Stereoselective synthesis of *trans*-β-lactams by palladium-catalysed carbonylation of vinyl aziridines†‡

Francesco Fontana,[ab] Gian Cesare Tron,[a] Nekane Barbero,[a] Serena Ferrini,[a] Stephen P. Thomas[a] and Varinder K. Aggarwal*[a]

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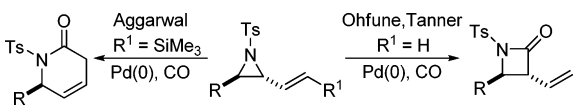
The palladium-catalysed carbonylation of vinyl aziridines can give either the *trans*- or *cis*-β-lactam preferentially or even the δ-lactam simply by adjusting the reaction parameters ([Pd], [CO], temperature).

β-Lactams have a long and illustrious history in the field of medicinal chemistry.[1] As such, methods for their construction with stereocontrol have been, and still are, highly important to the continued development of the area.[2] Amongst the methodologies, the Staudinger reaction is still pre-eminent: using chiral catalysts high yields, *d.r.*s and *e.e.*s can be achieved.[3,4] Limited reports from Ohfune *et al.*[5] and Tanner and Somfai[6] demonstrated another route to β-lactams through Pd-mediated carbonylation of vinyl aziridines, although they only reported unsubstituted vinyl aziridines.

As we had developed a simple route to vinyl aziridines *via* the reaction of sulfur ylides with imines,[7] we sought to expand the limited β-lactam methodology to a broader set of substrates. Surprisingly, however, using a silyl-substituted vinyl aziridine under the same conditions as reported by Tanner and Somfai[6] gave the δ-lactam[8] instead of the β-lactam (Scheme 1).[7] So what governs the outcome of this reaction—is it the terminal substituent or the nature of that substituent? In this communication we provide a mechanistic rationale for this unusual observation and through our analysis we have been able not only to switch from β-lactams to δ-lactams but also to switch the stereochemical outcome of the reaction simply by modifying the reaction parameters.

We initially studied the carbonylation of the cinnamyl phenyl aziridine **1a**. Using the pure *trans*-isomer **1a** the *trans*-β-lactam **5a** was obtained in good yield and with high



Scheme 1 Dichotomous pathways in carbonylation.

[a] *School of Chemistry, Cantock's Close, Bristol, UK. E-mail: V.Aggarwal@bristol.ac.uk; Fax: +44 (0)117 929 8611; Tel: +44 (0)117 954 6315*
[b] *Università degli Studi di Milano, Dipartimento di Chimica Organica e Industriale, Via Venezian 21, 20133, Milano, Italy*

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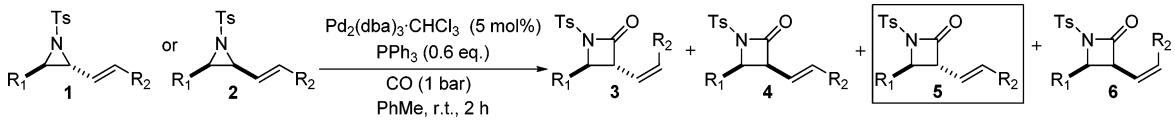
diastereoselectivity after substantial optimisation of the reaction conditions (Table 1, entry 1). Noteworthily (*vide infra*), the *cis*-vinyl aziridine **2a** or a mixture of the *cis*- and *trans*-isomers gave the same *trans*-β-lactam **5a** as the major product (entries 2 and 3). This has significant practical implications as sulfur-ylide-mediated aziridinations often lead to a mixture of *cis*- and *trans*-aziridines. Being able to use this mixture directly to generate essentially one diastereomer of the β-lactam both simplifies and enhances the yield of the overall process. The preference for formation of the *trans*-β-lactam **5a** and the high diastereoselectivity irrespective of the geometry of the starting aziridine was maintained for a range of diaryl vinyl aziridines bearing electron rich or electron deficient groups at either end (entries 4–12). Under standard conditions the alkyl substituted vinyl aziridine **1h** did not give any β- or δ-lactam, but decomposed instead. However, operating at 50 bar CO gave the β-lactam, although this time in favour of the *trans*-*Z*-isomer **3h** (entry 14). Using an enantioenriched aziridine, full chirality transfer was observed (entry 15).

The proposed mechanism for the formation of the β-lactams is shown in Scheme 2. Pd(0) has been shown to isomerise vinyl aziridines through oxidative addition followed by π–σ–π isomerisation (Scheme 2, **1** → **9** *via* **10**).[9] Capture of the intermediate π-allyl Pd complexes **7** and **10** with CO followed by ring closure would generate β-lactams **3** and **4**, but neither was observed to any significant extent from reactions of diaryl aziridines **1a–g**. Instead *trans*-β-lactam **5** was obtained which must arise from Pd(0)-mediated isomerisation[10] of **7** → **8** followed by carbonylation and ring closure. In a fully equilibrating system (where isomerisation, carbonylation and decarbonylation rates are fast) the product ratio will be determined by the equilibrium concentrations of the acyl Pd intermediates **11–14** and their relative rates of ring closure. The *Z*-acyl Pd intermediates **11** and **14** will be less favoured than the *E*-isomers **12** and **13** and of these species **13** should cyclise faster than **12** since it leads to the (observed) *trans*-isomer (β-lactam **5**).

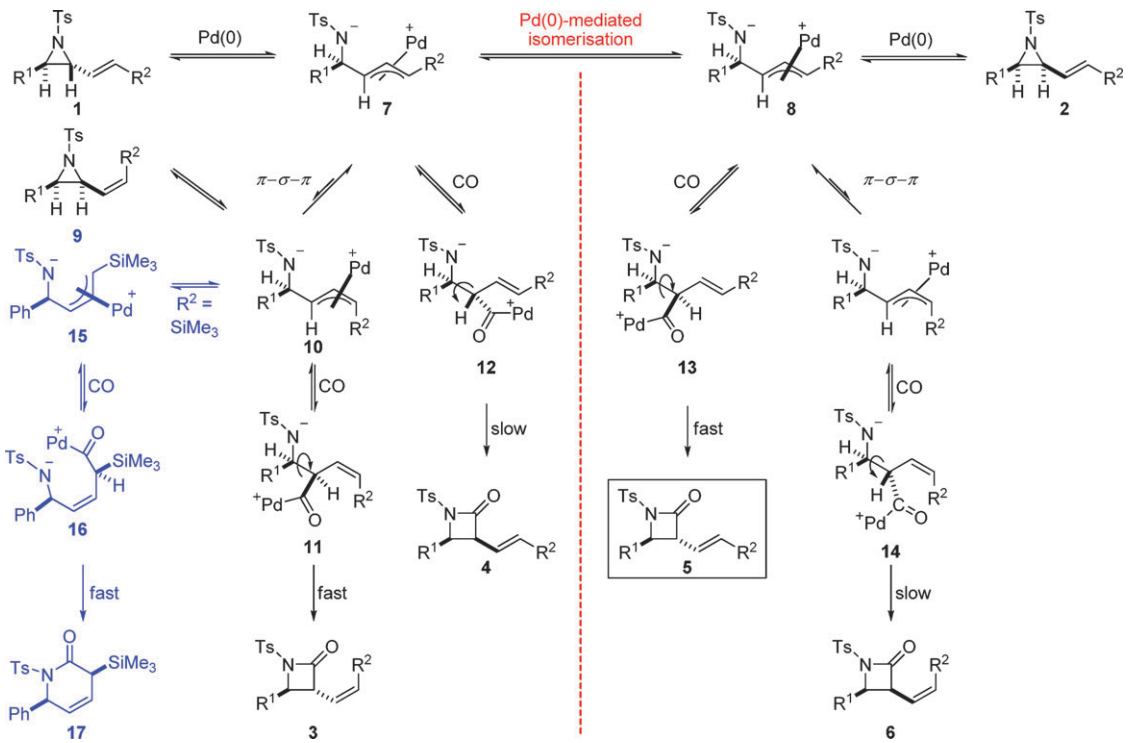
Based on this analysis, the subtle variations in product ratios from Table 1 can be rationalised. Starting with the *cis*-*E*-vinyl aziridine **2** leads to an even greater ratio of β-lactam **5** as Pd(0)-mediated isomerisation of the π-allyl Pd species is no longer needed (Table 1, compare entries 1/3 and 5/7). If R^1 is an electron rich substituent, the amide becomes more nucleophilic, thus increasing the rate of cyclisation. This reduces diastereoselectivity as the system is no longer fully equilibrating (Table 1, compare entries 9–12). Further evidence for this mechanistic rationale was gained from the

Table 1 Carbonylation of vinyl aziridines: scope and diastereoselectivity[a]



Entry		R^1	R^2	*d.r.* (**1**:**2**)	Yield (%)[b]	*d.r.* (**3**:**4**:**5**:**6**)[c]
1	**1a**	Ph	Ph	>98:2	77	3:3:94:0
2	**1a**/**2a**	Ph	Ph	50:50	75	2:2:96:0
3	**2a**	Ph	Ph	2:>98	73	1:2:97:0
4	**1b**	Ph	*p*-Me-Ph	>98:2	64	4:3:93:0
5	**1c**	Ph	*p*-OMe-Ph	96:4	71	5:3:92:0
6	**1c**/**2c**	Ph	*p*-OMe-Ph	75:25	59	2:2:96:0
7	**2c**	Ph	*p*-OMe-Ph	2:>98	76	0:0:100:0
8	**1d**	Ph	*p*-Cl-Ph	93:7	61	4:2:94:0
9	**1e**	*p*-Me-Ph	Ph	>98:2	71	9:9:82:0
10	**1f**	*p*-OMe-Ph	Ph	>98:2	67	9:15:76:0
11	**1g**	*p*-Cl-Ph	Ph	>98:2	65	2:2:96:0
12	**1g**/**2g**	*p*-Cl-Ph	Ph	75:25	60	6:4:90:0
13	**1h**	Ph	Me	>98:2	0	—
14[d]	**1h**	Ph	Me	>98:2	79	80:0:16:4
15	**1a** (98:2 *e.r.*)	Ph	Ph	>98:2	62 (98:2 *e.r.*)	2:2:96:0

[a] dba = dibenzylideneacetone; aziridine concentration = 6×10^{-2} M. [b] Isolated yield. [c] Determined by ^{1}H-NMR after chromatography. [d] 50 bar CO pressure.

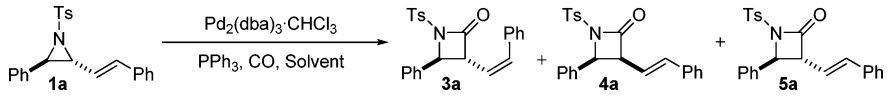


Scheme 2 Mechanism of conversion of vinyl aziridines into β- and δ-lactams.

following experiments. Reducing the concentration of Pd resulted in lower diastereoselectivity, presumably because we had reduced the extent of Pd(0)-mediated isomerisation (**7** → **8**) (Table 2, entries 1 and 2). Reducing the temperature now resulted in a reversal of diastereoselectivity (Table 2, entries 5 and 6). Presumably at lower temperature the concentration of CO in solution is higher, thereby reducing the rate of decarbonylation. This would result in limiting the extent of equilibration thereby lowering diastereoselectivity. It is also possible that at low temperature the rate of Pd(0)-mediated isomerisation (**7** → **8**) is reduced. Conversely, at low CO pressure, the system should be fully equilibrating due to fast decarbonylation (true Curtin–Hammett conditions) and the *trans-E-β*-lactam **5a** was now the only diastereoisomer of the product formed (entry 7). At high pressure and low Pd concentration we were able to switch from the *trans-β*-lactam **5a** to the *cis*-isomer **4a** as the main product (entries 9 and 10).

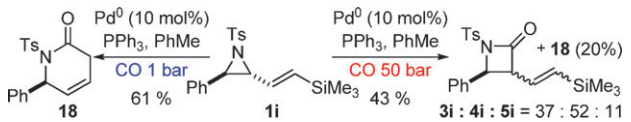
The outcome of the reaction of the alkyl substituted aziridine **1h** can also be rationalised based on the above

Table 2 Effect on β-lactam diastereoselectivity by variation of the reaction parameters[a]



Entry	[Pd] (mol%)	CO/Bar	Temperature	Solvent	Time/h	Yield (%)[b]	d.r. (**3a** : **4a** : **5a**)[c,d]
1	10	1	r.t.	Toluene	2	77	3 : 3 : 94
2	5	1	r.t.	Toluene	2	30	13 : 23 : 64
3	10	1	r.t.	1,2-DME	16	67	1 : 20 : 79
4	10	1	r.t.	CH_2Cl_2	5	44	0 : 8 : 92
5	10	1	−5 °C	Toluene	120	56	34 : 56 : 10
6	10	1	−5 °C to r.t.	1,2-DME	72	62	14 : 67 : 19
7	10	0.1	r.t.	Toluene	2	60	0 : 0 : 100
8	10	50	r.t.	Toluene	2	75	14 : 28 : 58
9	4	50	r.t.	Toluene	2	69	29 : 52 : 19
10	4	50	r.t.	CH_2Cl_2	20	44	10 : 79 : 11

[a] Aziridine concentration = 6×10^{-2} M. [b] Isolated yield. [c] Determined by ^{1}H-NMR after chromatography. [d] The *cis-Z* isomer was never observed.



Scheme 3 Effect of pressure on the regioselectivity of carbonylation.

mechanism. At atmospheric pressure the π-allyl Pd complex **7** decomposes, probably through an elimination pathway. However, at high pressure it is more rapidly captured by CO leading preferentially to the *trans-Z-*β-lactam **3**. In this case Pd(0)-mediated isomerisation is evidently slower than when R^2 = Ph (compare Table 1 entry 14 with Table 2 entry 8) and even though the concentration of **11** is expected to be lower than **12** its faster rate of cyclisation leads to **3** being the predominant isomer.

The preference for the silyl-substituted aziridine **1i** to give the δ-lactam over the β-lactam **3i** is intriguing (Scheme 3). It may result from an inherent preference for carbonylation to occur adjacent to Si due to the shorter C–Pd bond length[11] in the unsymmetrical π-allyl Pd complex **15** to give the acyl Pd species **16** (presumably other non-productive acyl Pd species are also generated but revert back to the one that is ultimately productive). This will subsequently undergo fast cyclisation to give δ-lactam **18** after protodesilylation. However, the acyl Pd species **16** must be in very low concentration since it suffers significant steric hindrance. We reasoned that since the equilibrium ratios of the different acyl Pd species present in solution could be influenced by the concentration of CO, a different outcome could be expected at high CO concentration since the system is less equilibrating. Indeed, operating at 50 bar now gave the β-lactam predominantly as a mixture of diastereomers (Scheme 3). This mixture is consistent with a reaction in which there is fast carbonylation with minimal Pd(0)-mediated isomerisation of the π-allyl Pd complex.

In conclusion, we have shown that β-substituted α,β-unsaturated aziridines undergo Pd-catalysed carbonylation reactions to give β-lactams. The π-allyl Pd intermediates undergo a high degree of isomerisation prior to formation of the β-lactam. By carefully controlling the reaction parameters (temperature, [Pd], [CO]) we can influence the degree of isomerisation and thereby control not only which diastereomer is formed but also (in one case) whether a β- or δ-lactam is obtained.

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