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

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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). 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-Spengler or Bischler-Napieralski condensations. Ideally, a key synthetic building block for the total synthesis of such targets would be the α-vinyl substituted tetrahydroisoquinoline, since the vinyl group can be readily manipulated (Scheme 1).

Scheme 1.

Recently, we described the Au(I) activation of allenamides and their subsequent reaction with electron rich arenes and arylamines to yield functionalised enamide building blocks (Scheme 3)[1]. This approach to allenamide activation, 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 2.

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.

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Temp.(ºC)</th>
<th>T (h)</th>
<th>Yield (%)f</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AuPPh3OTf</td>
<td>r.t.</td>
<td>1</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>AuPPh3NTf2</td>
<td>35</td>
<td>16</td>
<td>91</td>
</tr>
<tr>
<td>3</td>
<td>AgOTf</td>
<td>r.t.</td>
<td>s.m.</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>TFAa</td>
<td>r.t.</td>
<td>16</td>
<td>decomp.</td>
</tr>
<tr>
<td>5</td>
<td>AuPPh3OTfb</td>
<td>r.t.</td>
<td>16</td>
<td>96</td>
</tr>
</tbody>
</table>

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

bIsolated yield. 20 mol%, 2.5 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 synthesised 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 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 4. (a) DCC, CH3Cl, DMAP, N-methylpropargyl amine; (b) THF, KO’Bu [75% over 2-steps].

Scheme 5. (a) Boc2O, NEt3, H2O, dioxane; (b) MeI, K2CO3, DMF; NaH; (c) KO’Bu, propargyl bromide [60% over 3-steps]; (d) AuPPh3OTf or AuPPh3NTf2 (5 mol%), CH2Cl2, r.t 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. Alternatively, treatment of 15 under modified Heaney/Ley conditions 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 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’Bu, THF [62% over 2-steps]; (h) KO’Bu, propargyl bromide (80% in hexane), DMSO [60%].

Treatment of 22 with AuPPh3OTf (5 mol%) in CH2Cl2 delivered a single product 23 in quantitative yield. 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](image)

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 Rutjes1 for similar cyclisations, and the high yield is a significant improvement over that reported by Navarro-Vázquez and Domínguez2 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.

References and Notes


(13) (S)-4-(3,4-Dimethoxybenzyl)-3-(propa-1,2-diethyl) oxazolidin-2-one 22. To a solution of 15 (0.58 g, 2.45 mmol) in THF (20 mL) at 0ºC 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 EtO (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 0ºC followed by addition of BuOK (0.08 g, 0.66 mmol). The reaction mixture was then stirred for 2h at 0ºC after which the starting material had been consumed. The reaction mixture was then diluted with EtO 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 (Rf = 0.55, 1:1 ethyl acetate – petroleum ether) yielding the title compound as a colourless solid (0.40 g, 60%), m.p. 118°C. Colourless solid (0.40 g, 60%), m.p. 118°C was obtained from petroleum ether 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 (Rf = 0.55, 1:1 ethyl acetate – petroleum ether) yielding the title compound as a colourless solid (0.40 g, 60%), m.p. 118°C from CH2Cl2 – petroleum ether; νmax (solution, CHCl3) 3021, 1752, 1516, 1461, 1409, 1262, 1226, 1028 cm–1; δ400 (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), δc (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), 96.0(CH), 87.9(CH), 66.6(CH3), 56.0(CH3), 55.7(CH3), 36.6(CH3). HRMS M+Na+, C22H25NO3, found 398.1045, requires M+Na+ 398.1055; [q13]D +20.3 (c 1.00 CHCl3).


(15) Crystal data for 22: C22H25NO3, M = 275.30, orthorhombic, space group P21_21_21, a = 7.2379(10), b = 11.5884(15), c = 16.677(2) Å, β = 1398.8(3) Å2, T = 150 K, Z = 4, μ(Mo-Kα) = 0.95 mm-1, 14225 data measured using a Bruker APEX 2 CCD diffractometer with graphite-monochromated Mo-Kα radiation.
(λ=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 \( wR_2 = 0.0885 \) (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 SMART\(^{16}\), SAINT\(^{16}\), 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 \textit{via} www.ccdc.cam.ac.uk/data_request/cif.

(16) SMART and SAINT software for CCD diffractometers, Bruker AXS Inc, Madison, WI, 2008.


(19) To our knowledge the only previous example of a single crystal X-ray structure of an unsubstituted chiral allenamide was reported by the group of Hsung \textit{(see, Tracey, M. R.; Grebe, T. P. Brennessel, W. W.; Hsung, R. P. Acta Cryst. \textbf{2004}, \textit{C60}, o830)}.

(20) To a solution of \textit{22} (100 mg, 0.36 mmol) in CH\(_2\)Cl\(_2\) (2 mL) at room temperature was added a 5 mol\% solution of AuPPh\(_3\)OTf. (NB. The 5 mol\% solution of AgPPh\(_3\)OTf was prepared from the addition of AuClPPh\(_3\) (9 mg, 0.018 mmol) to AgOTf (4.7 mg, 0.018 mmol)) in CH\(_2\)Cl\(_2\) (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 \textit{in vacuo}. The crude product was then purified by column chromatography (\( R_f = 0.25 \)) to yield \textit{23} as a colourless oil (98 mg, quantitative); \( \nu_{\text{max}} \) (solution, CHCl\(_3\)) 3020, 2936, 1749, 1613, 1518, 1420, 1226, 1115 cm\(^{-1}\); \( \delta \)\(_H\) (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); \( \delta \)\(_C\) (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\(_3\)), 56.0(CH\(_3\)), 55.9(CH\(_3\)), 54.7(CH\(_3\)), 48.6(C), 33.8(CH\(_3\))\}; HRMS MNa\(^+\), C\(_{15}\)H\(_{17}\)NO\(_4\), found 298.1044, requires MNa\(^+\) 298.1055; [\( \alpha \)]\(^{21}\)\(_D\)-160.8 (c 1.00 CHCl\(_3\)).
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