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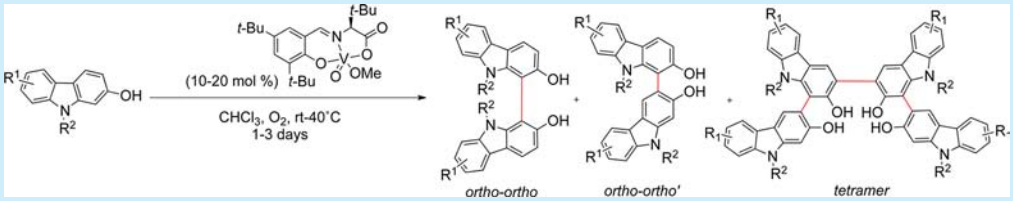
Vanadium-Catalyzed Regioselective Oxidative Coupling of 2-Hydroxycarbazoles

Lei Liu,[†,‡] Patrick J. Carroll,[‡] and Marisa C. Kozlowski*[,‡]

[†]Department of Applied Chemistry, China Agricultural University, Beijing 100193, People's Republic of China

[‡]Department of Chemistry, Penn Merck High Throughput Experimentation Laboratory, University of Pennsylvania, Philadelphia, Pennsylvania 19104-6323, United Sates

Supporting Information



ABSTRACT: The first regioselective oxidative coupling of 2-hydroxycarbazoles is described. With a vanadium catalyst and oxygen as the terminal oxidant, dimers with an ortho−ortho′ coupling pattern were obtained with high selectivity. Further oxidation led to ortho′−ortho′ coupling to generate a tetramer, which provided insight that the atropisomerization barriers of the unsymmetrical biaryl bonds are much lower than expected.

Bis(hydroxycarbazoles) are an important class of alkaloids with promising antimalarial, cytotoxic, anti-HIV, and antimicrobial activities.[1−3] There are over 20 naturally occurring bis(carbazole) alkaloids isolated from plants of the Rutaceae families, e.g. *Murraya*[4] and *Clausena*,[5] which comprise three structural subclasses including C−C and C−N linked biaryls (Figure 1).[6]

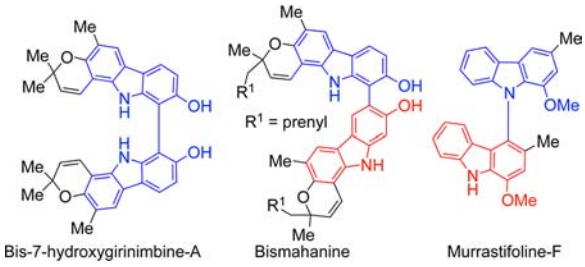


Figure 1. Selected bis(hydroxycarbazole) natural products.

To date, selective methods for the oxidative coupling to obtain dimeric hydroxycarbazoles have primarily relied upon substitution to block other potentially reactive sites of the phenol moiety (Scheme 1A−C).[7−9] With this caveat, a broad range of oxidants can be used to successfully couple 1-, 2-, and 3-hydroxycarbazoles. The reaction occurs on the phenolic ring, presumably due to less electron density at the C5−C8 positions.

In the case when more than one reactive site is present (Scheme 1D), mixtures of the isomeric products are obtained.[10] Herein, we describe the use of vanadium(V) catalysts to accomplish selective oxidative coupling of 2-hydroxycarbazoles using oxygen as the terminal oxidant.

Recently, we discovered that salen and salan metal complexes can use oxygen to catalyze the formation of phenolic dimers unattainable with conventional oxidants.[11] Encouraged by the success of these reactions, we turned our focus to the couplings of 2-hydroxycarbazoles (Table 1). Notably, selective coupling of this substrate was not observed with conventional oxidants, including di-*tert*-butyl peroxide, $CuCl_2$/TMEDA, $K_3Fe(CN)_6$, MnO_2, Ag_2CO_3, and *p*-chloroanil (see the Supporting Information). Screening of the salen/salan[12] catalyst library[11] containing Ru, Cr, Cu, V, Fe, and Mn complexes revealed that the V adducts provided the best reactivity, albeit at low levels (see the Supporting Information). Further optimization did not prove fruitful, and we theorized that complexes with less hindered coordination sites would be needed to obtain greater reactivity. We then examined vanadium complexes containing a portion of the salen framework (Figure 2),[13,14] as these catalysts have been effective with the more reactive 2-naphthol.[15]

Using 10 mol % of dimeric vanadium catalyst **V1** or **V2**, the reaction proceeded smoothly in chloroform at room temperature to afford the ortho−ortho′ (**2a**) and ortho−ortho (**3a**) products with excellent regioselectivity (Table 1, entries 1 and 2). The C1 position is the most reactive site, benefiting from the immediate proximity of both a donor phenol and aniline. On this basis, the ortho−ortho product **3a** should predominate. The generation of ortho−ortho′ adduct **2a** as the major product here leads us to conclude that the steric hindrance of

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Scheme 1. Approaches to Bis(hydroxycarbazoles)

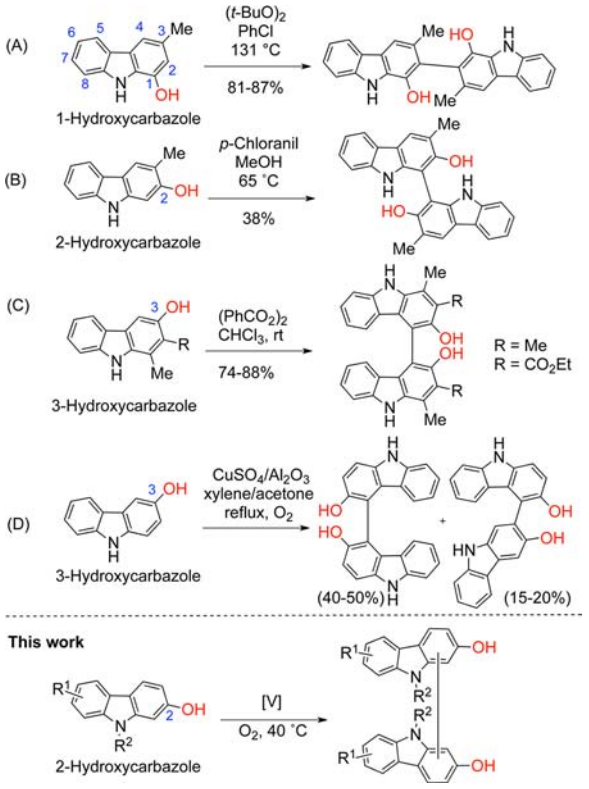
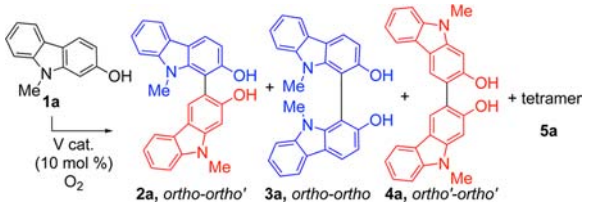


Table 1. Optimization of the Oxidative Coupling of 2-Hydroxycarbazole[a]



					yield (%)[b]		
entry	catalyst	solvent	temp (°C)	t (h)	**2a**	**3a**	**5a**
1	**V1**	$CHCl_3$	room temp	22	38	4	22
2	**V2**	$CHCl_3$	room temp	22	42	4	26
3	**V3**	$CHCl_3$	40	54	58	8	11
4	**V5**	$CHCl_3$	40	54	65	<2	10
5	**V4**	$CHCl_3$	room temp	22	45	6	30
6	**V6**	$CHCl_3$	room temp	22	49	<2	30
7	**V5**	$CHCl_3$	50	48	50	4	20
8	**V5**	DCE	40	54	40	<2	9
9	**V5**	PhCl	40	54	54	<2	14
10	**V5**	1,3-$Cl_2C_6H_4$	40	54	60	<2	10
11[c]	**V5**	$CHCl_3$	40	64	70	2	11

[a]Unless otherwise noted, reactions were conducted on a 0.1 mmol scale of **1a** and with catalyst (10 mol %) in 1 mL of solvent under O_2. [b]Yield determined by ^1H NMR with an internal standard. [c]Isolated yield.

the phenol-bound vanadium catalyst plays a large role. Thus, the most favorable combination with the vanadium catalyst is coupling of the most reactive C1 site with the secondmost reactive, and considerably less hindered, C3 site. In line with this theory, the ortho′-ortho′ product **4a**, which would require

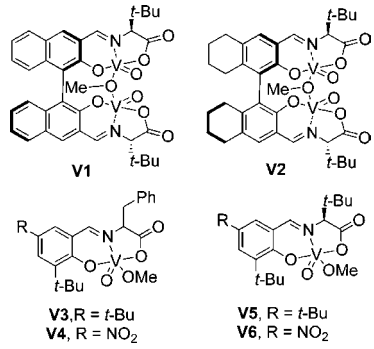


Figure 2. Vanadium catalysts used in this study.

the combination of two less reactive C3 sites, was not detected. The major byproduct was a tetrameric material, the structure of which could not be determined readily due to equilibrating mixtures of isomers (see below). Theorizing that a dimeric catalyst was not necessary and that the lower halves of catalysts **V1** and **V2** simply function as large substituents, we examined the monomers **V3** and **V5**, where the biaryl linkage is replace with a *tert*-butyl substituent (Table 1, entries 3 and 4). Both proved effective, although the more soluble **V5** compound was slightly better. To improve reaction times, a nitro group (**V4** and **V6**) was added to the ligand framework to withdraw electron density from the metal center, stabilize lower oxidation states, and thereby create a more reactive catalyst. These catalysts did give rise to faster reactions at lower temperatures, but the selectivity was compromised (Table 1, entries 5 and 6). Overall, **V5** presented the best balance of reactivity and selectivity. A further solvent (Table 1, entries 7−11) and concentration screen showed that 0.1 M $CHCl_3$ was superior, providing 70% of **2a** and minimal byproducts (Table 1, entry 11). Interestingly, the product **2a** was completely racemic with all of the catalysts, even though the same catalysts give high selectivity in asymmetric couplings of 2-naphthols[15] (see below).

With the optimal conditions in hand, we examined the substrate scope of various substituted 2-hydroxycarbazoles. In general, excellent selectivity for the ortho−ortho′ coupling was seen for various substrates (Table 2), with the exception of benzyl-protected hydroxycarbazole (**1b**; entry 1). Further, hydroxycarbazoles substituted at the C7 (Table 2, entries 2−11) or C6 position (Table 2, entries 12 and 13) exhibited moderate to good yields. Overall, substrates with electron-donating groups (Table 2, entries 8−11 and 13) reacted more quickly than those with electron-withdrawing groups (Table 2, entries 2−7 and 12).

The major byproduct in all of these transformations is the tetramer **5a**. Interestingly, trimers were not observed, which may arise from the greater reactivity of the dimer, as it can bind the vanadium catalyst more effectively via chelation. As discussed above, we conjecture that the C1 position (ortho) of 2-hydroxycarbazole is more reactive, but when this position is blocked, the C3-position (ortho′) can react well. Evidence for this assertion can be found in the structure of this tetramer, which was assigned by NMR spectroscopy to the isomer indicated and was confirmed by single-crystal X-ray measurements (Figure 3). This relative reactivity is further supported by the observation of tetramer **5a** upon treatment of pure dimer **2a** with catalyst **V5**.

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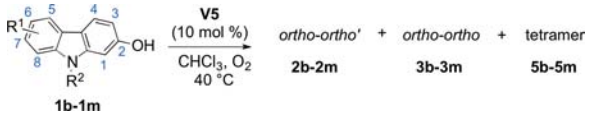
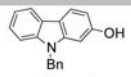
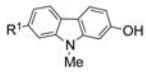
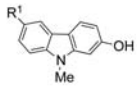
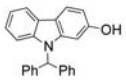
Table 2. Coupling of Various 2-Hydroxycarbazoles



entry	1	substrate		t (d)	yield (%)[a,b] 2	3	5
1[c]	1b			3	56	8	15
2	1c		R^1 = F	2	45 (78)	0	0
3[c]				3	62	2	17
4[c]	1d		R^1 = Br	2	40 (73)	0	0
5	1e		R^1 = Cl	2	40 (75)	0	0
6[c]				3	59	2	18
7[c]	1f		R^1 = Ph	1	43 (79)	0	0
8[c]	1g		R^1 = PMP[d]	1.5	39 (71)	0	0
9	1h		R^1 = TMS	2	77	3	4
10	1i		R^1 = Me	2	69	3	12
11[e]	1j		R^1 = OMe	3	51	2	25
12[c]	1k		R^1 = Br	2	41 (76)	0	0
13	1l			2	76	3	3
14	1m			2	<5	0	0

[a]Yields given in parentheses are based on recovered substrate. [b]Isolated yield. [c]20 mol % of **V5**. [d]PMP = 4-$MeOC_6H_4$. [e]At room temperature.

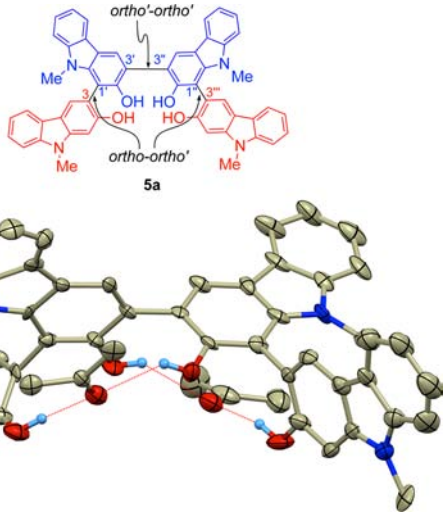


Figure 3. Structure of tetramer **5a**.

Notably, the ^1H and ^{13}C NMR of **5a** indicated the presence of two diastereomers that, when separated, interconverted over a period of 2.5 h at 18 °C to a 1.3:1 equilibrium ratio. Together with the observation that both of these diastereomers exhibit symmetric NMR spectra (e.g., two methyl peaks per diastereomer), we speculated that the ortho′−ortho′ axis undergoes free rotation, whereas the two ortho−ortho′ axes undergo slower rotation; the result would be two interconverting diastereomers, as observed. This latter proposal runs counter to the conventional stipulation that three ortho substituents adjacent to a biaryl axis give rise to atropisomerically stable axes at ambient temperature,[16] as has been proposed for bis-7-hydroxygirinimbine B and bismahanine (Figure 1).[6c]

To address this question, calculations (B3LYP/6-31G*) were undertaken with the tetramer **5a** (see the Supporting Information). As expected, rotation about the central ortho′-ortho′ axis was very facile with a barrier of 12−13 kcal/mol. The lowest barrier to rotation about the ortho−ortho′ axis was found to be ∼22 kcal/mol corresponding to a half-life of ∼1 h at ambient temperature, consistent with the observed isomerization. Furthermore, separation of the two enantiomers of **2a** by chiral HPLC followed by monitoring of the racemization over time (see the Supporting Information) revealed an atropisomerization half-life of 2.3 h corresponding to a barrier of 22.4 kcal/mol. We conclude that the geometry of the five-membered ring of the carbazole positions the amino substituent away from the axis so that it acts smaller than a typical substitutent ortho to a biaryl axis. Notably, these barriers are for the N−Me congener and natural products, such as bismahanine (Figure 1), with smaller N−H substituents are expected to display even lower atropisomerization barriers. Theorizing that a larger N-substituent would increase the atropisomerization barrier, benzhydryl compound **1m** was examined (Table 2, entry 14), but the increased steric bulk translated into very low reactivity.

With respect to the mechanism, TEMPO hampered the reaction, indicating a radical pathway. In addition, 50 mol % of catalyst **V5** with **1h** under anaerobic conditions generated the ortho−ortho′ product in 48% yield (no other isomers observed), in comparison to a 77% yield with 10 mol % of **V5** under an oxygen atmosphere (Table 2, entry 9). This result indicates that the active form of the catalyst is a vanadium(V) species, which causes a single-electron oxidation and conversion to vanadium(IV). The presence of O_2 is not integral to the coupling but is needed for turnover.

On the basis of these results and prior literature,[15] the mechanism in Scheme 2 is proposed. For the tetramer, first an ortho−ortho′ dimer forms. The biaryl bond of this species apparently increases the steric hindrance of hydroxyl adjacent to the single ortho site available for coupling. Thus, coupling of the dimer occurs instead at the less hindered ortho′ site.

In summary, we have developed the first regioselective oxidative coupling of 2-hydroxycarbazoles. With a vanadium Schiff base catalyst and oxygen as the terminal oxidant, the ortho−ortho′ dimers were obtained in good yields and high selectivity. Upon extended oxidation, the monomer afforded a tetramer resulting from coupling of the dimer at the less reactive, but more sterically accessible, site. On the basis of the behavior of the tetramer, the biaryl atropisomerization barriers were investigated and the ortho′−ortho′ axis was found to undergo free rotation, in line with expectations. However, the two ortho−ortho′ axes undergo substantial atropisomerization at ambient temperature, consistent with a barrier (22.4 kcal/mol) which is lower than the value expected when three ortho substituents are adjacent to a biaryl axis. As a consequence, natural products such as bismahanine are expected to be racemic mixtures under ambient conditions.

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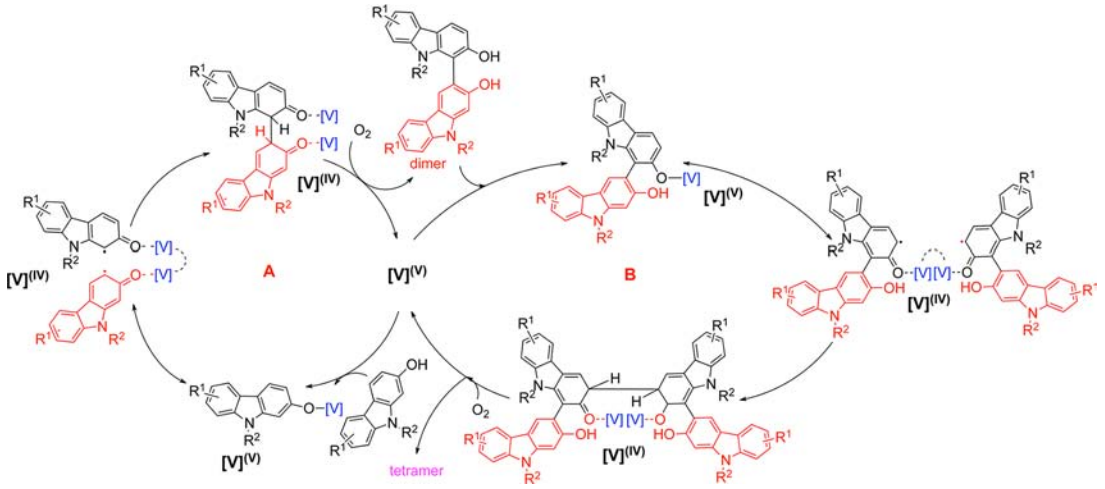
Scheme 2. Proposed Mechanism of the Homocoupling



■ ASSOCIATED CONTENT

Supporting Information

Text, figures, tables, and a CIF file giving experimental procedures, atropisomerization measurements, characterization data, crystallographic data, and calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail for M.C.K.: marisa@sas.upenn.edu.

Notes

The authors declare no competing financial interest.

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