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Synthesis of highly substituted pyrrolidines via palladium catalysed formal [2+3] cycloaddition of 5-vinyloxazolidin-2-ones to activated alkenes

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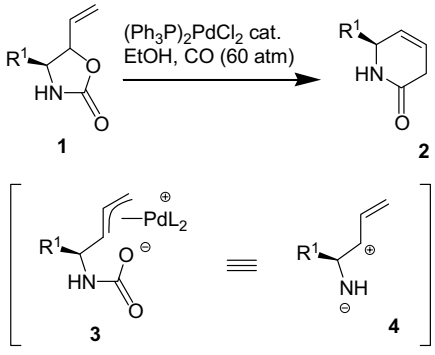
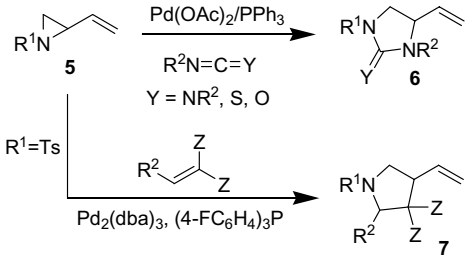
Abstract—Glycine-derived *N*-tosyl-5,5-divinyloxazolidin-2-one **10** undergoes a palladium catalysed decarboxylative ring-opening cyclization with strongly electron deficient alkylidenemalonate derivatives to give highly substituted pyrrolidines **14** containing two contiguous quaternary centres.

Transition metal mediated addition of amines to alkenes is an important method for the synthesis of functionalised nitrogen-containing compounds and has found many applications in the synthesis of biologically important species.[1] We have reported[2–4] the decarboxylative carbonylation of 5-vinyloxazolidin-2-ones **1** as a stereocontrolled route to piperidinones **2** and have used this reaction as the key step in the synthesis of the polyhydroxylated piperidines such as deoxymannojirimycin and mannolactam.[5]



This reaction is presumed to proceed via the π-allyl palladium cation **3**, which can be regarded, after loss of CO_2, as an equivalent to the 1,3-dipole **4**. This suggests the possibility of cycloaddition to suitably activated electrophilic alkenes, which would lead to pyrrolidines.



In fact, 2-vinylaziridines **5** (R^1 = alkyl) are known to undergo palladium-catalysed ring-opening cyclization with a range of heterocumulenes such as carbodiimides, isothiocyanates and isocyanates to give the corresponding five-membered heterocycles **6**: imidazolidinoneimines, imidazolidinethiones, and imidazolidinones, respectively.[6] An enantioselective synthesis of imidazolidinones based on this reaction has been recently reported using a chiral palladium catalyst.[7] In a similar way, *N*-tosyl 2-vinylaziridine **5** (R^1 = Ts) has been shown to undergo palladium-catalysed cyclization with a range of alkylidene malonate derivatives to give pyrrolidine derivatives **7**.[8]

Keywords: Pyrrolidine; Synthesis; Palladium; Catalytic; Cycloaddition.
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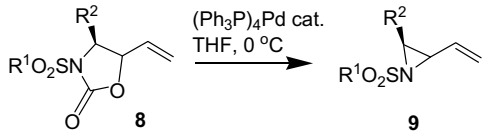
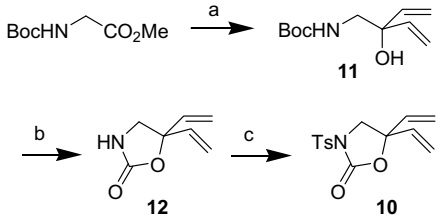
Ibuka has shown that *N*-sulfonyl-5-vinyloxazolidin-2-ones **8** are readily converted to the corresponding vinylaziridines **9** by palladium-catalysed decarboxylation[9] and this suggests that the more easily synthesised oxazolidinones **8** might be used in place of aziridines for the synthesis of pyrrolidine derivatives. Takemoto has shown that *N*-sulfonyloxazolidinones can be used in place of the corresponding aziridines in the palladium catalysed synthesis of γ-amino alcohols.[10] In this letter, we report the successful synthesis of highly substituted pyrrolidines via palladium-catalysed decarboxylative cycloaddition of an *N*-tosyl-5-vinyloxazolidin-2-one to highly electrophilic alkenes.

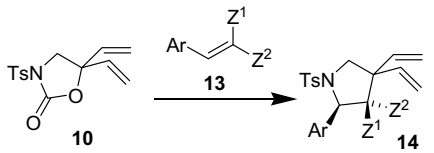


Yamamoto reported[8] low diastereoselectivity in the addition of vinylaziridines to activated alkenes and so, in order to avoid this complication, we carried out our initial investigation on the achiral 5,5-divinyloxazolidinone **10**. This was prepared in three steps from *N*-Boc glycine methyl ester (Scheme 1). Treatment of the amino ester with excess vinylmagnesium bromide gave the bisallylic alcohol **11** which, without purification, was cyclised to the oxazolidinone **12** by treatment with potassium *tert*-butoxide. Tosylation of the oxazolidinone nitrogen produced **10** in good yield.

The Meldrum's acid benzylidene derivative **13a** was used to investigate the optimum phosphine:palladium ratio. We were pleased to find that cyclisation of the oxazolidinone **10** with 10 mol % $Pd(PPh_3)_4$ in the presence of the Meldrum's acid derivative **13a** gave the pyrrolidine



Scheme 1. Reagents and conditions: (a) $CH_2CHMgBr$ (2.5 equiv), THF, −78 °C to rt, 4 h; (b) KO^{t}Bu, THF, 0 °C, 3 h, 45% for two steps; (c) NaH, THF, 0 °C, then TsCl, 90%.



Scheme 2. Reagents and conditions: $Pd_2(dba)_3{\cdot}CHCl_3$ (5 mol %), PPh_3, **13** (1.5 equiv), THF, 40 °C, 2 h.[11,12]

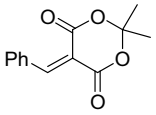
14a, albeit in low yield (23% by NMR,[11,12] Scheme 2, Table 1, entry 1). Replacing $Pd(PPh_3)_4$ by $Pd_2(dba)_3{\cdot}CHCl_3$ and PPh_3 (4 equivalents per palladium) had no significant effect on the yield (entries 1 and 2). The use of $Pd_2(dba)_3{\cdot}CHCl_3$ allowed investigation of the effect of changing the phosphine:palladium ratio (entries 2–4). In fact, the yield was essentially independent of the Pd:P ratio. From a practical point of view, the use of less phosphine made isolation of the product more straightforward and so the remaining reactions were conducted using a palladium:phosphine ratio of 1. Increasing the reaction time from 2 to 18 h, led to the complete disappearance of the oxazolidinone **10** but without any significant increase in the yield of the pyrrolidinone **14a**. The use of $Pd_2(dba)_3$ gave a similar yield to that obtained with the corresponding chloroform adduct (entry 5 vs entry 4).

Cyclization of the oxazolidinone **10** with 5 mol % $Pd_2(dba)_3{\cdot}CHCl_3$ and 10 mol % of Ph_3P in the presence of the more reactive benzylidinemalononitrile **13b** proceeded to give the pyrrolidine **14b** in excellent yield (Scheme 2, Table 1, entry 6).[11] The ease of this reaction is remarkable considering that the product is formed with two contiguous quaternary carbons. The results of other successful cyclizations to give a range of highly substituted pyrrolidines are shown in Table 1. As can be seen from Table 1, the pyrrolidine products were produced in excellent yields from arylidenemalononitriles (entries 6–8) whereas the yields were reduced when ethyl *E*-2-cyanocinnamate **13e** (entry 9) or the Meldrum's acid derivative **13a** were used (entry 4). Presumably, in these latter cases, the lower yields reflect the increasing steric demand in forming the pyrrolidines. The pyrrolidine **14e** formed from ethyl *E*-2-cyanocinnamate was obtained as a single diastereoisomer. The stereochemistry was assigned on the basis of the chemical shift ($\delta = 5.51$ ppm) of the proton on the 2-position of the pyrrolidine, which was much closer to the value observed for the Meldrum's acid derivative **14a** ($\delta = 5.35$) than those for the nitrile derivatives **14b** (5.09), **14c** (5.00), and **14d** (5.10), thus suggesting that H-2 in **14e** is *syn* to the ester rather than to the cyano group. This diastereoisomer would be expected to be lower in energy than the alternative in which the larger ester group is *syn* to the phenyl ring. The high stereoselectivity may result from enhanced steric interactions due to buttressing by the two adjacent quaternary centres.

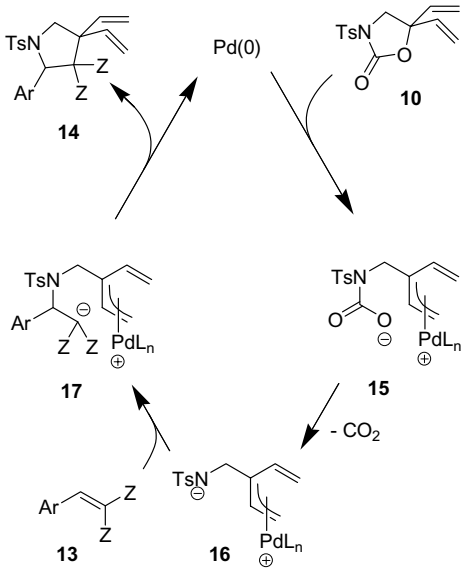
Attempts to use less highly activated Michael acceptors such as ethyl cinnamate, ethyl acrylate, acrylonitrile, maleic anhydride, and dimethyl acetylenedicarboxylate, were unsuccessful and approximately 50% of the oxazolidinone **10** was recovered from these reactions.

A possible catalytic cycle is proposed in Scheme 3. Coordination of Pd(0) and ring opening is expected to give the π-allyl cation **15**. Loss of CO_2 is no doubt facilitated by the electron withdrawing tosyl group, which can stabilize the resulting nitrogen anion **16**. Coordination of the nitrogen to the palladium may also help to stabilize this intermediate. The fact that only 50% of the vinyloxazolidinone was recovered intact when less reactive

Table 1. Palladium catalysed decarboxylative cyclisation of 5,5-divinyloxazolidin-2-one **10** with Michael acceptors **13**

Entry	Michael acceptor	Ar	Z^1	Z^2	P:Pd[a]	Prod.	Yield (%)
1	**13a**				4[b]	**14a**	23[c]
2	**13a**				4	**14a**	24[c]
3	**13a**				2	**14a**	21[c]
4	**13a**				1	**14a**	23[c]
5	**13a**				1[d]	**14a**	18[c]
6	**13b**	Ph	CN	CN	1	**14b**	95[e]
7	**13c**	4-$MeOC_6H_4$	CN	CN	1	**14c**	97[e]
8	**13d**	2-Furyl	CN	CN	1	**14d**	82[e]
9	**13e**	Ph	CN	CO_2Et	1	**14e**	65[e]

[a] Ratio of Ph_3P:Pd.
[b] $Pd(PPh_3)_4$ (10 mol %) was used in this case.
[c] NMR yield.[12]
[d] $Pd_2(dba)_3$ (5 mol %) was used in this case.
[e] Isolated yield.



Scheme 3. Proposed catalytic cycle.

Michael acceptors were used, and that extended reaction times led to complete disappearance of the oxazolidinone without a corresponding increase in yield of the pyrrolidine product, suggests that the intermediates **15** or **16** decompose by other pathways in the absence of reactive Michael acceptors. The presence of the extra alkene, in conjugation with the π-allyl system, may help to stabilize **16**. Michael addition of the nitrogen nucleophile **16** to the electrophile gives the stabilized carbanion **17**. The low nucleophilicity of the *N*-tosyl anion presumably results in the requirement for highly electrophilic Michael acceptors and the failure of the cyclisation in cases where the alkene is activated only by a single electron withdrawing group.

The cyclisation of a tethered carbanion such as **17** onto the π-allyl cation is similar to that involved in the approach to allokainoids recently reported by Cook and Sun.[13] In that work, a vinyloxazolidinone was reacted first with a diketene equivalent to make a β-keto-amide, which subsequently acted as a tethered nucleophile after palladium catalysed ring-opening and decarboxylation.

In summary, we have developed the palladium catalysed formal [3+2] cycloaddition of 5,5-divinyloxazolidinone **10** to highly activated Michael acceptors to give pyrrolidines **14** bearing two contiguous quaternary centres.

Further study of the diastereoselectivity of the reactions of chiral 5,5-divinyloxazolidinones derived from amino acids other than glycine is currently underway and will be reported in due course.

Acknowledgements

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References and notes

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11. Typical procedure: $Pd_2(dba)_3{\cdot}CHCl_3$ (41.4 mg, 0.04 mmol) was added to a stirred solution of the oxazolidinone **10** (234 mg, 0.8 mmol) and PPh_3 (21 mg, 0.08 mmol) in THF (10 mL). The mixture was stirred at 40 °C for 20 min and then a solution of **13b** (185 mg, 1.2 mmol) in THF (4 mL) was added dropwise. The resulting solution was stirred for 2 h, filtered through a plug of Celite and the solvent was removed under reduced pressure. Purification by flash column chromatography (SiO_2) eluting with petrol/EtOAc (5:1) gave the pyrrolidine **14b** (384 mg, 95%) as white prisms; mp 99–101 °C; ν_{MAX}/cm^{-1} (KBr) 2359, 2339, 1345, 1166; δ_H (300 MHz, $CDCl_3$) 7.80–7.00 (9H, m, Ar), 6.00–5.76 (2H, m, =CH), 5.61 (1H, d, *J* 18.7, =CH), 5.54 (1H, d, *J* 8.9, =CH), 5.50 (1H, d, *J* 10.8, =CH), 5.39 (1H, d, *J* 17.3, =CH), 5.09 (1H, s, H-2), 4.45 (1H, d, *J* 11.7, H-5), 3.80 (1H, d, *J* 11.7, H-5), 2.30 (3H, s, Me); δ_C (125 MHz, $CDCl_3$) 143.0, 134.7, 133.4, 130.7, 130.5, 129.7, 129.5, 128.6, 128.3, 127.2, 126.1, 125.8, 120.9, 120.3, 67.9, 54.5, 52.7, 52.3, 21.7; *m/z* (EI) 403 (M^+, 45%), 248 (27), 118 (100), 91 (60); Found (M^+): 403.1372, $C_{23}H_{21}N_3O_2S$ requires 403.1354.
12. For the initial comparative study of $Pd(PPh)_3$ and $Pd_2(dba)_3$ with varying amounts of PPh_3, yields were measured by ^1H NMR as follows: the crude product was filtered through Celite, washed through with CH_2Cl_2 (30 mL) and then the solvent was removed under reduced pressure. The resulting oil was dissolved in $CDCl_3$ (2.0 mL). 250 μL of this solution was placed into an NMR tube and 250 μL of a solution of 1,3-dinitrobenzene [0.8 mmol in $CDCl_3$ (2.0 mL)] was added. The resulting mixture was diluted with $CDCl_3$ and the ^1H NMR spectrum was recorded. The NMR yield was calculated from the relative integrals of the signals from 1,3-dinitrobenzene (δ 9.00, 1H, H-2; δ 8.50, 2H, H-4) and the pyrrolidine product **14**. (δ 5.14–4.95, 3H, vinyl-H; δ 4.41, 1H, H-5; δ 3.95, 1H, H-5). In the case of Table 1, entry 4, purification of the product resulted in an isolated yield of 17%, close to the NMR yield of 23%.
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