Stereoselective γ-lactam synthesis *via* palladium-catalysed intramolecular allylation†

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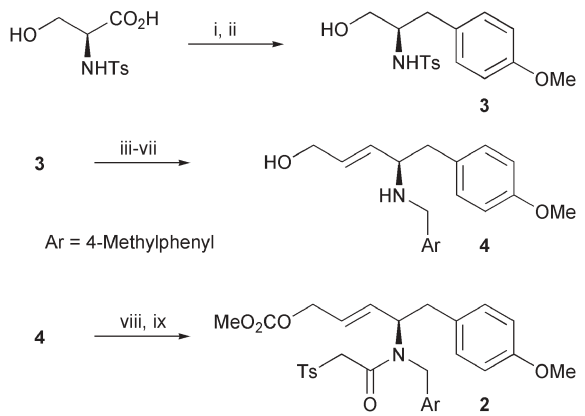
A novel route to the synthesis of 3-(tolylsulfonyl)-4,5-*cis*-disubstituted γ-lactams using a diastereoselective palladium-catalysed intramolecular allylation of amino acid-derived allylic carbonates has been developed.

During a programme directed towards the synthesis of alkaloids related to morphine we required a stereoselective method for the assembly of 3-(tolylsulfonyl)-4,5-*cis*-disubstituted γ-lactams **1**. A search of the literature revealed few methods for the synthesis of the thermodynamically disfavoured 4,5-*cis*-disubstituted isomers, and it was felt that given their chemical and biological significance[1] the development of a general route to these structures was worthwhile.

The use of π-allyl palladium chemistry for the construction of γ-lactams *via* formation of the C3–C4 bond has been described extensively by Poli *et al.*[2] Trost has reported the palladium-catalysed cyclisation of allylic substrates to give cyclopentyl products where the *cis* diastereoisomer was favoured as a result of a metal-template effect.[3] In light of these findings it was proposed that palladium-catalysed cyclisation of amino acid-derived allylic carbonates such as **2** might offer a diastereoselective route to 4,5-*cis*-disubstituted γ-lactams.[4]

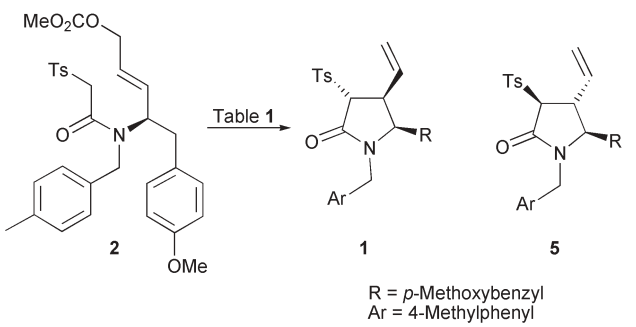


Scheme 1 *Reagents and conditions*: (i) BrMgArOMe (8 equiv.), *n*-BuLi (2 equiv.), rt, 37 h, 73%; (ii) Et_3SiH (10 equiv.), TFA (20 equiv.), 45 °C, 24 h, 80%; (iii) (a) $(COCl)_2$ (1.2 equiv.), DMSO (2.4 equiv.), CH_2Cl_2, −78 °C, 45 min; (b) Et_3N (5 equiv.), rt, 10 min; (iv) Ph_3PCHCO_2Et (4 equiv.), CH_2Cl_2, rt, 12 h, 86% over two steps; (v) DIBAL-H (3.6 equiv.), CH_2Cl_2, −78 °C, 1 h, 78%; (vi) Na (5 equiv.), naphthalene (5.3 equiv.), THF, rt, 1 h or NH_3(l), Na (6 equiv.), −78 °C, 15 min; (vii) (a) 4-methylbenzaldehyde (4 equiv.), 4 Å MS, AcOH, THF, rt, 1 h; (b) $NaCNBH_3$ (5 equiv.), −78 °C → rt, 10 h, 60% over two steps; (viii) DCC (2.1 equiv.), $TsCH_2CO_2H$ (2 equiv.), THF, rt, 12 h; (ix) methyl chloroformate (2 equiv.), pyridine (2 equiv.), DMAP (cat.), CH_2Cl_2, rt, 2 h, 87% over two steps.

Initial cyclisation studies were carried out on the L-serine derived cyclisation substrate **2**, which was synthesised as shown in Scheme 1. *N*-Tosyl-L-serine[5] was subjected to Grignard addition[6] followed by reduction of the resulting ketone with Et_3SiH–TFA to give **3**. Subsequent Swern oxidation and Wittig homologation was followed by DIBAL-H-mediated reduction of the resulting ester. The resultant alcohol was detosylated under dissolving metal conditions and reductive amination carried out on the crude amine product to yield **4**. Finally, a DCC-assisted coupling with tosylacetic acid and formation of the carbonate provided the desired cyclisation substrate **2**.

For the proposed cyclisation $Pd_2(dba)_3$ was chosen as the Pd(0) source due to its air stability and ease of handling, whilst the highly basic tris(2,4,6-trimethoxyphenyl)phosphine (TTMPP)[7] was chosen as the ligand. The results of the investigation are summarised in Table 1. It was found that the use of TTMPP in MeCN as

Table 1 Optimisation of palladium-catalysed cyclisation



Entry	Conditions[a]	*cis* : *trans* ratio[b]
1	TTMPP, PhMe, rt → 50 °C, 12 h	No reaction
2	TTMPP, THF, rt → 50 °C, 12 h	65 : 35
3	TTMPP, MeCN, rt, 30 min	85 : 15[c]
4	TTMPP, MeCN, 50 °C, 15 min	78 : 22
5	TIPP, MeCN, rt → 50 °C, 12 h	67 : 33
6	*n*-Bu_3P, MeCN, rt → 50 °C, 12 h	67 : 33
7	$P(Cy)_3$, MeCN, rt → 50 °C, 12 h	63 : 37
8	PPh_3, MeCN, rt → 50 °C, 12 h	63 : 37
9	dppe, MeCN, rt → 50 °C, 12 h	50 : 50

[a] All reactions were carried out using 5 mol% $[Pd_2(dba)_3]$ and 50 mol% phosphine ligand. [b] Isomer ratios were determined by ^{1}H NMR analysis of crude products; reactions proceeded in > 90% yield by ^{1}H NMR. [c] Product **1** + **5** was obtained in 90% isolated yield.

† Electronic supplementary information (ESI) available: experimental details and full spectroscopic data for all synthetic intermediates, allylic carbonate substrates and lactam cyclisation products. See http://www.rsc.org/suppdata/cc/b5/b504731e/index.sht

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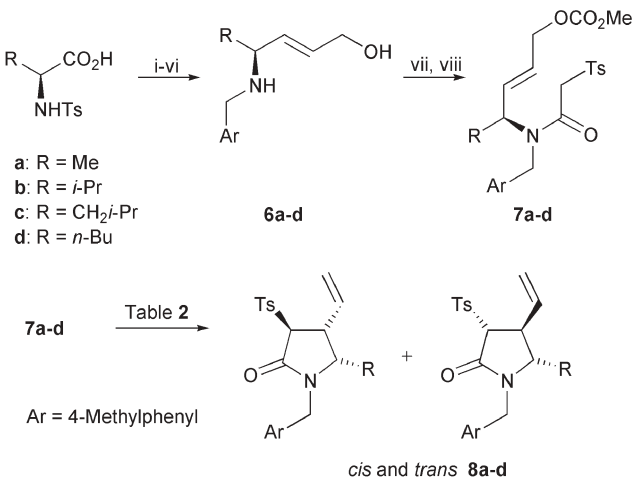
solvent resulted in a rapid (< 30 min) *cis*-selective cyclisation (85 : 15) producing γ-lactams **1** and **5** in excellent yield (90%) (Table 1, entry 3). The *cis*-relationship of the vinyl and *p*-methoxybenzyl groups was assigned unambiguously from the observation of NOE interactions between H-4 and H-5. With TTMPP as the ligand, use of solvents other than MeCN resulted in either lower selectivity or unviably slow reactions, even at elevated temperatures. A range of other phosphines in conjunction with MeCN were investigated for the cyclisation (entries 5–9), but no increase in selectivity was observed. Interestingly, only with TTMPP in MeCN did the reaction proceed at room temperature.

With the conditions optimised for the synthesis of 4,5-*cis*-γ-lactam **1** from substrate **2**, we wished to investigate the generality of the procedure for other amino acid-derived substrates **7a–d**, and in particular the effect of the steric bulk of R on the selectivity of the cyclisation (Scheme 2). The required substrates were synthesised from L-alanine, L-valine, L-leucine and DL-norleucine respectively *via* an adaptation of the route used for **2**. Thus, the *N*-tosylamino acids were reduced with $LiAlH_4$ and then subjected to Swern oxidation and Wittig homologation. The resulting unsaturated esters were reduced with DIBAL-H, desulfonylated and the crude amines then subjected to reductive amination to give secondary amines **6a–d**. Amines **6a–d** were coupled with tosylacetic acid using PyBOP,[8] and the resulting allylic alcohols carboxymethylated under standard conditions to give the desired cyclisation substrates **7a–d**. All steps proceeded in good to excellent yield for all substrates.

The allylic carbonates **7a–d** were subjected to the conditions optimised for substrate **2** (entry 3, Table 1; entry 1, Table 2).‡ All substrates underwent facile *cis*-selective cyclisation (Table 2). The *cis*-diastereoselectivity of the cyclisation may be explained by the



Scheme 2 *Reagents and conditions*: (i) $LiAlH_4$ (3.0 equiv.), THF, reflux, 2 h; (ii) (a) $(COCl)_2$ (1.2 equiv.), DMSO (2.4 equiv.), CH_2Cl_2, −78 °C, 45 min; (b) Et_3N (5 equiv.), rt, 10 min; (iii) Ph_3PCHCO_2Et (4 equiv.), CH_2Cl_2, rt, 12 h; (iv) DIBAL-H (3.6 equiv.), CH_2Cl_2, −78 °C, 15 min, then rt, 2 h; (v) NH_3 (l), Na (6 equiv.), −78 °C; (vi) (a) 4-methylbenzaldehyde (2 equiv.), MeOH, 4 Å MS, 12 h, rt; (b) $NaBH_4$ (2.4 equiv.), 0 °C–rt, 1 h; (vii) DCC (2.1 equiv.), HOBt (2.1 equiv.), $TsCH_2CO_2H$ (2 equiv.), CH_2Cl_2, rt, 12 h or PyBOP (2 equiv.), Hünig's base (5.5 equiv.), $TsCH_2CO_2H$ (2 equiv.), CH_2Cl_2, rt, 12 h; (viii) methyl chloroformate (2 equiv.), pyridine (2 equiv.), DMAP (cat.), CH_2Cl_2, 1 h.

Table 2 Palladium-catalysed cyclisation of **2** and **7a–d**

Entry	Substrate	R	*cis* : *trans* ratio[a]	Isolated yield
1	**2**	CH_2ArOMe	85 : 15	90%
2	**7a**	Me	86 : 14	90%
3	**7b**	*i*-Pr	67 : 33	78%
4	**7c**	CH_2*i*-Pr	90 : 10	85%
5	**7d**[b]	*n*-Bu	83 : 17	79%

[a] Determined by ^1H NMR analysis of the crude product and NOE or NOESY experiments. [b] Racemic substrate.

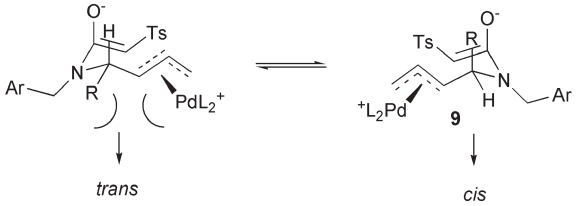


Fig. 1 Proposed model for *cis* diastereoselectivity of the cyclisation.

preferred reactive conformation **9**, where the palladium and its associated ligands avoid unfavourable interactions with the R group. As a linear relationship between the size of the R group and the selectivity of the reaction was not observed, it is assumed that there are other factors controlling the selectivity. For example, a 1,3-diaxial interaction between R and the enolate oxygen and/or H[1] might be considered in addition to the Pd–R interaction (Fig. 1).

In conclusion, we have developed a new method for the efficient, diastereoselective synthesis of *cis*-4,5-disubstituted γ-lactams through the Pd(0)-catalysed cyclisation of α-tosyl-substituted amides. These are the first examples of such cyclisations to be carried out on acyclic substrates having this level of complexity,[2] and the substrates are readily synthesised as single enantiomers using routine transformations starting from α-amino acids. A model to explain the observed stereoselectivity has been proposed. In addition, the highly functionalised nature of γ-lactams **1** and **8a–d** render them amenable to further substitution. For example, **1** undergoes alkylation of the derived sulfone-substituted enolate on the less hindered face with complete stereoselectivity to provide **10** in good yield (Scheme 3).

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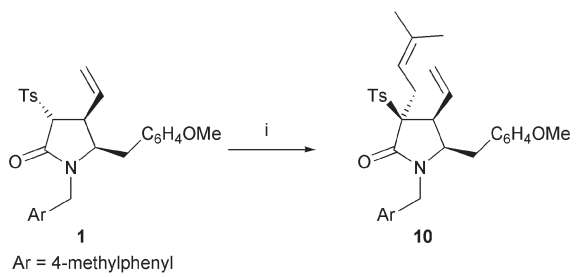

Scheme 3 *Reagents and conditions*: KH (1.1 equiv.), prenyl bromide (10 equiv.), DMF, 0 °C, 30 min, 78%.

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Notes and references

‡ *Typical experimental procedure for cyclisation reactions of carbonates* **2**, **7a–d**: A solution of the carbonate (0.103 mmol, 1.0 equiv.) in MeCN (1 ml) was added to a flask charged with $Pd_2(dba)_3$ (5.0 mol%) and TTMPP (0.052 mmol, 0.5 equiv.) at rt. After the carbonate had been consumed as indicated by tlc, the mixture was concentrated under reduced pressure. Chromatography (30% EtOAc–petrol) then gave the γ-lactams as an inseparable *cis* : *trans* mixture.

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