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Palladium-Catalyzed Insertion of CO_2 into Vinylaziridines: New Route to 5-Vinyloxazolidinones

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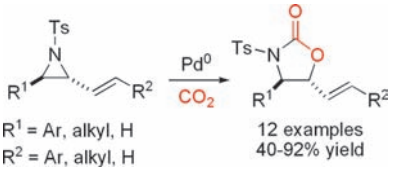
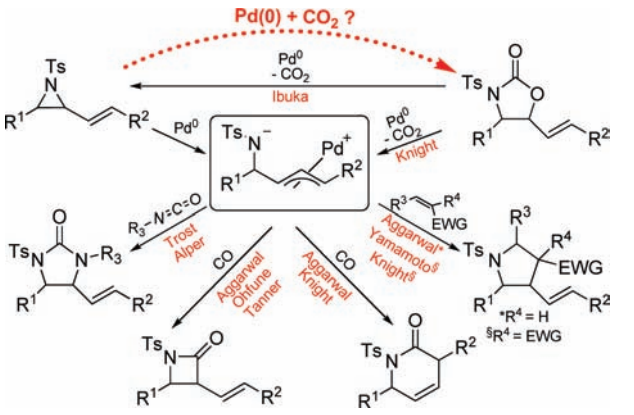
ABSTRACT



2-Vinylaziridines undergo a mild Pd-catalyzed ring-opening cyclization reaction with an ambient atmosphere of carbon dioxide to give 5-vinyloxazolidinones. The process is high yielding as well as regio- and stereoselective.

Vinylaziridines are valuable synthetic intermediates[1] which, as an illustration, undergo a host of very useful palladium-catalyzed transformations (Scheme 1). For example, we[2] and others[3] showed that they could be converted into unsaturated β-lactams with a high level of stereocontrol. In the presence of doubly activated Michael acceptors they can also be converted into pyrrolidines.[4a,b] We recently extended this methodology to singly activated acceptors and demonstrated its utility in a stereocontrolled synthesis of (+)-kainic acid.[4c] The Pd-catalyzed reaction of vinylaziridines with heterocumulenes (e.g., isocyanates, carbodiimides, and isothiocyanates) is also well established,[5] but insertion into the archetypal heterocumulene, CO_2, has not been reported.[6] Such a reaction would give vinyloxazolidinones, important motifs in both synthesis[7–9] and pharmacology.[10] However, this reaction did not seem promising since Ibuka had reported that 3-tosyl-5-vinyloxazolidin-2-ones underwent Pd-catalyzed *decarboxylation* to give *cis*-*N*-tosyl-2-vinylaziridines (Scheme 1).[11] Furthermore, Knight[4b,12] had shown that vinyloxazolidinones bearing electron-withdrawing groups

Scheme 1. Pd-Catalyzed Applications of Vinylaziridines



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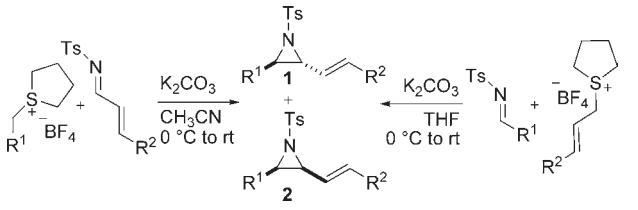
on nitrogen readily lost CO_2 upon treatment with Pd(0) and that the resulting π-allyl Pd intermediate could be trapped with CO or dipolarophiles.

Thus, the potential for incorporating CO_2 into vinylaziridines,[13] perhaps because of its high thermodynamic and kinetic stability, seemed remote. Nevertheless, our interest in the synthesis[14] and utility[2] of vinylaziridines together with the contemporary environmental need to find further uses of CO_2 as a raw material[15,16] prompted us to investigate this area further.

Scheme 2. Synthesis of Vinylaziridines



We initially synthesized a series of *N*-tosyl-2-vinylaziridines **1** using our sulfur ylide methodology as shown in Scheme 2 (see Supporting Information (SI)).[2] Treatment of the vinylaziridine **1a** with $Pd_2(dba)_3 \cdot CHCl_3$ in the presence of Ph_3P and just an *ambient* atmosphere of CO_2 gave the *trans*-vinyloxazolidinone **3a** in a promising 61% yield. In addition, *cis*-aziridine **2a** was also obtained together with traces of the starting material, *trans*-aziridine **1a** (Table 1, entry 1).[17]

The formation of the *cis*-aziridine **2a** is in keeping with Ibuka's observations as he had previously found that *trans*-*N*-tosyl aziridines readily isomerized to *cis*-aziridines (98:2) in the presence of Pd(0).[11]

The isolation of the isomerized starting material **2a** implicated a slow reaction between the amide anion and CO_2. We reasoned that ion pairing of the amide anion with the cationic Pd complex might compromise its reactivity and that increased nucleophilicity of the aza-anion could be achieved by rendering the Pd center neutral. Such a change had been pivotal in the successful reactions of vinyl aziridines with singly activated Michael acceptors.[4c] We therefore decided to add tetrabutylammonium chloride (TBAC).[18] While reaction at RT was lower yielding, at 0 °C the product vinyloxazolidinone **3a** was obtained in 86% yield (entries 2 and 3). We were able to achieve similar results at a lower phosphine loading (entry 4). Replacing the highly hygroscopic TBAC with the more easily manageable fluoride source tetrabutyl-ammonium difluorotriphenylsilicate (TBAT) led to a further increase in yield (92%) with no detectable traces of starting material **1a** or *cis*-aziridine **2a**. Furthermore the reaction was now completed over a shorter reaction time (entry 5). A control experiment in the absence of TBAT or Pd (entries 6, 7) confirmed the beneficial effects of both species in promoting the carboxylation.

Having developed an optimized protocol we then screened the scope of the reaction (Table 2). Carboxylation occurred uneventfully for a series of diaryl-substituted *trans*-aziridines **1b**–**1g** bearing either electron-donating or -withdrawing *para* substituents (entries 2, 3, 6, 7, 9). However, when R^1 possessed greater electron-donating character the addition of TBAT became detrimental and

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(17) To avoid any further reaction of the desired oxazolidinone, the reaction mixture was promptly filtered through a pad of silica to remove the catalyst (see Supporting Information).

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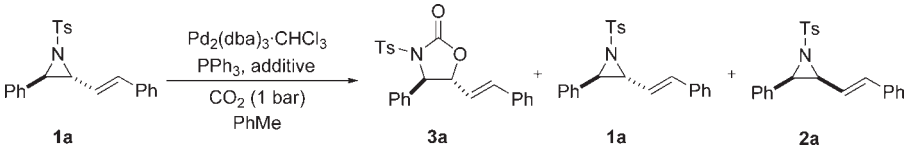
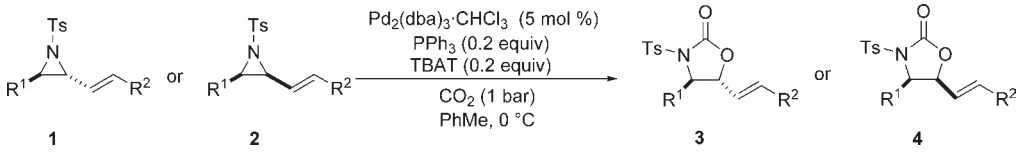
Table 1. Optimization of the Carboxylation Reaction[a]



entry	[Pd] mol %	PPh_3/Pd	additive (equiv)	t (°C)	time (h)	conversion (%)[b]	yield **2a** (%)[b]	yield **3a** (%)[b]
1	10	6	–	rt	8	98	29	61
2	10	6	TBAC (0.2)	rt	18	99	11	42
3	10	6	TBAC (0.2)	0	18	100	traces	86
4	10	2	TBAC (0.2)	0	4	100	–	86
5	**10**	**2**	**TBAT (0.2)**	**0**	**2**	**100**	–	**92**[c]
6	10	2	–	0	2	98	–	71
7[d]	–	–	TBAT (0.2)	0	2	0[e]	–	–

[a] dba = dibenzylideneacetone. TBAC = tetrabutylammonium chloride. TBAT = tetrabutylammonium difluorotriphenylsilicate. Aziridine concentration = 6×10^{-2} M. [b] Determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as an internal standard. [c] Isolated yield. [d] Carried out in the presence of PPh_3 (0.2 equiv). [e] Only starting material was recovered.

Table 2. Scope of Pd-Catalyzed Carboxylation Reaction[a]



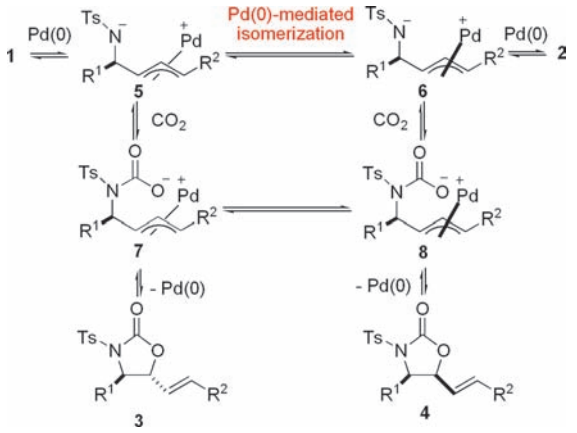
entry	aziridine	R^1	R^2	*dr* (**1**:**2**)	time (h)	yield (%)[b]	*dr* (**3**:**4**)[c]
1	**1a**	Ph	Ph	>98:2	2	92	>98:2
2	**1b**	Ph	*p*-Me-C_6H_4	>98:2	2	86	>98:2
3	**1c**	Ph	*p*-OMe-C_6H_4	97:3	4	87	97:3
4	**1c/2c**	Ph	*p*-OMe-C_6H_4	52:48	4	62[d]	79:21
5	**2c**	Ph	*p*-OMe-C_6H_4	2:>98	4	40	8:92
6	**1d**	Ph	*p*-Cl-C_6H_4	>98:2	4	86	>98:2
7	**1e**	*p*-Me-C_6H_4	Ph	>98:2	4	89	>98:2
8[e]	**1f**	*p*-OMe-C_6H_4	Ph	>98:2	4	91	>98:2
9	**1g**	*p*-Cl-C_6H_4	Ph	>98:2	2	84	>98:2
10	**1h**	Ph	Me	>98:2	3	78	96:4
11	**1i**	Ph	TMS	>98:2	24	40	>98:2
12[e]	**1j**	Cy	Ph	>98:2	4	83	>98:2
13	**1k/2k**	Ph	H	85:15	0.5	71[f]	85:15
14[e]	**1l**	H	H	-	0.5	68	–
15	(2*R*,3*R*)-**1a** (98:2 *er*)	Ph	Ph	>98:2	2	89 (>99:1 *er*)[g]	>98:2

[a] dba = dibenzylideneacetone. TBAT = tetrabutylammonium difluorotriphenylsilicate. Aziridine concentration = 6×10^{-2} M. [b] Isolated yield. [c] Determined by ^{1}H NMR of the crude. [d] Determined by ^{1}H NMR with 1,1,2,2-tetrachloroethane as internal standard. [e] Conducted in the absence of TBAT. [f] ^{1}H NMR of the crude showed the desired oxazolidinones together with *cis*-aziridine **2j** in a ratio of 85:15. [g] Determined by chiral HPLC (see SI).

higher yields were achieved without it (entry 8). Alkyl residues were well tolerated on both the vinyl moiety, **1h** (R^2 = Me), **1i** (R^2 = $SiMe_3$), and the aziridine core, **1i** (R^1 = Cy) (entries 10, 11, 12). The unsubstituted aziridine **1l** underwent carboxylation, but as before, higher yields were observed in the absence of TBAT (entry 13). Interestingly, the ratio of *trans*- and *cis*-vinyloxazolidinones reflected the ratio of *trans*- and *cis*-aziridines that we started with. Using enantioenriched aziridine (2*R*,3*R*)-**1a**, the *trans*-vinyloxazolidinone (+)-**3a** was obtained with very high er, indicating that no erosion in enantiopurity took place (entry 14). We were also able to test the *cis*-aziridine **2c** and a ~1:1 mixture of *cis*/*trans* isomers **1c**/**2c** (entries 4, 5). Unexpectedly, the *cis*-aziridine mainly gave the *cis*-oxazolidinone **4c** and the ~1:1 mixture led to a 79:21 mixture of *trans*/*cis* oxazolidinones.

On the basis of these observations together with previous studies,[2] we propose the mechanism shown in Scheme 3. The *trans*-*E*-vinylaziridine can react with Pd(0) to give the π-allyl palladium intermediate **5**. Pd−Pd

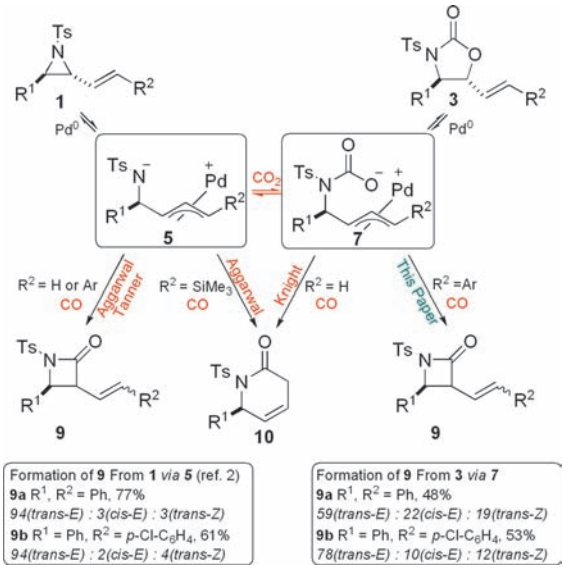
Scheme 3. Proposed Mechanism



mediated isomerization[19] would give the isomeric complex **6** which can ring close to the *cis*-*E*-vinylaziridine **2**. This is the accepted mechanism for isomerization of *trans*- and *cis*-vinylaziridines. Capture of the π-allyl palladium intermediates **5** and **6** by CO_2 then give the vinyloxazolidinones **3** and **4** respectively. The fact that *cis*-aziridine **2c** gives mostly the *cis*-oxazolidinone **4c** implies that isomerization of the π-allyl palladium intermediates **5** and **6** has been significantly suppressed under the reaction conditions. Factors that reduce the extent of such isomerization include (i) a lower temperature and (ii) use of a halide additive.[20,4c] Indeed, at RT and in the absence of halide salts the *cis*-aziridine **2c** gave considerably more of *trans*-oxazolidinone (68 *cis*/32 *trans*) indicating that a greater degree of isomerization had taken place. Moreover, subjecting the *cis*-oxazolidinone **4c** (91 *cis*/9 *trans*) to the reaction conditions resulted in the same ratio of isomers indicating that no isomerization occurred. Again, at RT but in the absence of halide salts the isomerization of **4c** was much more rapid giving increased amounts of *trans*-oxazolidinone (76 *cis*/24 *trans*). These experiments show that *cis*−*trans* isomerization of both the aziridines and oxazolidinones is largely arrested under the reaction conditions (kinetic control) but can occur in the absence of halide ions and higher temperatures (thermodynamic control).

Knight has shown that 5-vinyloxazolidinones can serve as substrates for Pd(0)-catalyzed reactions, e.g. carbonylation, in a manner analogous to vinylaziridines.[12] However, subtle differences in product distributions are observed (Scheme 4). For example, *N*-tosyl-2-vinylaziridines where R^2 = H or Ar are known to afford β-lactams **9**.[2,3a] However, Knight reported that submission of the corresponding *N*-tosyl-vinyloxazolidinones (R^2 = H) to carbonylation gave the δ-lactam derivative **10** instead.[12c] The same regioisomers were obtained from vinylaziridines when $R^2 = SiMe_3$.[2,21] Surprisingly, we observed that carbonylation of vinyloxazolidinones **3a** (R^1, R^2 = Ph) and **3d** (R^1 = Ph, R^2 = *p*-Cl-C_6H_4) afforded the β-lactams **9**, albeit in lower yields and diastereoselectivity as compared to the corresponding aziridines (see SI for details).[2] This indicates that the intermediates involved prior to insertion of CO are subtly different. It is likely that decarboxylation is not instantaneous and that the product distribution is influenced by the rates of isomerization of the π-allyl Pd species and by the rates of carbonylation and decarboxylation, all of which will be substrate-dependent.

Scheme 4. Regioselectivity of Carbonylation



In conclusion, we have discovered that readily available *trans*-vinylaziridines can be converted into *trans*-vinyloxazolidinones through a Pd-catalyzed carboxylation process. The use of CO_2 in such processes is rare because CO_2 is widely regarded as thermodynamically stable and kinetically unreactive. The results presented herein show that it is far from kinetically unreactive, as should be expected for an electron-deficient carbon atom bearing two strongly activated electron sinks.

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Supporting Information Available. Synthesis and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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