Simultaneous Generation and Subsequent Cycloaddition of ortho-Quinonemethides and Cyclic Enecarbamates Promoted by a Gold / Lewis Acid Catalytic System

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Dedication ((optional))

Abstract: A new catalytic reaction to synthesize structurally complex hexahydrochromeno[2,3-b]pyrrole derivatives from simple 3-butyamine and 2-(hydroxymethyl)phenol derivatives is described. The process is promoted by a dual catalytic system formed by a gold complex and a Lewis acid (boron trifluoride). The reaction involves the synchronized transformation of the starting materials into two reactive intermediates, a cyclic enamine derivative and an ortho-quinone methide, that subsequently react between them through a formal [4+2] cycloaddition to furnish the final poly-heterocyclic product in a straightforward way.

Introduction

In recent years, the development of new chemical transformations involving the intermediacy of ortho-quinone methides (o-QM) has experienced a considerable growth.[1] This kind of reactive species are usually in situ generated by treatment of appropriate precursors under acidic[2] or basic[3] conditions. They can be also accessed by elimination reactions promoted by different agents,[4] or through thermal processes.[5] Regarding the reactivity of o-QMs, they have been mainly used as heterodienes in cycloaddition processes.[4,6] In this type of reactions, the corresponding o-QM is in situ generated in the presence of suitable cycloaddition partners. Moreover, the development of reactions where both the o-QM and the dienophile are catalytically and simultaneously generated, is an appealing research field. In this context, a gold-catalysed process recently reported by our group is to be mentioned (Scheme 1a).[7] In this reaction, the gold catalyst promotes the formation of enamines I (a dienophile) from alkynamines 1 and also the generation of isochromanone II (a heterodiene) from ortho-alkynylsalicylaldehyde 2. The subsequent reaction between intermediates I and II leads to pyranochromeno[2,3-b]pyrrole derivatives 3. In this context, we envisioned that 2-(hydroxymethyl)phenol derivatives 4 could be suitable precursors of o-QMs III (Scheme 1b). Since o-QMs usually behave as heterodienes in formal cycloaddition processes, intermediates III should react with cyclic enamines I delivering hexahydrochromeno[2,3-b]pyrrole derivatives 5. In contrast with our previous work, the planned reaction would require two different catalysts to promote the formation of the heterodiene III and dienophile I.[8]

Scheme 1. Previous work and the new proposal for the synthesis of hexahydrochromeno[2,3-b]pyrrole derivatives.

With all this in mind, we initiated our investigation to find appropriate catalysts and conditions to perform the desired transformation. For the initial experiments, we selected tert-butyl 4-(4-bromophenyl)but-3-yn-1-yl]carbamate 1a and 2-[hydroxyl(phenyl)methyl]phenol 4a as model substrates. For the in-situ generation of the corresponding enecarbamates I from 1a different gold catalysts were considered. On the other hand, the dehydration reaction of 4a to obtain the corresponding o-QM III...

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would require a Brønsted or Lewis acid as catalyst. In this sense, it should be noted that the use of binary metal / Brønsted acid catalytic systems are well documented in the bibliography and represents an appealing field to which our research group has recently contributed. For this reason, we started our investigation by trying the model reaction in the presence of (JohnPhos)AuN(Tf2 (5 mol%) as the gold-catalyst and different Brønsted acids (5 mol%) including triflic acid, tetrafluoroboric acid and diphenylphosphate among others. Although in some cases we observed the formation of the desired hexahydrochromeno[2,3-b]pyrrole 5a, neither the yield nor the reproducibility were good.

\[
\begin{align*}
\text{Ar}1 & = 4-\text{BrC}_6\text{H}_4, 85\%, \text{single diast.} \\
\text{Ar}1 & = 4-\text{NO}_2\text{C}_6\text{H}_4, 99\%, \text{single diast.} \\
\text{Ar}1 & = 4-\text{PhC}_6\text{H}_4, 85\%, \text{single diast.} \\
\text{Ar}1 & = 2-\text{FC}_6\text{H}_4, 99\%, \text{d.r.} = 4:1 \\
\text{Ar}1 & = 4-\text{OME}_{2}\text{C}_6\text{H}_4, 74\%, \text{d.r.} = 1:4:1 \\
\end{align*}
\]

At this point, we turned our attention to the use of a Lewis acid in combination with the gold-catalyst. It should be noted that this type of binary catalytic systems has been less used than those others formed by a gold-catalyst and a Brønsted acid. However, after some experimentation we found that (JohnPhos)AuNTf2 / BF3·OEt2 was an appropriate catalytic system to promote the target transformation (Scheme 2). Thus, when diol 1a and alkyamine 4a (2 equiv) were reacted in dichloromethane at room temperature in the presence of 5 mol% of (JohnPhos)AuNTf2 and 10 mol% of BF3·OEt2 we observed the formation of hexahydrochromeno[2,3-b]pyrrole 5a in almost quantitative yield (98%). Noteworthy, three new bonds and three stereocentres were created in this transformation. Furthermore, 5a was obtained as a single diastereoisomer and the reaction could be scaled up to synthesize 2.15 grams of hexahydrochromeno[2,3-b]pyrrole 5a in one batch without observing major changes in yield or diastereoselectivity. The structure of 5a was determined by NMR studies and confirmed by X-ray diffraction analysis.

\[
\begin{align*}
\text{Ar}1 & = 4-\text{BrC}_6\text{H}_4, 85\%, \text{single diast.} \\
\text{Ar}1 & = 4-\text{NO}_2\text{C}_6\text{H}_4, 99\%, \text{single diast.} \\
\text{Ar}1 & = 4-\text{PhC}_6\text{H}_4, 85\%, \text{single diast.} \\
\text{Ar}1 & = 2-\text{FC}_6\text{H}_4, 99\%, \text{d.r.} = 4:1 \\
\text{Ar}1 & = 4-\text{OME}_{2}\text{C}_6\text{H}_4, 74\%, \text{d.r.} = 1:4:1 \\
\end{align*}
\]

**Scheme 2.** Proof of concept and initial result.

**Results and Discussion**

Having identified the optimized reaction conditions, we next studied the scope of the transformation using a series of substrates with different substitution patterns (Scheme 3). For the first set of experiments we used different 2-(hydroxymethyl)phenol derivatives 4 substituted with an aromatic group (Ar1) in combination with a series of alkynamines 1. Thus, as far as seventeen different hexahydrochromeno[2,3-b]pyrrole derivatives 5 could be accessed in good yields and as single diastereoisomers in most of the cases. In those cases where two diastereoisomers were obtained, the structure of the minor one differs from that of the major one only in the relative configuration of the stereocenter at 4-position (Scheme 3).

\[
\begin{align*}
\text{Ar}1 & = 4-\text{BrC}_6\text{H}_4, 85\%, \text{single diast.} \\
\text{Ar}1 & = 4-\text{NO}_2\text{C}_6\text{H}_4, 99\%, \text{single diast.} \\
\text{Ar}1 & = 4-\text{PhC}_6\text{H}_4, 85\%, \text{single diast.} \\
\text{Ar}1 & = 2-\text{FC}_6\text{H}_4, 99\%, \text{d.r.} = 4:1 \\
\text{Ar}1 & = 4-\text{OME}_{2}\text{C}_6\text{H}_4, 74\%, \text{d.r.} = 1:4:1 \\
\text{Ar}1 & = 4-\text{BrC}_6\text{H}_4, 88\%, \text{single diast.} \\
\text{Ar}1 & = 4-\text{PhC}_6\text{H}_4, 88\%, \text{single diast.} \\
\text{Ar}1 & = 2-\text{FC}_6\text{H}_4, 99\%, \text{d.r.} = 4:1 \\
\text{Ar}1 & = 4-\text{OME}_{2}\text{C}_6\text{H}_4, 98\%, \text{d.r.} = 4:1 \\
\end{align*}
\]

**Scheme 3.** Scope of the reaction with different arene-substituted 2-(hydroxymethyl)phenol derivatives 4.
These results demonstrated that a wide range of substitution pattern was well tolerated. Thus, diverse substitution (ortho, meta, para and disubstitution) was allowed on the aromatic ring (Ar1) of the initial alkynamine derivative 1. However, we were not able to isolate the corresponding hexahydrochromeno[2,3-b]pyrrole derivatives when the alkynamine derivative 1 was unsubstituted at the terminal position of the alkyne or substituted with an alkyl group. Although most of the experiments were performed with alkynamine derivative 1 substituted with a tert-butoxycarbonyl (Boc) group on the nitrogen atom, we proved that other substituents such as a methoxycarbonyl (5h,j) or a tosyl group (5i) were also allowed. Regarding the substitution of the 2-(hydroxymethyl)phenol 4, reactions with starting materials containing different aromatic rings (Ar2) and substituents on the central arene (R’) were successfully accomplished.

In order to expand the scope of the transformation we performed a second set of experiments with alkyne-containing 2-(hydroxymethyl)phenol derivatives 6 (Scheme 4). These precursors of α-QMs III are particularly interesting as they should lead to a new type of alkynesubstituted hexahydrochromeno[2,3-b]pyrrole derivatives 7 that could be further functionalized through reactions involving the carbon-carbon triple bond.

As shown, under the optimized reaction conditions previously found, we were able to obtain a series of products 7 in good to excellent yields but in these cases as mixtures of two diastereoisomers with selectivities ranging from 3:1 to 1:1 (Scheme 4). The structure of the major diastereoisomer is shown in scheme 4 while the minor diastereoisomer differs in the relative configuration of the stereocenter at propargylic position. Though, apart from aromatic rings (Ar1) including heteroaromatics (7e) were tolerated at the alkynamine derivative 1. As before, we were not able to obtain the desired hexahydrochromeno[2,3-b]pyrrole derivatives when the alkynamine derivative 1 was unsubstituted at the terminal position of the alkyne or substituted with an alkyl group. Finally, the tert-butoxycarbonyl (Boc) substituent on the nitrogen of alkynamine 1 could be replaced by methoxycarbonyl or tosyl groups (7h,i).

A plausible mechanism for the formation of hexahydrochromeno[2,3-b]pyrrole derivatives 5 or 7 involving three independent catalytic cycles is shown in Scheme 5.

Scheme 5. Mechanistic proposal.

In the first catalytic cycle, the Lewis acid (BF₃) coordinates the alcohol functionality of 2-(hydroxymethyl)phenol derivatives 4 to form the new species 8. This coordination favours a dehydration reaction to generate the ortho-quinone methide (α-QM) derivative 9 in a process where the Lewis acid is regenerated. Simultaneously, the gold catalyst, JohnPhosAuNTf₂, coordinates the alkynie functionality of 1 as shown in 10. This coordination...
favours a 5-endo addition of the nitrogen atom to the alkylene to form intermediate 11. A final protodemetalation step closes the second catalytic cycle affording the enamine derivative 12 and regenerating the gold catalyst. At this point, we propose that QM 9 enters a new catalytic cycle where the Lewis acid (BF₃) coordinates to the oxygen atom as shown in 13. We propose that this coordination favours the subsequent formal [4+2] cycladdition reaction of this adduct 13 with enamine derivative 12 to afford the hexahydrochromeno[2,3-b]pyrrole derivatives 5 generating the Lewis acid catalyst. The relative configuration observed at the new stereocentres in the single or major diastereoisomer of 5 could be explained through an endo approach of the dienophile and the diene as shown in 13A (endo refers to the orientation of the nitrogen in dienophile 12 with respect to the diene 13). Interestingly, the global process could be considered a particular type of metal / Lewis acid relay one pot catalysis with two different catalysts and three independent catalytic cycles.[13]

Conclusions

In conclusion, a new protocol for the synthesis of hexahydrochromeno[2,3-b]pyrrole derivatives from simple 3-butyamine and 2-(hydroxymethyl)phenol derivatives has been developed. The reaction required the use of a dual catalytic system consisting of a gold complex and a Lewis acid, boron trifluoride. The cited catalytic system promotes the in-situ formation of an enecarbamate and an ortho-quinone methide that subsequently suffer a formal [4+2] cycladdition reaction to yield the final product. The reaction is shown to be straightforward, high-yielding and easy to scale-up, while it paves the way for interesting poly-heterocyclic products, which are otherwise difficult to obtain.

Experimental Section

General Procedure for the Synthesis of Hexahydrochromeno[2,3-b]pyrrole Derivatives 5 or 7: The corresponding alkylnalnine 1 (0.3 mmol, 2 equiv.), diol 4 or 6 (0.15 mmol, 1 equiv.) and 4Å powder (0.01 mmol, 10 mol%) were sequentially added at 20 °C for 15 hours. Then, 2 mL of hexane were added to the reaction mixture and the resulting suspension was filtered through a path of celite eluting with diethyl ether. Solvents were removed under reduced pressure and the crude was purified by flash column chromatography on silica gel using mixtures of hexane and ethyl acetate as eluent to give the corresponding pure products 5 or 7.

tert-Butyl (3aR,4R,9aR*)-9a-(4-bromophenyl)-4-phenyl-2,3,3a,9a-tetrahydrochromeno[2,3-b]pyrrole-1(4H)-carboxylate (5a): White solid. Rₜᵣᵢₜ₂ = 0.19 (hexane/ethyl acetate 10:1). Melting point: 229-231 °C. ¹H NMR (400 MHz, 330K, CDCl₃) δ (ppm) 8.21 (s, J = 9.0 Hz, 2H), 7.56 (d, δ = 9.0 Hz, 1H), 7.38-7.23 (m, 4H), 7.14-7.05 (m, 3H), 6.91-6.86 (m, 2H), 3.92-3.82 (m, 2H), 3.55 (dd, J = 10.7, 6.9 Hz, 1H), 2.76-2.67 (m, 1H), 2.07-1.92 (m, 1H), 1.71 (dt, J = 12.5, 6.4 Hz, 1H), 1.22 (s, 9H). ¹³C NMR (100 MHz, 330K, CDCl₃): δ (ppm) 153.3, 153.1, 150.7, 147.0, 145.0, 129.4, 129.0, 128.6, 128.7, 127.3, 125.4, 121.6, 121.1, 116.4, 93.9, 80.7, 53.5, 46.7, 40.3, 28.0, 24.0. HMRS: calculated for C₂₆H₂₃Na₂O₇ [M+Na⁺] 528.1144, found 528.1142.

tert-Butyl (3aR,4R,9aR*)-9a-(4-nitrophenyl)-4-phenyl-2,3,3a,9a-tetrahydrochromeno[2,3-b]pyrrole-1(4H)-carboxylate (5b): White solid. Rₜᵣᵢₜ₂ = 0.51 (hexane/ethyl acetate 10:1). Melting point: 212-215 °C. ¹H NMR (400 MHz, 330K, CDCl₃) δ (ppm) 7.66-7.60 (m, 2H), 7.59-7.55 (m, 2H), 7.49-7.41 (m, 4H), 7.39-7.24 (m, 5H), 7.16 (dd, J = 7.9, 1.5 Hz, 2H), 7.10 (d, δ = 8.0 Hz, 1H), 6.90-6.84 (m, 2H), 4.04 (d, J = 5.2 Hz, 1H), 3.86 (app t, δ = 9.8 Hz, 1H), 3.57 (td, J = 10.7, 6.9 Hz, 1H), 2.85-2.71 (m, 1H), 2.09-1.90 (m, 1H), 1.88 (dt, J = 12.5, 6.4 Hz, 1H), 1.20 (s, 9H). ¹³C NMR (100 MHz, 330K, CDCl₃): δ (ppm) 153.8, 153.7, 141.2, 140.8, 140.3, 129.6, 129.0, 129.7, 128.4, 128.3, 127.2, 127.0, 126.8, 125.9, 121.9, 120.5, 116.4, 94.5, 80.0, 53.5, 46.7, 41.0, 28.0, 23.9. HMRS: calculated for C₂₆H₂₃Na₂O₇ [M+Na⁺] 528.2532, found 528.2345.

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References

Methyl (3aR,4R,9aR)-4,9a-diphenyl-2,3,3a,9a-tetrahydrochromeno[2,3-b]pyrrole-1(4H)-carboxylate (5a): White solid. Rf = 0.32 (hexane/ethyl acetate 5:1). Melting point: 212-214 °C. 1H NMR (600 MHz, 330K, CDCl3): δ (ppm) 7.41-7.22 (m, 9H), 7.15-7.08 (m, 3H), 6.88-6.83 (m, 2H), 3.99 (d, J = 5.2 Hz, 1H), 3.86 (app, t, J = 9.8 Hz, 1H), 3.63-3.51 (m, 1H), 2.81-2.68 (m, 1H), 2.07-1.92 (m, 1H), 1.68 (dt, J = 12.9, 6.8 Hz, 1H). 13C NMR (100 MHz, 330K, CDCl3): δ (ppm) 154.8, 153.5, 141.9, 140.7, 129.5, 128.9, 128.4, 128.3, 128.2, 127.6, 127.1, 125.3, 121.8, 120.6, 116.5, 94.7, 53.1, 52.0, 47.0, 40.8, 24.1. HMRS: calculated for C32H29NaNO3 [M+Na]+ 582.0708, found 582.0712.

Methyl (3aR,4R,9aR)-9a-(3,5-bis(trifluoromethyl)phenyl)-4-phenyl-2,3,3a,9a-tetrahydrochromeno[2,3-b]pyrrole-1(4H)-carboxylate (5b): White solid. Rf = 0.62 (hexane/ethyl acetate 5:1). Melting point: 162-164 °C. 1H NMR (400 MHz, 330K, CDCl3): δ (ppm) 7.89-7.84 (m, 3H), 7.39-7.27 (m, 4H), 7.14 (dd, J = 7.8, 1.7 Hz, 2H), 7.10 (d, J = 8.1 Hz, 1H), 6.96-6.92 (m, 2H, 2H), 7.65-7.61 (m, 3H), 3.77 (d, J = 5.1 Hz, 1H), 3.63-3.43 (m, 2H), 2.68 (dt, J = 12.5, 6.4 Hz, 1H), 2.39 (s, 3H), 1.85-1.65 (m, 1H), 1.60-1.50 (m, 1H). 13C NMR (75 MHz, CDCl3): δ (ppm) 152.8, 154.3, 142.0, 139.7, 136.8, 137.1, 129.5, 129.1, 128.6, 128.7, 128.1, 127.4, 126.7, 123.4, 121.9, 121.8, 121.6, 121.4, 116.5, 94.3, 53.0, 52.2, 46.9, 40.8, 24.1. HMRS: calculated for C33H32F3CINaO3 [M+Na]+ 484.1649, found 484.1649.

Methyl (3aR,4R,9aR)-9a-(4-bromophenyl)-4-phenyl-1-tosyl-1,2,3,3a,4,9a-hexahydrochromeno[2,3-b]pyrrole (5c): Yellow solid. Rf = 0.66 (hexane/ethyl acetate 5:1). Melting point: 190-192 °C. 1H NMR (300 MHz, CDCl3): δ (ppm) 7.76 (d, J = 8.3 Hz, 2H), 7.42 (d, J = 8.6 Hz, 2H), 7.33-7.17 (m, 7H), 7.13 (t, J = 7.0 Hz, 1H), 6.98-6.92 (m, 2H, 2H), 7.65-7.61 (m, 3H), 3.77 (d, J = 5.1 Hz, 1H), 3.63-3.43 (m, 2H), 2.68 (dt, J = 12.5, 6.4 Hz, 1H), 2.39 (s, 3H), 1.85-1.65 (m, 1H), 1.60-1.50 (m, 1H). 13C NMR (75 MHz, CDCl3): δ (ppm) 152.8, 154.3, 142.0, 139.7, 136.8, 137.1, 129.5, 129.1, 128.6, 128.7, 128.1, 127.4, 126.7, 123.4, 121.9, 121.8, 121.6, 121.4, 116.5, 94.3, 53.0, 52.2, 46.9, 40.8, 24.1. HMRS: calculated for C33H26BrNaO3 [M+Na]+ 486.0765, found 486.0765.
tert-Butyl (3aR,4'R,9a'R)-9a-(3-methoxyphenyl)-4-phenyl-2,3,3a,9a-
tetrahydrochromeno[2,3-b]pyrrole-1(4'H)-carboxylate (5n): White solid. Rf = 0.54 (hexane/ethyl acetate 5:1). Melting point: 181-183 °C. 1H NMR (400 MHz, 330K, CDCl3; δ ppm) 7.37-7.20 (m, 5H), 7.17 (d, J = 6.9 Hz, 2H), 7.03 (d, J = 8.1 Hz, 1H), 6.97 (d, J = 2.3 Hz, 1H), 6.95-6.91 (m, 1H), 6.89-6.82 (m, 2H), 6.44 (d, J = 5.2 Hz, 1H), 3.76 (app t, J = 9.8 Hz, 1H), 3.50 (td, J = 10.7, 7.0 Hz, 1.92-2.56 (m, 1H), 1.98-1.85 (m, 1H), 1.68-1.55 (m, 1H), 1.30 (s, 9H). 13C NMR (100 MHz, 330K, CDCl3; δ ppm) 157.3, 153.7, 146.6, 140.7, 126.9, 128.9, 128.5, 128.2, 127.1, 124.6, 124.4, 121.9, 120.8, 119.6, 116.7, 92.7, 80.2, 54.6, 46.4, 41.4, 28.1, 23.6. HRMS: calculated for C36H33N2O2S [M+H]+ 543.2174, found 543.2177.

tert-Butyl (3aR,4'R,9a'R)-4-phenyl-9a-(thiophen-2-yl)-3a,9a-
tetrahydrochromeno[2,3-b]pyrrole-1(4'H)-carboxylate (5o-diaist. 1): White solid. Rf = 0.54 (hexane/ethyl acetate 5:1). Melting point: 181-183 °C. 1H NMR (400 MHz, 330K, CDCl3; δ ppm) 7.28-7.24 (m, 1H), 7.16-7.08 (m, 4H), 7.02 (d, J = 4.9 Hz, 1H), 6.97-6.86 (m, 4H), 6.77 (d, J = 2.8 Hz, 1H), 6.74-6.69 (m, 1H), 4.08 (d, J = 4.2 Hz, 1H), 3.75-3.63 (m, 1H), 3.06-3.02 (m, 1H), 2.23 (td, J = 12.5, 6.8 Hz, 1H), 1.93-1.81 (m, 1H), 1.30 (s, 9H). 13C NMR (100 MHz, 330K, CDCl3; δ ppm) 154.0, 153.5, 148.9, 143.1, 130.1, 128.7, 128.6, 125.6, 126.1, 124.9, 124.5, 122.1, 111.8, 93.2, 80.5, 55.6, 46.0, 44.8, 28.5, 28.1. HRMS: calculated for C31H26N2O2S [M+H]+ 434.1784, found 434.1776.

tert-Butyl (3aR,4'S,9a'S)-4-phenyl-9a-(thiophen-2-yl)-3a,9a-
tetrahydrochromeno[2,3-b]pyrrole-1(4'H)-carboxylate (5o-diaist. 2): White solid. Rf = 0.40 (hexane/ethyl acetate 5:1). Melting point: 120-122 °C. 1H NMR (400 MHz, 330K, CDCl3; δ ppm) 7.28-7.24 (m, 1H), 7.16-7.08 (m, 4H), 7.02 (d, J = 4.9 Hz, 1H), 6.97-6.86 (m, 4H), 6.77 (d, J = 2.8 Hz, 1H), 6.74-6.69 (m, 1H), 4.08 (d, J = 4.2 Hz, 1H), 3.75-3.63 (m, 1H), 3.06-3.02 (m, 1H), 2.23 (td, J = 12.5, 6.8 Hz, 1H), 1.93-1.81 (m, 1H), 1.30 (s, 9H). 13C NMR (100 MHz, 330K, CDCl3; δ ppm) 154.0, 153.5, 148.9, 143.1, 130.1, 128.7, 128.6, 125.6, 126.1, 124.9, 124.5, 122.1, 111.8, 93.2, 80.5, 55.6, 46.0, 44.8, 28.5, 28.1. HRMS: calculated for C31H26N2O2S [M+H]+ 434.1784, found 434.1769.

tert-Butyl (3aR,4'R,9a'R)-9a-(4-bromophenyl)-6-methoxy-4-phenyl-
2,3,3a,9a-tetrahydrochromeno[2,3-b]pyrrole-1(4'H)-carboxylate (5p): White solid. Rf = 0.58 (hexane/ethyl acetate 5:1). Melting point: 182-184 °C. 1H NMR (400 MHz, 330K, CDCl3; δ ppm) 7.47 (d, J = 8.7 Hz, 2H), 7.38-7.22 (m, 7H), 7.17-7.10 (m, 2H), 6.99 (d, J = 8.8 Hz, 1H), 6.83 (dd, J = 8.8, 3.0, 0.9 Hz, 1H), 6.41 (d, J = 3.0, 1.1 Hz, 3.92 (d, J = 5.2 Hz, 1H), 3.82 (app t, J = 9.8 Hz, 1H), 3.65 (s, 3H), 3.56-3.42 (m, 1H), 2.72-2.60 (m, 1H), 2.01-1.86 (m, 1H), 1.64 (dt, J = 12.7, 6.5 Hz, 1H), 1.23 (s, 9H). 13C NMR (100 MHz, 330K, CDCl3; δ ppm) 153.8, 153.6, 147.5, 142.4, 140.3, 131.2, 129.5, 128.7, 127.4, 122.7, 121.2, 117.0, 114.4, 114.1, 94.8, 91.0, 53.5, 53.6, 46.6, 41.3, 28.0, 23.9. HRMS: calculated for C32H26BrN2O2S [M+Na]+ 588.1250, found 588.1251.

tert-Butyl (3aR,4'R,9a'R)-9a-(4-bromophenyl)-8-methyl-4-phenyl-
2,3,3a,9a-tetrahydrochromeno[2,3-b]pyrrole-1(4'H)-carboxylate (5q): White solid. Rf = 0.50 (hexane/ethyl acetate 5:1). Melting point: 219-221 °C. 1H NMR (400 MHz, 330K, CDCl3; δ ppm) 7.47 (d, J = 8.2 Hz, 2H), 7.34-7.26 (m, 7H), 7.22 (d, J = 8.2 Hz, 2H), 7.16-7.10 (m, 3H), 6.77 (t, J = 7.4 Hz, 1H), 6.70 (d, J = 7.4 Hz, 1H), 3.96 (d, J = 4.4 Hz, 1H), 3.84 (t, J = 9.4 Hz, 1H), 3.56-3.43 (m, 1H), 2.75-2.63 (m, 1H), 2.36 (s, 3H), 2.01-1.84 (m, 1H), 1.72-1.61 (m, 1H), 1.21 (s, 9H). 13C NMR (100 MHz, 330K, CDCl3; δ ppm) 153.8, 151.3, 143.0, 140.6, 131.2, 129.5, 129.5, 128.4, 127.2, 127.0, 126.4, 125.3, 121.8, 121.2, 120.2, 94.3, 80.0, 53.6, 46.7, 41.1, 28.0, 24.0, 15.9. HRMS: calculated for C32H26BrN2O2S [M+Na]+ 564.1301, found 564.1297.

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tert-Butyl (3aR,4S,9aR)-9a-(3-methoxyphenyl)-4-[(4\-methoxyphenyl)ethynyl]tetrahydrochromeno[2,3-\f]
1.37 (m, 1H), 1.21 (s, 9H), 0.20 (s, 9H). \( ^13C\) NMR (400 MHz, 330K, CDCl3): \( ^\delta \) ppm = 153.4, 152.1, 151.2, 147.7, 129.0, 128.4, 128.3, 128.2, 128.1, 128.0, 128.0, 126.5, 123.6, 121.4, 115.4, 115.4, 112.5, 112.4, 112.4, 94.0, 87.5, 82.8, 79.9, 55.1, 52.3, 46.1, 30.8, 28.0, 26.8. HMRS: calculated for C\textsubscript{28}H\textsubscript{30}N\textsubscript{2}O\textsubscript{6}Na\textsubscript{2} [M+Na\textsuperscript{+}•] 534.2250, found 534.2260.

tert-Butyl (3aR,4S,9aR)-9a-(3-methoxyphenyl)-4-[(4\-methoxyphenyl)ethynyl]tetrahydrochromeno[2,3-\f]
1.39 (dd, \( J = 1.0, 2.5 \) Hz, 1H), 1.22 (s, 9H). \( ^13C\) NMR (400 MHz, 330K, CDCl3): \( ^\delta \) ppm = 159.4, 159.2, 152.5, 142.0, 132.9, 129.3, 129.2, 128.7, 128.7, 128.6, 128.3, 128.1, 115.4, 115.3, 115.4, 112.5, 112.4, 112.4, 94.0, 87.5, 82.8, 79.9, 55.1, 52.3, 46.1, 30.4, 28.0, 26.8. HMRS: calculated for C\textsubscript{28}H\textsubscript{30}N\textsubscript{2}O\textsubscript{6}Na\textsubscript{2} [M+Na\textsuperscript{+}•] 534.2250, found 534.2260.

tert-Butyl (3aR,4'R,9aR)-4-\( (\text{hex-1-yn-1-y1})-9\)-\( (\text{thiophen-2-yl})-2,3,3a,9tetrachromendo[2,3-\f]
1.39 (d, \( J = 10.6, 7.0 \) Hz, 1H), 1.30 (d, \( J = 12.1, 7.0 \) Hz, 1H), 1.22 (td, \( J = 7.0, 2.3 \) Hz, 1H), 1.20 (s, 9H), 0.20 (s, 9H). \( ^13C\) NMR (400 MHz, 330K, CDCl3): \( ^\delta \) ppm = 159.4, 159.2, 152.5, 142.0, 132.9, 129.3, 129.2, 128.7, 128.7, 128.6, 128.3, 128.1, 115.4, 115.3, 115.4, 112.5, 112.4, 112.4, 94.0, 87.5, 82.8, 79.9, 55.1, 46.3, 31.0, 28.5, 28.0, 23.2, 21.9, 18.4, 13.4. HMRS: calculated for C\textsubscript{28}H\textsubscript{30}N\textsubscript{2}O\textsubscript{6}Na\textsubscript{2} [M+Na\textsuperscript{+}•] 534.2297, found 534.2297.

tert-Butyl (3aR,4'R,9aR)-4-\( (\text{hex-1-yn-1-y1})-9\)-\( (\text{thiophen-2-yl})-2,3,3a,9tetrachromendo[2,3-\f]
1.39 (d, \( J = 10.6, 7.0 \) Hz, 1H), 1.30 (d, \( J = 12.1, 7.0 \) Hz, 1H), 1.22 (td, \( J = 7.0, 2.3 \) Hz, 1H), 1.20 (s, 9H), 0.20 (s, 9H). \( ^13C\) NMR (400 MHz, 330K, CDCl3): \( ^\delta \) ppm = 159.4, 159.2, 152.5, 142.0, 132.9, 129.3, 129.2, 128.7, 128.7, 128.6, 128.3, 128.1, 115.4, 115.3, 115.4, 112.5, 112.4, 112.4, 94.0, 87.5, 82.8, 79.9, 55.1, 46.3, 31.0, 28.5, 28.0, 23.2, 21.9, 18.4, 13.4. HMRS: calculated for C\textsubscript{28}H\textsubscript{30}N\textsubscript{2}O\textsubscript{6}Na\textsubscript{2} [M+Na\textsuperscript{+}•] 534.2297, found 534.2297.

tert-Butyl (3aR,4'R,9aR)-4-\( (\text{hex-1-yn-1-y1})-9\)-\( (\text{thiophen-2-yl})-2,3,3a,9tetrachromendo[2,3-\f]
1.39 (d, \( J = 10.6, 7.0 \) Hz, 1H), 1.30 (d, \( J = 12.1, 7.0 \) Hz, 1H), 1.22 (td, \( J = 7.0, 2.3 \) Hz, 1H), 1.20 (s, 9H), 0.20 (s, 9H). \( ^13C\) NMR (400 MHz, 330K, CDCl3): \( ^\delta \) ppm = 159.4, 159.2, 152.5, 142.0, 132.9, 129.3, 129.2, 128.7, 128.7, 128.6, 128.3, 128.1, 115.4, 115.3, 115.4, 112.5, 112.4, 112.4, 94.0, 87.5, 82.8, 79.9, 55.1, 46.3, 31.0, 28.5, 28.0, 23.2, 21.9, 18.4, 13.4. HMRS: calculated for C\textsubscript{28}H\textsubscript{30}N\textsubscript{2}O\textsubscript{6}Na\textsubscript{2} [M+Na\textsuperscript{+}•] 534.2297, found 534.2297.

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Keywords: heterocycles • homogeneous catalysis • multiscatalytic reactions • ortho-quinonemethides • synthetic methods


[12] CCDC 1576398 (S) 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.

A gold / BF$_3$ catalytic system promotes the transformation of simple 3-butenamines and 2-(hydroxymethyl)phenol derivatives into cyclic enamines and ortho-quinone methide derivatives. The subsequent formal [4+2]-cyclization reaction between these two intermediates gives rise to hexahydrochromeno[2,3-b]pyrrole derivatives.