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Gold(I)-catalysed intramolecular hydroamination of α-quaternary alkynes: synthetic studies towards spiroimine marine toxins

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ABSTRACT

Cyclic spiroimines form an essential component of the bioactive pharmacophore in a number of potent fast-acting marine biotoxins, including the pinnatoxins, gymnodimine and the spirolides. These present a significant challenge for the total synthesis of this class of natural products. A novel approach to these cyclic spiroimines based on metal-catalysed hydroamination of spiroaminoalkyne precursors is reported herein. $Au(PPh_3)SbF_6$ was found to effect the formation of bench-stable 5,6- and 6,6-spiroimine systems in high yields, although the 7,6-analogue remained elusive. To the best of our knowledge these are the first reported examples of α-quaternary cyclic imines formed via alkyne hydroamination.

Marine natural products containing a cyclic imine unit form an important subclass of fast-acting toxins responsible for incidents of shellfish toxicity.[1] In addition to their potent biological activity, the complex molecular architecture of compounds such as the pinnatoxins (**1a**–**d**) (Fig. 1), gymnodimine (**2**) and the spirolides (**3a**–**f**) has inspired synthetic endeavours in several laboratories.[2] Interestingly, the observed inactivity of spirolides E and F (**3e**,**f**) in which the cyclic imine has been hydrolysed, highlights the importance of this motif in effective binding to its cellular target, the nicotinic acetylcholine receptor.[3]

Previous synthetic studies towards the pinnatoxins and gymnodimine report the necessity to use forcing conditions to form the cyclic imine from azido-ketone or amino-ketone precursors via an *aza*-Wittig or condensation reaction, respectively.[4] These cyclisations are typically performed at a late stage due to the susceptibility of imines to hydrolytic cleavage. The cyclic imines present in natural products **1**–**3**, however, are unusual in being highly resistant to hydrolysis when incorporated into the complete macrocycle and exist as protonated iminium salts in acidic aqueous solution. The adjacent quaternary centre is proposed to impart steric protection from hydrolysis, along with the vicinal methyl groups present in the pinnatoxins and spirolides. In support of this hypothesis, a number of simple imine systems containing a quaternary centre prepared by the Romo group proved similarly resistant to acidic and basic hydrolysis, although the methodology developed was not applicable to total synthesis.[5]

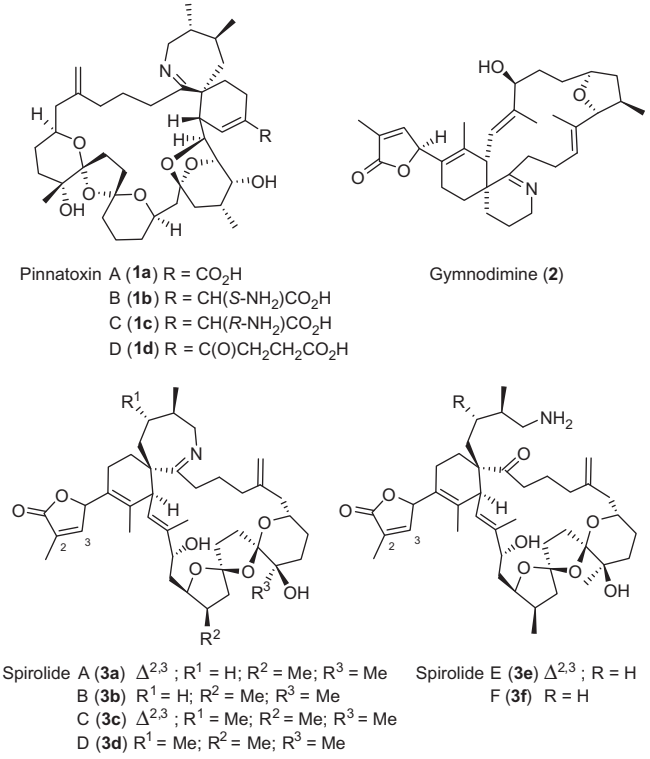

Figure 1. Spiroimine-containing marine natural products.

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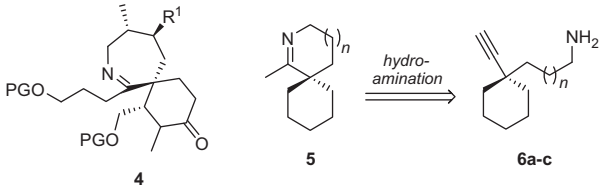
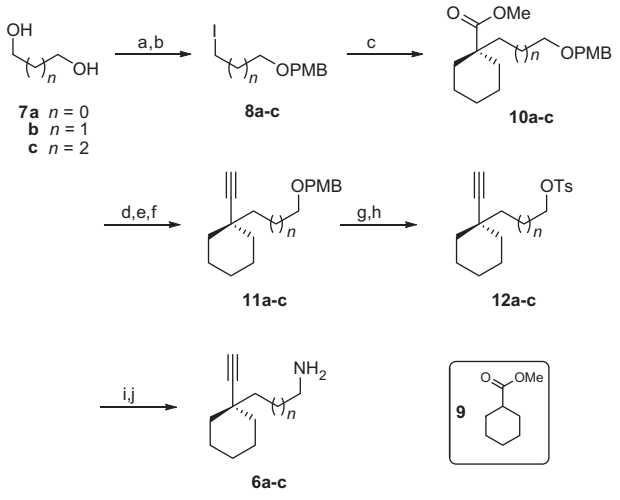


Figure 2. Putative advanced spirolide AE ring intermediate **4** and model system **5** selected for this study.

We were interested to investigate alternative synthetic methods for preparation of these key spiroimines that either (a) were suitable for mild late-stage cyclic imine formation involving advanced intermediates, or (b) enabled access to highly functionalised imines that might be stable enough to be viable synthetic intermediates themselves. In addition, any spiroimines prepared would be novel entities and potentially interesting subjects for biological activity investigations.

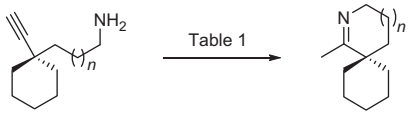
In recent years hydroamination has received an increasing amount of attention as a direct and atom-efficient method to access nitrogen-containing compounds.[6] Catalysts based on a variety of metals including titanium,[7] zirconium, yttrium, lanthanides and most notably, gold,[8] have been found to promote intramolecular hydroamination affording cyclic imines from amino-alkynes, including two seven-membered examples.[9] It seemed reasonable that similar cyclisation of a suitable amino-alkyne precursor might afford the bicyclic spiroimine ring systems of possible imine-containing intermediates (e.g., **4**, Fig. 2) required for synthesis of the complex marine natural products **1**-**3**. To this end, we designed a simplified model system **5** that would allow us to investigate the feasibility of this approach, starting from amino-alkynes **6a**-**c**.

In parallel sequences, readily available diols **7a**–**c** (Scheme 1) were monoprotected as PMB ethers and converted into the iodides **8a**–**c**. Formation of lithium enolate of commercially available methyl cyclohexane carboxylate (**9**) at −78 °C using LDA, followed by addition of **8a**–**c** and slow warming to room temperature



Scheme 1. Preparation of hydroamination precursors **6a**–**c**. Reagents and conditions: (a) NaH, PMBCl, DMF, 0 °C to rt, 18 h; (b) PPh_3, I_2, imidazole, CH_2Cl_2, 0 °C to rt, 2 h, **8a** (70%), **8b** (65%), **8c** (83%) over 2 steps; (c) LiHMDS, **9**, THF, −78 °C then **8a**–**c**, −78 °C to rt, 18 h, **10a** (81%), **10b** (83%), **10c** (89%); (d) $LiAlH_4$, THF, rt, 3 h; (e) $(COCl)_2$, DMSO, Et_3N, −78 °C; (f) diethyl 1-diazo-2-oxopropylphosphonate, K_2CO_3, MeOH, 0 °C to rt, 18 h, **11a** (43%), **11b** (59%), **11c** (78%) over 3 steps; (g) DDQ, CH_2Cl_2-H_2O (10:1), rt, 2 h; (h) TsCl, Et_3N, DMAP, CH_2Cl_2, rt, 18 h, **12a** (70%), **12b** (62%), **12c** (85%) over 2 steps; (i) NaN_3, DMF, 50 °C, 3 h; (j) PPh_3, THF-H_2O (40:1), 50 °C, 4 h, **6a** (73%), **6b** (74%), **6c** (74%) over 2 steps.

Table 1
Hydroamination of amino alkynes **6a–c**



6a-c **5a-c**

Substrate	Cat.[a]	Conditions	Result (%)
6b	**13**	NH_4PF_6,[a] 100 °C, PhMe, 4 h	c.m.[b]
6c	**13**	NH_4PF_6, 100 °C, PhMe, 4 h	c.m.
6c	**14**	rt, CH_2Cl_2, 3 d	—[c]
6c	**15**	rt, CH_2Cl_2, 3 d	—
6c	**14**	80 °C, PhMe, 1 d	—
6a	**16**	95 °C, MeCN, 1 h	c.m.[d]
6b	**16**	95 °C, MeCN, 1 h	c.m.[d]
6c	**16**	95 °C, MeCN, 1 h	—
6c	**16**	95 °C, MeCN, 1 d	c.m.
6c	**17**	100 °C, PhMe, 2 d	—
6b	**17**	Et_3N,[a] 100 °C, PhMe, 2 d	—
6c	**17**	Et_3N, 100 °C, PhMe, 2 d	—
6a	**17**	**Et_3N, 95 °C, MeCN, 0.5 h**	**5a** (91)
6b	**17**	**Et_3N, 95 °C, MeCN, 0.5 h**	**5b** (80)
6c	**17**	Et_3N, 95 °C, MeCN, 2 d	—

[a] 5 mol %.
[b] Complex mixture.
[c] No reaction, starting material recovered.
[d] Contained trace spiroimine by ^1H NMR spectroscopy.

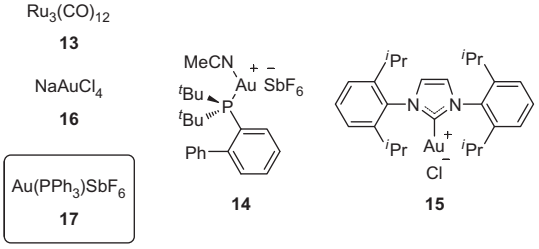


Figure 3. Hydroamination catalysts examined in this study.

afforded methyl esters **10a**–**c** containing a quaternary centre, in excellent yields.

The resulting methyl esters were then transformed into the corresponding alkynes **11a**-**c** by a standard three-step sequence involving reduction to the alcohol with lithium aluminium hydride, Swern oxidation and alkyne formation from the aldehyde with freshly-prepared Ohira-Bestmann reagent. It is worth noting that the Corey–Fuchs protocol failed to yield any of the desired alkyne in the last step of this sequence. Installation of the primary amine was achieved by oxidative PMB deprotection and subsequent tosylation to give **12a**–**c**, followed by nucleophilic displacement with sodium azide in DMF at 50 °C and Staudinger reduction using triphenylphosphine, to give the desired amino-alkynes **6a**-**c**.

With required precursors **6a**–**c** in hand, the hydroamination reaction was investigated (Table 1) using readily available catalysts, stable under standard laboratory conditions, that would be applicable to a robust and scalable synthetic program (Fig. 3). $Ru_3(CO)_{12}$ (**13**) has been reported to be effective for the formation of imines, including a cyclic seven-membered example, albeit in low yield under forcing conditions.[10] Unfortunately, no cyclisation products were obtained under these conditions, even with the additive NH_4PF_6.[11] Among a number of gold catalysts recently developed for alkyne hydroamination, both phosphine **14**[12] and *N*-heterocyclic carbene **15**[13] have been applied successfully in a range of systems. Disappointingly, however, neither catalyst was effective in cyclisation of any of the amino-alkyne precursors

6a-**c**. Reasoning that the reaction might be hindered by the bulky ligands of catalysts **14** and **15**, especially given the presence of the quaternary spirocentre α to the acetylene, it was decided to investigate simple gold salts **16** and **17**. Elevated temperatures initially failed to provide any cyclised product **5c** in either acetonitrile or toluene.

Finally, we were pleased to discover that heating **6a** or **6b** in acetonitrile under sealed-tube conditions, in the presence of gold phosphine catalyst **17** and triethylamine,[14] afforded the respective five- and six-membered cyclic imines **5a** and **5b** in 91% and 80% yields. Based on these results, use of the non-coordinating antimony hexafluoride counterion appears important for any reaction to occur. The reactions were notably rapid, affording a single product cleanly according to TLC in less than 30 min and requiring only simple filtration to provide nearly pure products.[15,16] Contrary to our initial concerns, the imines **5a** and **5b** appeared relatively resistant to hydrolysis, proving stable to benchtop storage open to air for prolonged periods. However, despite all efforts, it remained impossible to isolate any of the corresponding seven-membered cyclic imine **5c** upon subjecting amino-alkyne **6c** to the same conditions used successfully for **6a** and **6b**. Further studies will be required to determine whether this is due to a prohibitive energy barrier or the instability of the product.

In summary, we have described the successful synthesis of spirocyclic imines **5a** and **5b** in high yield via intramolecular alkyne hydroamination, using the convenient gold phosphine catalyst $Au(PPh_3)SbF_6$. All efforts to obtain the analogous seven-membered imine **5c** have proved fruitless to date. These results demonstrate the feasibility of hydroamination of α-quaternary alkyne substrates and also suggest that the five- and six-membered cyclic imine products may be stable enough to be utilised as viable intermediates in synthesis.

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15. Cyclic imines **5a** and **5b** were stable to TLC and flash chromatography using 10% EtMA (ethyl acetate containing 10% 9:1 MeOH-aq.NH_3).
16. *General hydroamination procedure:* To a stirred solution of amino-alkyne **6a** (20.0 mg, 0.13 mmol) in MeCN (0.5 ml) in a sealed tube were added $Au(PPh_3)Cl$ (3.30 mg, 6.60 mmol), $AgSbF_6$ (2.30 mg, 6.60 mmol) and Et_3N (0.9 μl, 6.60 mmol). The mixture was heated at 95 °C for 0.5 h then filtered and concentrated in vacuo to afford cyclic imine **5a** (18.2 mg, 91%) as a yellow oil: R_f 0.85 (10% EtMA); IR ν_{max}(film) 2926, 2855, 1641, 1437, 750, 694, 623 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.11–1.50 (6H, m, 6-H′, 7-H, 9-H, 10-H′), 1.68–1.73 (4H, m, 6-H″, 8-H, 10-H″), 1.82 (2H, t, J = 7.2 Hz, 4-H), 1.96 (3H, t, J = 1.6 Hz, 1′-H), 3.68–3.72 (2H, m, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.9 (CH_3, C-1′), 23.1 (CH_2, C-6, C-10), 25.7 (CH_2, C-8), 32.8 (CH_2, C-7, C-9), 33.3 (CH_2, C-4), 54.7 (C, C-5), 56.9 (CH_2, C-3), 182.5 (C=N, C-1); m/z (ESI+, %) 152 ($M+H^+$, 100); HRMS M^+ found 152.1432, $C_{10}H_{18}N^+$ requires 152.1434.
Data for **5b**: R_f 0.85 (10% EtMA); IR ν_{max}(film) 2927, 2855, 1644, 1449, 695, 657, 623 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.44–1.72 (14H, m, 4-H, 5-H, 7-H, 8-H, 9-H, 10-H, 11-H), 2.02 (3H, s, 1′-H), 3.51–3.54 (2H, m, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.7 (CH_2, C-9), 20.6 (CH_2, C-7, C-11), 22.7 (CH_3, C-1′), 25.7 (CH_2, C-5), 27.6 (CH_2, C-4), 33.1 (CH_2, C-8, C-10), 39.6 (C, C-6), 49.6 (CH_2, C-3), 177.0 (C=N, C-1); m/z (ESI+, %) 166 ($M+H^+$, 100); HRMS M^+ found 166.1594, $C_{11}H_{20}N^+$ requires 166.1590.