Total Syntheses of Clausenawallines A and E

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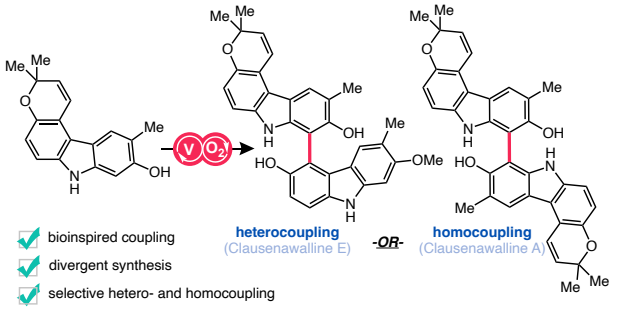
Supporting Information Placeholder

ABSTRACT: The first total syntheses of glycoborinine, clausenawalline A, and clausenawalline E were achieved. The key step employed a vanadium-catalyzed oxidative coupling of two hydroxycarbazole monomers. High-throughput experimentation was used to identify conditions favoring selective hetero-coupling of these monomers that possess similar redox potentials. A combination of a vanadium catalyst and 4-acetamido-TEMPO gives rise to greatly enhanced cross selectivity relative to the vanadium catalyst alone. Conditions to selectively form homodimer clausenawalline A or heterodimer clausenawalline E as the major product were found.



Dimeric clausenawallines are a class of bis(carbazole) alkaloids that were first isolated from *Clausena wallichii* roots.[1,2] Although these compounds exhibit a range of biological activity, there are no reported literature syntheses.[3–5] We envisioned synthesizing homodimeric clausenawalline A and heterodimeric clausenawalline E (**Figure 1**) via an oxidative coupling of two hydroxycarbazole monomers.

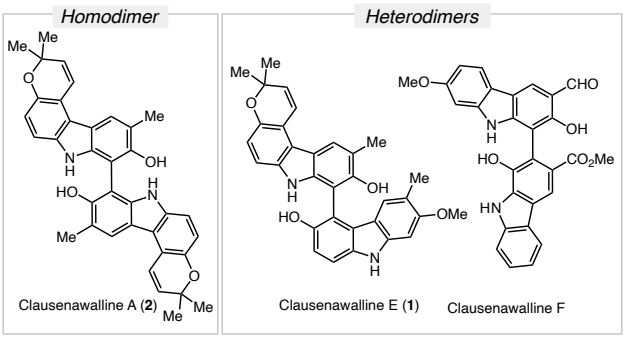
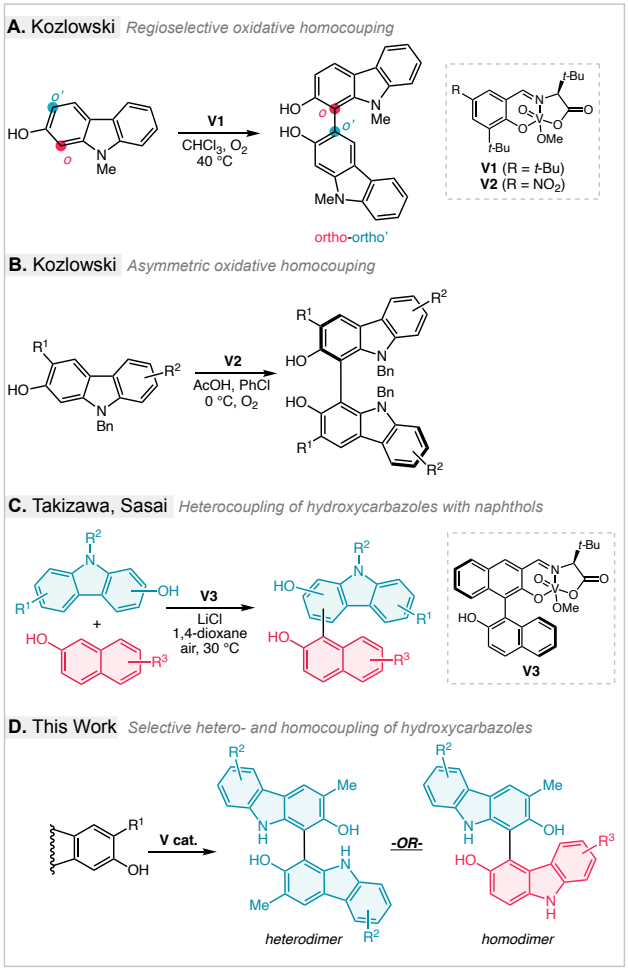


Figure 1. Structures of dimeric clausenawallines A, E, and F

Oxidative couplings are advantageous in synthesis because they eliminate the need to pre-functionalize the aryl rings. Homo-couplings of hydroxycarbazoles have been studied extensively in the literature.[6–8] Our group has previously investigated regioselective and asymmetric oxidative couplings of 2-hydroxycarbazoles using a vanadium catalyst (**Scheme 1A and B**).[9–11] Takizawa and Sasai have investigated asymmetric oxidative couplings of hydroxycarbazoles including homo-couplings[12,13] and hetero-couplings with 2-naphthol (**Scheme 1C**).[14–17] In addition, they have reported one hetero-coupling between two different hydroxycarbazoles (**Scheme 1C**).[18] To our knowledge, this is the only literature example of an oxidative hetero-coupling between

Scheme 1. Oxidative couplings of hydroxycarbazoles



two hydroxycarbazoles. In this Letter, we report both homo-couplings and hetero-couplings of complex hydroxycarbazoles to accomplish the first syntheses of dimeric clausenawalline natural products.

Our envisioned synthesis of clausenawalline E involved an oxidative hetero-coupling of two different hydroxycarbazole monomers. Such hetero-couplings have been understudied in the literature with the only example utilizing a less reactive 3-hydroxycarbazole and a 4-hydroxycarbazole. In particular, there is no precedent for the coupling of 2-hydroxycarbazole with a 3-hydroxycarbazole or for the incorporation of the more complex chromene heterocycle needed for clausenawalline E. As such, initial investigations were conducted using a simplified model system which was designed such that hetero-coupled and homo-coupled products could be easily distinguishable by mass, enabling rapid assessment by high-throughput experimentation (HTE). Notably, these two monomers had very similar oxidation potentials (**3** E^o = 0.45 V, **4** E^o = 0.48 V). Further, *N*-methylated carbazoles were used to prevent undesired C-N coupling.

An HTE screen using two different vanadium catalysts (**V1**, **V2**) at two different catalyst loadings (10 and 30 mol%) with **3** and **4** showed two major products arising from hetero-coupling (**5**) and homo-coupling (**6**) of **3** (**Figure 2**). Conditions with lithium chloride and acetic acid additives were also included as our previous studies showed they activated the vanadium catalyst.[11] In most cases, lithium chloride did not significantly affect the conversion or amount of product formed, when compared to analogous entries with no additive present. Acetic acid increased the consumption of starting materials, but often resulted in a substantial amount of over-oxidation products, such as trimers and other oligomers, resulting in a lower ratio of product to internal standard. Similarly, more over-oxidation products were observed with catalyst **V2** than **V1**. The presence of a strong electron withdrawing group renders the vanadium catalyst **V2** a stronger oxidant, leading to more undesired over-oxidation products. Increasing the catalyst loading of **V1** from 10 mol% to 30 mol% resulted in increased conversion of starting materials as well as the highest ratio of hetero-coupling product **5** to the internal standard.

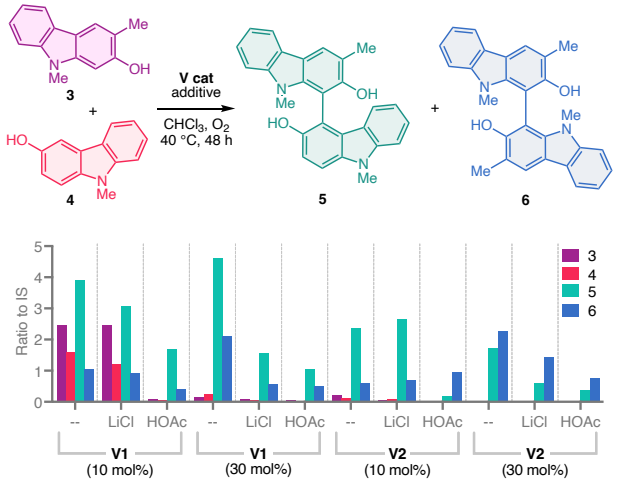
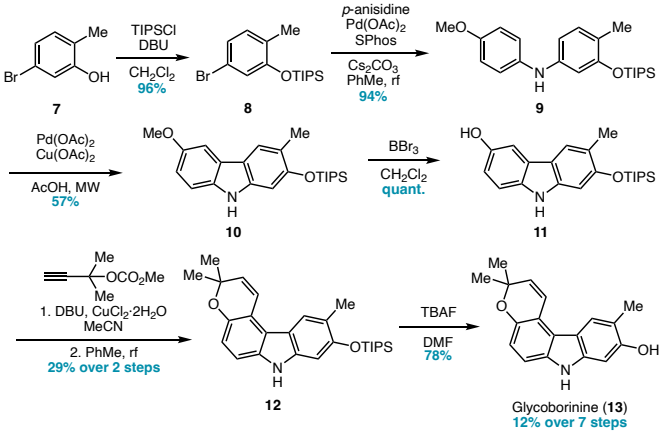


Figure 2. Results of model system HTE screen.

The conditions that afforded the highest ratio of desired product **5** to internal standard were 30 mol% **V1** with no additive. A scaled-up reaction utilizing these conditions provided hetero-coupled product **5** in 46% yield. Notably, the unprotected versions of **3** and **4** provided the unprotected hetero-coupled product in 48% yield, and no significant amount of reaction was observed at the *N*-position. Thus, we moved forward with the synthesis of clausenawalline A and E using *N*-unprotected hydroxycarbazoles.

Clausenawalline A is a homodimer of glycoborinine (**13**) and clausenawalline E is a heterodimer of glycoborinine and glycozolidol (**14**). Glycozolidol has been previously synthesized in the literature.[19,20] However, there are no previously reported literature syntheses for the alkaloid natural product glycoborinine. Therefore, we designed and optimized a synthetic route for the synthesis of glycoborinine (**Scheme 2**).

Scheme 2. Synthetic route to glycoborinine



Protection of 5-bromo-2-methyl phenol (**7**) with triisopropylsilyl chloride provided the silyl ether **8**. A subsequent Buchwald-Hartwig coupling between **8** and *p*-anisidine gave diarylamine **9** in excellent yield. An intramolecular palladium(II)-catalyzed oxidative microwave cyclization of **9** gave carbazole **10**.[19,20] Demethylation of **10** gave hydroxycarbazole **11**.

Formation of chromene **12** was particularly challenging. Several routes were explored to form the chromene either earlier in the synthesis (prior to cyclization of the carbazole) or through a different late-stage functionalization (after the cyclization of the carbazole), but all resulted in poor yields with complicated mixtures of undesired byproducts. Ultimately, the chromene was synthesized using the method of Godfrey,[21] which involves alkylation of hydroxycarbazole **11** followed by a thermal [3,3]-sigmatropic rearrangement of the resulting aryl ether to give **12**. While undesired by-products were still observed, likely similar to those reported in the literature using the method of Godfrey on structurally similar carbazoles,[22–24] these conditions afforded to highest amount of desired product **12**. Removal of the silyl protecting group provided **13** in a 12% overall yield over 7 steps. When the optimal model hetero-coupling conditions were used with **13** and **14** to form clausenawalline E, a 21% yield was observed which was significantly lower than the 48% yield obtained with the unprotected model

system. As both **13** and **14** incorporate one additional electron donating oxygen in a distal position, this result was unexpected. The formation of a significant amount of homo-coupled product **2** indicates that the chromene ring renders **13** significantly more reactive.

As result, an HTE screen was conducted with **13** and **14** with the goal of promoting hetero-coupling while suppressing homo-coupling. An excess of **13** was employed to increase hetero-coupling while two catalysts (**V1** and **V2**), four solvents ($CHCl_3$, CCl_4, PhCl, and HFIP), and two additives (ACT, LiCl) were examined (**Figure 3**). Since prior work indicated that the reaction proceeds through a radical-radical pathway,[11] radical inhibitor 4-acetamido-TEMPO (ACT) was added to slow the overall reaction and prevent over-oxidation (to trimers and tetramers), which contributed to lower yields. HFIP was screened due to its ability to stabilize electron-deficient intermediates.[25] Additionally, in our previous work, using HFIP as a solvent in a vanadium-catalyzed intramolecular phenol coupling improved yield and conversion by enabling the formation of an HFIP-coordinated V(V)-oxo catalyst.[26] ACT in HFIP afforded the best ratio of hetero-coupled product **1** to the internal standard, as well as the best ratio of **1** to homo-coupled product **2**.

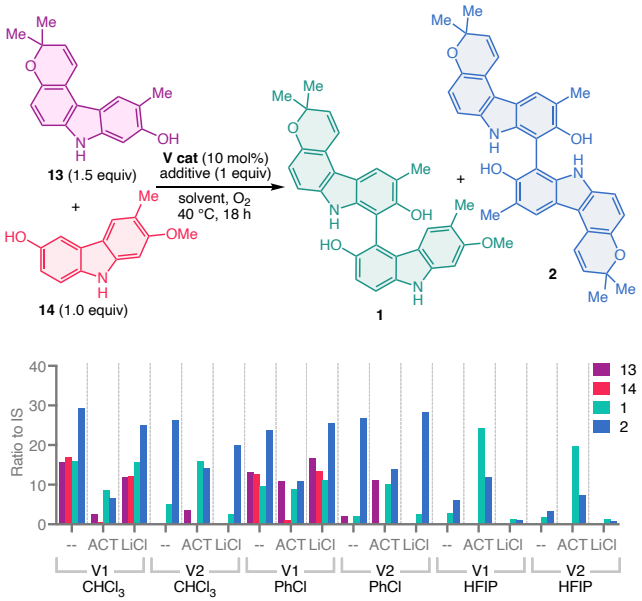
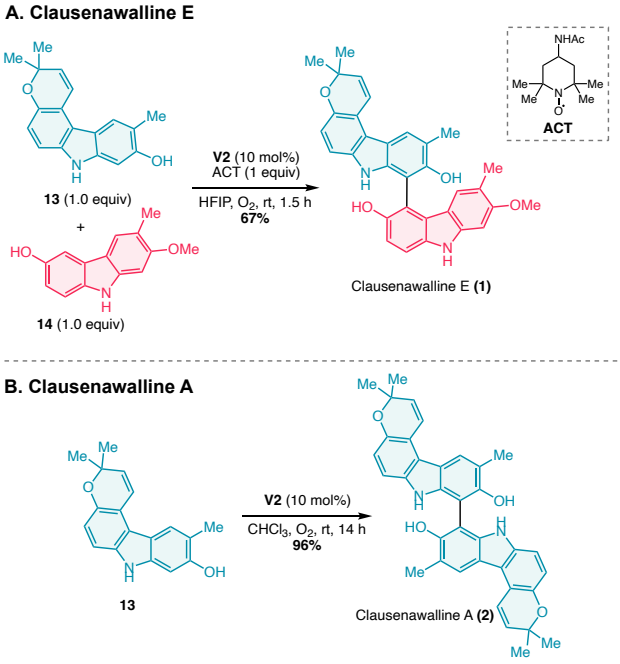


Figure 3. Results of clausenawalline E HTE screen.

Further benchtop optimizations explored the effect of catalyst, the ratio of **13:14**, the temperature, and the effect of ACT (see Table S4 in SI). As the results with both catalysts were similar in the HTE screen, they were assessed on a larger scale which revealed that catalyst **V1** was slower than that of catalyst **V2**, but yields were not significantly different. The use of excess **13** was not desirable so a 1:1 ratio of **13:14** was examined which led to similar results and was used going forward. Over-oxidation was found to erode yields so several efforts were made to limit it. For example, lowering the temperature to 0 °C did slow conversion but did not significantly change the amount of **1** obtained. With 0.5 equiv ACT, both lower yields and selectivities were observed while similar yields and selectivities were seen with 2 equiv ACT. Replacing ACT with TEMPO resulted in a decreased yield, but still gave a higher yield, conversion, and selectivity than the reaction with only catalyst. Notably, the reaction rate did increase with ACT and a control reaction with ACT but without the vanadium catalyst revealed slow formation of products (18% vs 50% at the same time point) favoring the heterodimer. Thus, it appears that ACT acts in concert with the vanadium catalyst to cause selective formation of the heterodimer **1**. For the synthesis of clausenawalline E (**1**), the optimal conditions were determined to be 10 mol% **V2** with 1 equiv ACT in HFIP at room temperature, providing the natural product in a 67% yield (**Scheme 3A**).

Scheme 3. Optimized couplings for clausenawallines E and A



Treatment of glycoborinine with 10 mol% **V2** in $CHCl_3$ under oxygen at room temperature afforded clausenawalline A in 96% yield (**Scheme 3B**). Three chiral catalysts (**V1**, **V2**, and **V3**) were screened, but none resulted in any significant enantiomeric excess in the product.

In summary, the first total syntheses of glycoborinine, clausenawalline E, and clausenawalline A were achieved. A model system was developed to initially probe the optimal hetero-coupling conditions. Additional optimizations conducted on the natural product precursors showed that HFIP and ACT improved the ratio of hetero-coupling to homo-coupling and gave clausenawalline E as the major product. Further studies to understand how ACT functions and to explore the use of such radical reagents in combination with other oxidative catalysts in phenol couplings are warranted.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the

published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
Experimental procedures, product characterization, and NMR spectral copies (PDF).
FAIR data, includes the primary NMR FID files (ZIP).

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Notes

The authors declare no competing financial interest.

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