the starting substrate. When a 1.4:1 *trans:cis* ratio of **9a** was subjected to the reaction conditions in THF for 30 minutes, an enhanced 2.5:1 *trans:cis* ratio of **10a** was obtained. Carrying out the reaction in toluene afforded an improved 6:1 ratio.[11] Attempts to form the oxazoline from **9b**, derived from phenyl glycine, resulted in only elimination products (entry 3). On the other hand, **9c**, derived from phenyl alanine, gave **10c** in high yield (entries 4-6). Toluene was the optimal solvent for this substrate giving rise to a 15.5:1 *trans:cis* ratio in comparison to THF (9:1) and acetonitrile/THF (5:1). Interestingly, the methionine derivative **9d** showed the opposite trend (entries 7 and 8). THF afforded the optimal selectivity (14.5:1) as compared to toluene (8.5:1). Serine derived oxazolidinone **9e** afforded **10e** in a 13:1 *trans:cis* ratio in THF at room temperature after 3.5 hours (entry 9). As the diastereomers of **9e** were easily separated, reaction of the diastereomerically pure oxazolidinone was investigated. Entries 10-12 show the results of this study. Starting with pure *trans*-**9e**, the isomer ratio of **10e** was determined at three different times. Interestingly, the initial decarboxylation and oxazoline ring formation occurred with little selectivity, and a 4:1 ratio was obtained after 1 hour at room temperature in THF. This

result shows that the π–allyl complex underwent rapid inversion[12] prior to cyclization. After 5 hours, the selectivity climbed to 15:1, and at equilibrium (23 hours) the ratio was 16:1.[13] Again, the selectivity was slightly less (13:1) when the reaction was carried out in toluene. The nature of the π–allyl intermediate is not clear. Initial oxidative insertion of Pd(0) would afford diastereomeric intermediates **A** and **B**, and loss of CO_2 would give rise to **C** and **D**. Either or both pairs of intermediates may be in rapid equilibration. Studies to elucidate the mechanism are currently underway.

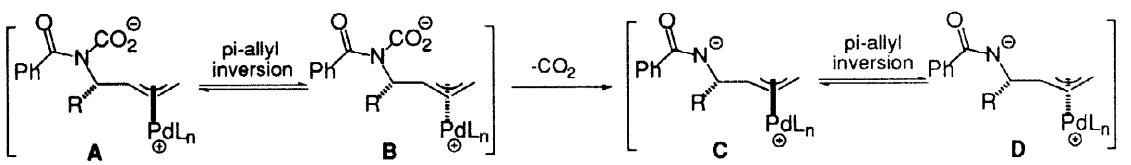


(eq 3)

Table 2. Formation and Isomerizaton of Oxazoline **10** from Oxazolidinone **9**

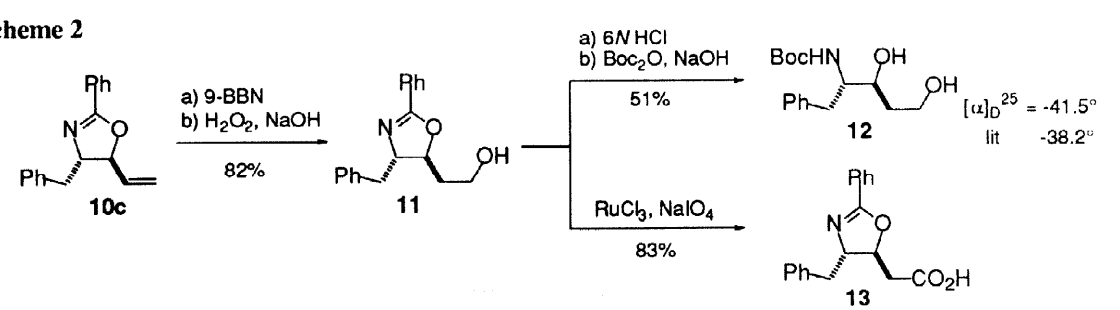
Entry	9	*trans:cis*	Solvent	T (°C)	t (h)	Yield 10[a]	*trans:cis*[b]
1	**a**	1.4 : 1	THF	55	0.5	98	2.5 : 1
2	**a**	2.2 : 1	Toluene	45	1	93[c]	6.0 : 1
3	**b**	3.3 : 1	THF	60	0.5	0[d]	---
4	**c**	1.5 : 1	THF	55	2	89	9.0 : 1
5	**c**	1.5 : 1	CH_3CN/THF[e]	60	1	92	5.0 : 1
6	**c**	1.5 : 1	Toluene	45	2	84	15.5 : 1
7	**d**	1.7 : 1	THF	60	0.5	77	14.5 : 1
8	**d**	1.7 : 1	Toluene	45	1	100[c]	8.5 : 1
9	**e**	1.6 : 1	THF	25	3.5	96	13.0 : 1
10	**e**	*trans only*	THF	25	1	*f*	4.0 : 1
11	**e**	*trans only*	THF	25	5	*f*	15.0 : 1
12	**e**	*trans only*	THF	25	23	*f*	16.0 : 1
13	**e**	1.6 : 1	Toluene	25	25	95	13.0 : 1

[a]Isolated yields. [b]Determined by ^1H NMR. See ref. 14. [c]Crude Yield. [d]Elimination to *N*-1-phenyl-1,3-butadienyl-benzamide (90% yield). [e]CH_3CN:THF 5:1. [f]Yield not determined.



The utility of the oxazoline products was demonstrated in the synthesis of *N*- and *N,O*-protected 4-amino-3-hydroxy-5-phenylpentanoic acid, a key component of aspartic protease inhibitors.[14,15] As shown in scheme 2, oxidation of **10c** with 9-BBN gave the alcohol **11** in 82% yield. Acidic hydrolysis and protection afforded the known *N*-Boc aminodiol **12**,[14] a precursor to AHPPA. Direct oxidation of **11** to the carboxylic acid **13** with $RuCl_3/NaIO_4$ was more efficient, and afforded AHPPA, conveniently protected as the oxazoline, in good yield.

Scheme 2



In conclusion, 5-vinyloxazolidinones undergo facile palladium-catalyzed decarboxylation and cyclization to afford 5-vinyloxazolines. Rapid π-allyl palladium inversion led to enhanced diastereomeric ratios, and may be a general isomerization process. The oxazoline products were demonstrated to be useful precursors to biologically important β-hydroxy-γ-amino acids. Further studies to improve the diastereomeric ratios through kinetic trapping of the π-allyl palladium intermediate with external nucleophiles are currently being pursued.

Acknowledgments: We thank NSF (OSR 9452892) and North Dakota State University for support.

References and Notes

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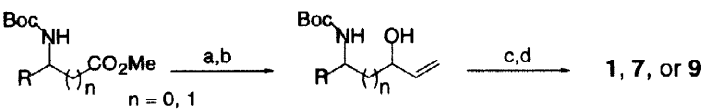
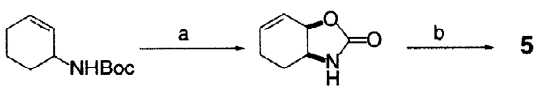
5. *Anti*-selective allylation has been reported with one example giving 20.6:1: (a) Vara Prasad, J. V. N.; Rich, D. H. *Tetrahedron Lett.* **1990**, *31*, 1803. *Syn*-selective vinylation with 2-trimethylsilylethylidenetriphenylphosphorane gave excellent selectivites: (b) Franciotti, M.; Mann, A.; Taddei, M. *Tetrahedron Lett.* **1991**, *32*, 6783. Tandem DIBAL reduction of aminoesters and *in-situ* addition of vinyl nucleophiles has led to improved selectivity: (c) Ibuka, T.; Habashita, H.; Otaka, A.; Fujii, N.; Oguchi, Y.; Uyehara, T.; Yamamoto, Y. *J. Org. Chem.* **1991**, *56*, 4370. (d) Polt, R.; Peterson, M. A.; DeYoung, L. *J. Org. Chem.* **1992**, *57*, 5469. (e) Angle, S. R.; Henry, R. M. *J. Org. Chem.* **1997**, *62*, 8549.
6. Oxazolidinones **1, 9** and oxazinone **7** were prepared from the corresponding *N*-Boc-aminoesters according to the following scheme, and were fully characterized by ^{1}H, ^{13}C NMR and IR Spectroscopy:



a) DIBAL-H, toluene, -78 °C; b) vinylmagnesium bromide, THF; c) NaH, THF; d) PhCOCl, Et_3N

7. All compounds were fully characterized by ^{1}H, ^{13}C NMR and IR Spectroscopy.
8. For another example of an amide cyclization onto a π-allylpalladium complex, see: Hansel, J.-G.; O'Hogan, S.; Lensky, S.; Ritter, A. R., Miller, M. J. *Tetrahedron Lett.* **1995**, *36*, 2913.
9. The oxazolidinone **5** was prepared from *N*-Boc-3-aminocyclohexene according to the following scheme and was fully characterized by ^{1}H, ^{13}C NMR and IR Spectroscopy:



a) I_2, CH_2Cl_2 then DBU; b) RCOCl, Et_3N

10. The cyclization of amides onto double bonds activated by sulphenylation has been limited to aryl amides as alkyl amides gave low (10%) yields. See ref 3a and Abd El Samii, Z. K. M.; Al Ashmay, M. I.; Mellor, J. M. *Tetrahedron Lett.* **1987**, *28*, 1929.
11. AB INITIO calculations (Spartan) for the alanine derived oxazoline gave *trans:cis* ratios of 5.7:1 (STO-3G) and 6.7:1 (630G).
12. Palladium π-allyl complexes are known to undergo inversion. For mechanistic discussions, see: (a) Bäckvall, J.-E.; Granberg, K. L. *J. Am. Chem. Soc.* **1992**, *114*, 6858. (b) Mackenzie, P. B.; Whelan, J.; Bosnich, B. *J. Am. Chem. Soc.* **1985**, *107*, 2046.
13. Good diastereoselectivity with serinal derivatives has been particularly problematic. See refs. 5b and 5c.
14. *Cis* and *trans* configurations were determined by ^{1}H NMR chemical shifts of the ring protons (0.3 to 0.5 ppm upfield shift for *trans* relative to *cis*) in analogy to the reported oxazolidinones. Sakaitani, M.; Ohfune, Y. *J. Am. Chem. Soc.* **1990**, *112*, 1150.
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