Communications to the Editor

Enantioselective Synthesis of 3,6-Dihydro-1*H*-pyridin-2-ones: Unexpected Regioselectivity in the Palladium-Catalyzed Decarboxylative Carbonylation of 5-Vinyloxazolidin-2-ones

Julian G. Knight,*[,†] Simon W. Ainge,[†] Andrew M. Harm,[†] Simon J. Harwood,[†] Haydn I. Maughan,[†] Duncan R. Armour,[‡] David M. Hollinshead,[§] and Albert A. Jaxa-Chamiec[‡]

Department of Chemistry, Bedson Building
Newcastle University
Newcastle upon Tyne, NE1 7RU, UK
GlaxoWellcome
Medicines Research Centre, Gunnels Wood Road
Stevenage, Hertfordshire, SG1 2NY, UK
Zeneca Pharmaceuticals, Mereside, Alderley Park
Macclesfield, Cheshire, SK10 4TG, UK

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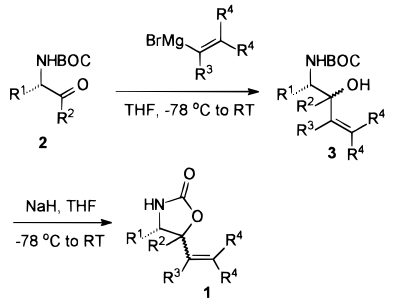
Transition metal catalyzed carbonylation of organic substrates has proved an important method for the synthesis of carbon−carbon and carbon−heteroatom bonds.[1] The synthesis of β-lactams by transition metal catalyzed processes is well documented[2,3] and has been accomplished by the carbonylation of aziridines,[4] 2-bromoallylamines,[5] propargylamines,[6] 4-amino-2-alkynyl carbonates,[7] and allyl phosphates in the presence of imines.[8] Transition metal catalyzed carbonylative syntheses of lactams with ring sizes larger than 4 include: benzo-fused five-, six-, and seven-membered lactams by cyclocarbonylation of 2-aminostyrenes and 2-allylanilines;[9] four-, five-, six-, and seven-membered α,β-unsaturated lactams from amino vinyl-halides[10a,b] and -triflates;[10c] five-, and six-membered lactams by hydrocarbonylation of amino-alkenes[11a,b] and -alkynes;[11c] five-, and six-membered lactams by carbonylative ring-expansion of azetidines[12a] and pyrrolidines;[12b] and five-membered lactams by decarboxylative carbonylation of 6-vinyltetrahydro-2*H*-1,3-oxazin-2-ones.[13]

Scheme 1. Synthesis of 5-Vinyloxazolidinones **1**



Since the decarboxylative carbonylation of vinyltetrahydro-oxazinones[13] leads to ring contraction to form γ-lactams, we envisaged a similar process leading from 5-vinyloxazolidin-2-ones **1** to β-lactams. In this contribution we report that palladium-catalyzed decarboxylative carbonylation of amino acid-derived 5-vinyloxazolidin-2-ones does not give the expected β-lactams. Instead, the corresponding δ-lactams, 3,6-dihydro-1*H*-pyridin-2-ones, are formed.

The required 5-vinyloxazolidin-2-ones **1** were synthesized from the corresponding α-amino aldehydes[14] **2** (R^2 = H) or ketone **2d** (R^1 = *i*-Pr, R^2 = Me) (Scheme 1). Aldehydes **2** (R^2 = H) were obtained by Swern oxidation[15] of the corresponding *N*-BOC protected α-amino alcohols. Ketone **2d** (R^1 = *i*-Pr, R^2 = Me) was prepared by the addition of MeMgBr to the corresponding Weinreb amide.[16] Grignard additions to **2** proceeded, as expected,[14] with low diastereoselectivity to produce the alcohols **3** as 1−5:1 mixtures of diastereoisomers which were cyclized to the oxazolidinones **1** by treatment with sodium hydride.

Attempted carbonylation of **1a** under the conditions reported for ring-expansion of aziridines[4c] (20 mol % $Pd_2(dba)_3{\cdot}CHCl_3$, 160 mol % PPh_3, 1 atm CO, rt, C_6H_6) gave complete recovery of starting material. Indeed, we were unable to find any catalyst/solvent system which would enable the carbonylation of vinyloxazolidinones to proceed at 1 atm of CO. Even at higher pressures (up to 60 atm) the carbonylation was unsuccessful in aprotic solvents such as THF, DMF, and MeCN. However, carbonylation was successful using $Pd(OAc)_2(PPh_3)_2$ (5 mol %) at a CO pressure of 65 atm in a protic solvent, ethanol.[17] The product from this reaction was not the expected β-lactam but the δ-lactam **4a**. The reaction was not catalyzed by either $Pd(OAc)_2$ or PPh_3 alone. Table 1 shows that this reaction is successful for a range of oxazolidinones providing δ-lactams in good to excellent yields.[18] The reaction tolerates substitution at C-5 (R^2 = Me, see entry for **1g**) and on the central carbon of the allyl system (R^3 = Me, entries for **1d**−**f**), but fails in the case of the terminally disubstituted vinyl derivative **1h** (R^4 = Me) probably due to the requirement for carbonylation to form a quaternary center in this case. Comparison of **4a** and **4g** with *ent*-**4a** and *ent*-**4g** (prepared

† Newcastle University.
‡ GlaxoWellcome.
§ Zeneca Pharmaceuticals.

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(17) These conditions are similar to those reported by Bando for the decarboxylative carbonylation of vinyloxazinones.[13]
(18) See the Supporting Information for experimental procedures.

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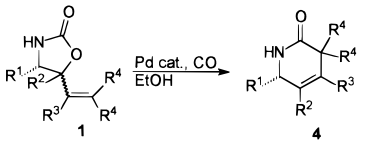
Table 1. Palladium Catalyzed Decarboxylative Carbonylations of 5-vinyloxazolidinones **1**[a]



1 **4**

1	R^1	R^2	R^3	R^4	yield[b] (%)
a	*i*-Pr	H	H	H	87
b	Bn	H	H	H	78
c[c]	Ph	H	H	H	58
d	*i*-Pr	H	Me	H	74
e	Bn	H	Me	H	66
f[c]	Ph	H	Me	H	57
g	*i*-Pr	Me	H	H	86
h	*i*-Pr	H	H	Me	0[d]

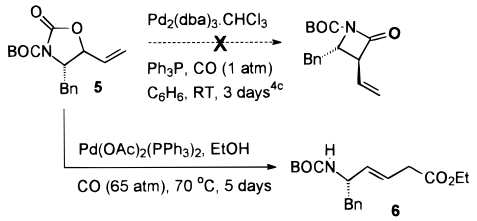
[a] $Pd(Ph_3P)_2(OAc)_2$ (5 mol %), EtOH, CO (65 atm), 65−70 °C, 120 h. [b] Isolated yield. [c] The (4*R*)-isomer (derived from *R*-phenylglycine) was used. [d] Starting material was recovered.

from (*R*)-valine) by chiral GC[19,20] showed that no loss of stereochemical integrity had occurred during the syntheses.

The reason for the unexpected regioselectivity of carbonylation is unclear. Endo-type cyclizations of π-allyl palladium intermediates to give the larger of the two available ring sizes are commonly seen in macrolide and medium ring carbocycle synthesis.[21] However, when the selectivity is between formation of four- and six-membered rings, kinetic control usually leads to the smaller ring size (as seen in the formation of carbocycles[21] and β-lactams[4c,d]). With heteroatom nucleophiles, such as nitrogen, formation of the larger ring size is possible due to thermodynamic control resulting from reversible cyclization.[21,22] It is therefore possible that kinetic formation of the β-lactam is followed by equilibration to the more stable δ-lactam in our case. It should be noted that treatment of *N*-tosyl vinyloxazolidinones with $Pd(PPh_3)_4$ catalyst is reported to lead to the corresponding vinylaziridines by loss of CO_2.[23] Treatment of the vinyloxazolidinone **1a** with $Pd(PPh_3)_4$ catalyst in either THF or EtOH leads to recovery of the oxazolidinone as a single (*trans*) diastereoisomer. Thus, ring opening of the oxazolidinone to form the π-allyl palladium species is reversible and is not accompanied by fast decarboxylation.

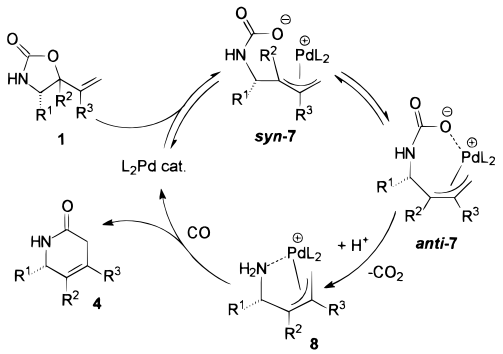
In the formation of β-lactams from vinylaziridines, the nitrogen carries an electron-withdrawing group (BOC or Ts). We therefore prepared the *N*-BOC-protected vinyloxazolidinone **5** and subjected it to carbonylation under Ohfune's conditions.[4c] The only identifiable compound from this reaction was unreacted **5** (35%); however, the ^1H NMR spectrum of the crude product mixture

Scheme 2. Carbonylation of *N*-BOC-Protected 5-Vinyloxazolidinone **5**



5 **6**

Scheme 3. Proposed Catalytic Cycle for Carbonylation Reaction



showed no evidence of β-lactam formation (in particular, no signals between δ 3.5−4 for the azetidinone 3- and 4-protons[4c]). The π-allyl intermediate formed in this reaction clearly does not decarboxylate since this would produce an intermediate identical to that formed in the carbonylation of vinylaziridines. Subjecting **5** to our carbonylation conditions did not lead to the *N*-BOC-protected δ-lactam but gave the ethoxycarbonylated allylic amine **6** in 48% yield (Scheme 2).

Formation of the *anti* complex **7** (Scheme 3) and decarboxylation may be favored by interaction between the nucleophilic amine and Pd; *anti* intermediate **8** has the required geometry to form the six-membered ring. In the case of **5**, the electron-withdrawing nature of the BOC group may lead to decarboxylation to form allyl species with no N−Pd coordination. Protonation of the nitrogen by ethanol will render it a rather poor nucleophile; hence, the formation of the ethoxycarbonylated species **6**.

In summary, we have demonstrated that palladium-catalyzed decarboxylative carbonylation of 5-vinyloxazolidin-2-ones, which are readily prepared from amino acid precursors, leads to 3,6-dihydro-1*H*-pyridin-2-ones in good yields. Further studies into the mechanism of this reaction and synthetic applications of the lactam products are underway and will be reported in due course.

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Supporting Information Available: Experimental procedures, spectroscopic and analytical data for compounds **1a**−**h**, **3a**−**h**, **4a**−**g**, **5**, and **6** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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