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An Au(I) catalysed allenamide cyclisation giving access to a α -vinyl substituted tetrahydroisoquinoline building block

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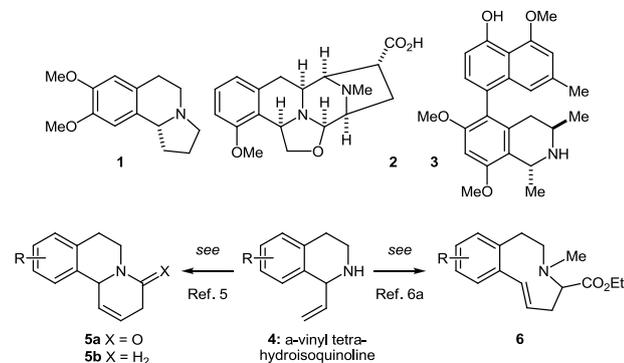
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Abstract: An Au(I) catalysed intramolecular hydroarylation of an enantiopure allenamide has been achieved and has given access to a key α -vinyl substituted tetrahydroisoquinoline. Additionally this has been accomplished in very high yield and high diastereoselectivity.

Key words: Alkaloids, allenamide, tetrahydroisoquinoline, Au(I)-catalysis, diastereoselective.

Tetrahydroisoquinolines are highly significant synthetic subunits contained within many biologically active alkaloids (Figure 1).¹ Contained within many of these alkaloids is a stereogenic centre at the α -position on the ring which is commonly installed, either enantio- or diastereoselectively, *via* a Pictet-Spengler² or Bischler-Napieralski³ condensations.⁴ Ideally, a key synthetic building block for the total synthesis of such targets would be the α -vinyl substituted tetrahydroisoquinoline **4**, since the vinyl group can be readily manipulated (Scheme 1).^{5,6}

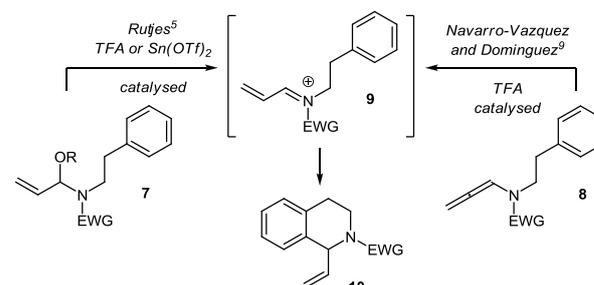


Scheme 1. Tetrahydroisoquinoline natural products crispine A (**1**), quinocarcin (**2**), korumpensamine (**3**) and α -vinyl tetrahydroisoquinoline building block (**4**) and its known conversion to **5** and **6**.

However, access to α -vinyl substituted tetrahydroisoquinolines using the Pictet-Spengler or Bischler-Napieralski approaches is somewhat problematic and therefore unsuitable.⁵ To overcome this chemical issue a number of approaches have been disclosed, including; (a) vinyl organometallic addition to suitable quinoline substrates,⁶ (b) Pd-catalysed addition to allenamides,⁷ (c) iridium^{8a} and palladium^{8b} catalysed intramolecular allylic amination, and finally, (d) an intramolecular hydroarylation on a masked conjugated *N*-acyl iminium species (Scheme

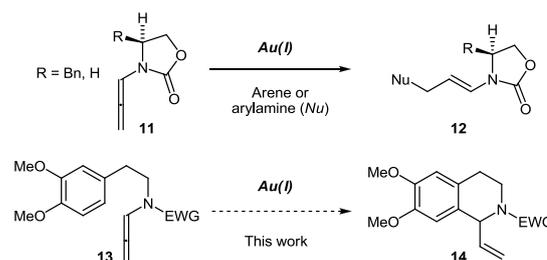
2),^{5,9} and it is this last approach that is the focus of this letter.

In 2005 Rutjes⁵ reported a synthetically flexible route to α -vinyl substituted tetrahydroisoquinoline building blocks (**10**) *via* a Sn(II) or TFA catalysed cyclisation of allylic *N,O*-acetals (**7**). This was followed in 2007 by Navarro-Vazquez and Dominguez⁹ who elegantly illustrated that allenamides (**8**) could be cyclised under acidic condition to yield α -vinyl substituted tetrahydroisoquinolines (**10**) in good yield. While both authors used a masked conjugated *N*-acyl iminium (**9**) to generate their α -vinyl tetrahydroisoquinoline substrates (**10**), it was only the work of Rutjes who investigated any diastereoselectivity in their transformation, which was found to be modest.



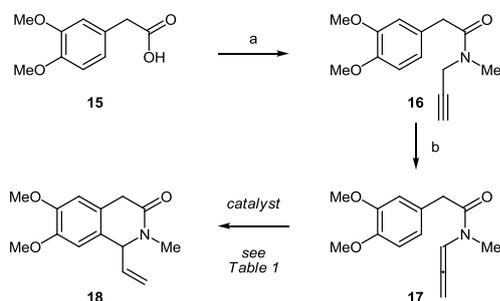
Scheme 2. Previous *N*-acyl iminium approaches to α -vinyl tetrahydroisoquinolines

Recently, we described the Au(I) activation of allenamides¹⁰ and their subsequent reaction with electron rich arenes and arylamines to yield functionalised enamide building blocks (Scheme 3).¹¹ This approach to allenamide activation,¹² under such mild conditions, led us to consider whether an intramolecular arene cyclisation could be accomplished. Therefore, in this brief Letter we would like to disclose a concise and yet highly diastereoselective route to a key α -vinyl substituted tetrahydroisoquinoline building blocks.



Scheme 3.

To test our approach to Au(I)-catalysed intramolecular cyclisation we synthesised allenamide **17** in two steps from the known acid **15** (Scheme 4). Allenamide **17** was then exposed to a variety of cyclisation conditions as shown in Table 1.



Scheme 4. (a) DCC, CH₂Cl₂, DMAP, *N*-methylpropargyl amine; (b) THF, KO^tBu [75% over 2-steps].

Table 1. Conditions for the intramolecular cyclisation of **17** to **18**.^a

Entry	Catalyst	Temp.(°C)	T (h)	Yield (%) ^b
1	AuPPh ₃ OTf	r.t.	1	95
2	AuPPh ₃ NTf ₂	35	16	91
3	AgOTf	r.t.	16	<i>s.m.</i>
4	TFA ^c	r.t.	16	<i>decomp.</i>
5	AuPPh ₃ OTf ^d	r.t.	16	96

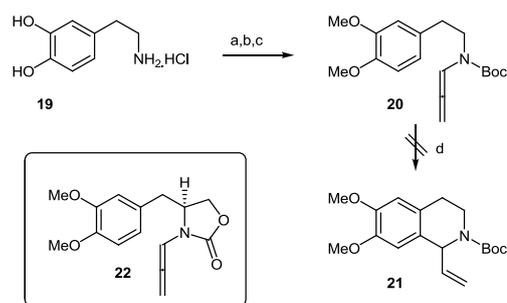
^aAll reactions were performed under an atmosphere of N₂ unless otherwise stated and with 5 mol% catalysts unless otherwise states.

^bIsolated yield. ^c20 mol%. ^d2.5 mol%.

Exposure of **17** to 5 mol% AuPPh₃OTf gave the desired intramolecular cyclisation product in an excellent yield with tlc showing full consumption of the starting material within an hour (entry 1). A switch to the AuPPh₃NTf₂ did give the desired product but the reaction time was extended considerably (entry 2). To show the requirement of Au(I) catalysts the reaction was undertaken with AgOTf which gave only starting material (entry 3), while TFA did catalyse the reaction but gave predominantly decomposition products (entry 4). Finally, we decreased the catalysts loading of AuPPh₃OTf to 2.5mol% which furnished the cyclized product in 96% yield but required an extended reaction time as compared to entry 1.

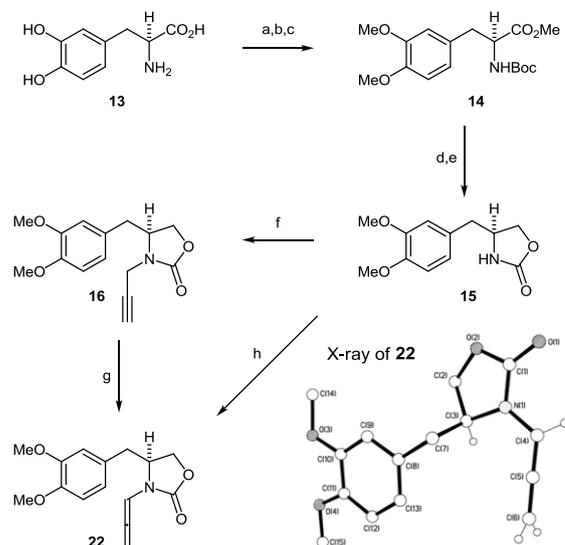
With result in hand we then investigated the cyclisation the Boc protected allenamide **21** which was synthesized in 3-steps from the known acid **19** (Scheme 5). Unfortunately, exposure of this substrate to our Au(I) catalyzed cyclisation conditions, failed to deliver any of the desired product with only starting material being returned. We believe that this maybe a consequence of the bulky Boc protecting group contained within **21** hampering activation of the allenamide by the Au(I) catalyst.

Consequently, based on our previous investigations on intermolecular allenamide activation we targeted an oxazolidinone protected allenamide **22** as a Boc surrogate.



Scheme 5. (a) Boc₂O, NEt₃, H₂O, dioxane; (b) MeI, K₂CO₃, DMF; NaH; (c) KO^tBu, propargyl bromide [60% over 3-steps]; (d) AuPPh₃OTf or AuPPh₃NTf₂ (5 mol%), CH₂Cl₂, rt or reflux, 16h.

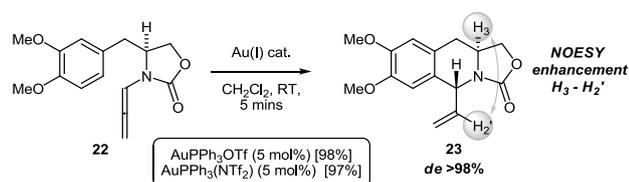
The synthesis began with conversion of *L*-DOPA (**13**) to its Boc protected methyl ester under standard conditions, followed by global methylation with MeI and K₂CO₃ to give **14** in 92% overall yield over the 3-steps. Subsequent LiBH₄ reduction of **14** and treatment of the crude product with thionyl chloride in THF delivered the oxazolidinone **15** in 88% yield over the 2-steps. Finally, **15** was alkylated with propargyl bromide to furnish the alkyne **16** which could then be rearranged under basic conditions to give the desired chiral allenamide **22** in 62% yield.¹³ Alternatively, treatment of **15** under modified Heaney/Ley conditions¹⁴ with propargyl bromide directly gave **22** in 60% yield. Allenamide **22** proved to be crystalline and crystals suitable for single crystal X-ray analysis were obtained. The X-ray¹⁵⁻¹⁸ depiction is shown below in Scheme 6.



Scheme 6. (a) MeOH, SOCl₂; (b) Boc₂O, Et₃N, MeOH; (c) MeI, K₂CO₃, DMF [92% over 3-steps]; (d) LiBH₄, THF; (e) SOCl₂, THF [88% over 2-steps]; (f) NaH, propargyl bromide (80% in hexane); (g) KO^tBu, THF [62% over 2-steps]; (h) KO^tBu, propargyl bromide (80% in hexane), DMSO [60%].

Treatment of **22** with AuPPh₃OTf (5 mol%) in CH₂Cl₂ delivered a single product **23** in quantitative yield.²⁰ The reaction time was remarkably short, with the reaction completion within minutes of the addition of the Au(I) salt, indicating a very facile reaction. Exhaustive NMR analysis indicated a single product with a *de* > 98% and with an

absolute stereochemistry as shown in *Scheme 7*. The relative stereochemistry of the product was assigned on the basis of a NOESY enhancement between H₃ and the vinylic H₂ proton.



Scheme 7. Au(I) catalysed cyclisation of **22**

Treatment of allenamide **22** with AuPPh₃NTf₂ (5 mol%) also gave the tetrahydroisoquinoline **23** quantitatively and in excellent *de*. It must be noted this high diastereoselectivity is in contrast to the moderate *de*'s reported by Rutjes⁵ for similar cyclisations, and the high yield is a significant improvement over that reported by Navarro-Vázquez and Domínguez⁹ for their TFA catalysed cyclisations of allenamides.

In summary, a brief, yet high yielding synthesis of a key α -vinyl substituted tetrahydroisoquinoline has been achieved. The key step was an Au(I)-catalysed hydroarylation of a chiral pool derived allenamide delivering the key building block in high diastereoselectivity. Use of this building block and this synthetic approach for the synthesis of alkaloid natural products is currently under investigation.

Supporting Information for this article include ¹H and ¹³C NMR of **22** and **23** and the Crystallographic data for **22**.

Acknowledgments

The authors thank Loughborough University for funding and Mark Edgar for NMR analysis.

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- (S)-4-(3,4-Dimethoxybenzyl)-3-(propa-1,2-dienyl) oxazolidin-2-one **22**. To a solution of **15** (0.58 g, 2.45 mmol) in THF (20 mL) at 0°C under a N₂ atmosphere was added NaH (0.12 g, 2.93 mmol) and the mixture stirred at room temperature for 2h. After this period propargyl bromide (0.32 mL, 2.88 mmol) was added cautiously and the reaction mixture stirred for a further 24h at room temperature. After this period sat. NH₄Cl was added and the resultant aqueous layer extracted with Et₂O (x2). The combined organic layers were then washed with brine, dried (Na₂SO₄), filtered and the solvent removed *in vacuo*. The crude product was then dissolved in THF (20 mL) and cooled to 0°C followed by addition of ^tBuOK (0.08 g, 0.66 mmol). The reaction mixture was then stirred for 2h at 0°C after which all the starting material had been consumed. The reaction mixture was then diluted with Et₂O and washed sequentially with H₂O and brine. The combined organic layers were then dried (Na₂SO₄), filtered and the solvent removed *in vacuo*. The crude product was then purified by column chromatography (R_f = 0.55, 1:1 ethyl acetate – petroleum ether) yielding the title compound as a colourless solid (0.40 g, 60%), m.p. 118-120°C from CH₂Cl₂ – petroleum ether; ν_{\max} (solution, CHCl₃) 3021, 1752, 1516, 1461, 1409, 1262, 1226, 1028 cm⁻¹; δ_{H} (400 MHz; CDCl₃) 6.84 (t, *J* = 6.8 Hz, 1H), 6.76 – 6.73 (m, 1H), 6.64 – 6.62 (m, 1H), 6.58 (d, *J* = 1.6 Hz, 1H), 5.51 (dd, *J* = 6.4, 10.0 Hz, 1H), 5.44 (dd, *J* = 6.4, 10.0 Hz, 1H), 4.20 (t, *J* = 8.4 Hz, 1H), 4.08 (dd, *J* = 3.6, 8.8 Hz, 1H), 4.05 – 4.00 (m, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 3.06 (dd, *J* = 3.2, 14.0 Hz, 1H), 2.65 (dd, *J* = 8.8, 14.0 Hz, 1H); δ_{C} (100 MHz; CDCl₃) 201.7(C), 155.0(C), 149.2(C), 148.3(C), 127.7(C), 121.4(CH), 112.4(CH), 111.5(CH), 111.5(CH), 96.00(CH), 87.9(CH₂), 66.6(CH₂), 56.0(CH₃), 55.7(CH₃), 36.6(CH₂); HRMS MNa⁺, C₁₅H₁₇NO₄, found 298.1045, requires MNa⁺ 298.1055; $[\alpha]_{\text{D}}^{21} +20.3$ (*c* 1.00 CHCl₃).
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($\lambda=0.71073$ Å). 2026 data were unique, $R_{\text{int}} = 0.0329$; all unique data used in refinement against F^2 values to give final $wR2 = 0.0885$ (on F^2 for all data), $R = 0.0338$ {for 1831 data with $F^2 > 2\sigma(F^2)$ }, absolute structure could not be determined from the diffraction data; Friedel pairs were merged}. H atoms on C(6) had coordinates freely refined; all other H atoms were constrained. Programs used were Bruker SMART¹⁶, SAINT¹⁶, SHELXTL^{17,18} and local programs. CCDC 838703 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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- (20) To a solution of **22** (100 mg, 0.36 mmol) in CH_2Cl_2 (2 mL) at room temperature was added a 5 mol% solution of AuPPh_3OTf . (NB. The 5 mol% solution of AgPPh_3OTf was prepared from the addition of AuClPPh_3 (9 mg, 0.018 mmol) to AgOTf (4.7 mg, 0.018 mmol)) in CH_2Cl_2 (1 mL) and the resultant suspension stirred for 10 min. at room temperature). After 5 min. the starting material was consumed after which the solvent was removed *in vacuo*. The crude product was then purified by column chromatography ($R_f = 0.25$, 1:1 ethyl acetate – petroleum ether) to yield **23** as a colourless oil (98 mg, quantitative); v_{max} (solution, CHCl_3) 3020, 2936, 1749, 1613, 1518, 1420, 1226, 1115 cm^{-1} ; δ_{H} (400 MHz; CDCl_3) 6.62 (s, 1H), 6.58 (s, 1H), 5.98 – 5.90 (m, 1H), 5.29 – 5.24 (m, 3H), 4.57 – 4.52 (t, $J = 8.4$ Hz, 1H), 4.15 – 4.12 (dd, $J = 8.4, 8.8$ Hz, 1H), 4.05 – 3.99 (m, 1H), 3.89 (s, 3H), 3.84 (s, 3H), 2.83 (d, $J = 7.7$ Hz, 2H); δ_{C} (100 MHz; CDCl_3) 156.7(C), 148.3(C), 148.0(C), 136.4(CH), 125.2(C), 127.7(C), 117.5(CH_2), 111.6(CH), 110.4(C), 68.5(CH_2), 56.0(CH_3), 55.9(CH_3), 54.7(CH_2), 48.6(C), 33.8(CH_2); HRMS MNa^+ , $\text{C}_{15}\text{H}_{17}\text{NO}_4$, found 298.1044, requires MNa^+ 298.1055; $[\alpha]_{\text{D}}^{21} -160.8$ (c 1.00 CHCl_3).

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