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Asymmetric oxidative coupling of hydroxycarbazoles: Facile synthesis of (+)-bi-2-hydroxy-3-methylcarbazole

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Dedicated to Professor Dr. Dale L. Boger on the occasion of his 65th birthday.

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ABSTRACT

Asymmetric oxidative coupling reactions of hydroxycarbazoles have been established using a chiral dinuclear vanadium complex. To demonstrate the utility of vanadium-catalyzed reactions, we have used them to synthesize (+)-bi-2-hydroxy-3-carbazole in three steps from cyclohexanone and commercially available aniline derivatives.

Hydroxycarbazoles and bihydroxycarbazoles (Fig. 1) have garnered considerable attention from many research groups because they can serve as biological compounds, such as antibiotics, antibacterial and anti-yeast agents, and free-radical scavengers.[1] So far, many efforts have been made to develop metal-catalyzed and organocatalyzed methodologies for synthesizing hydroxycarbazole derivatives.[2] However, despite numerous studies, there have been few reports on efficient asymmetric oxidative couplings of hydroxycarbazoles.[3,4e] It is still highly desirable to explore new methods of synthesis to enable current synthetic chemistry to capitalize on the diverse structural features of hydroxycarbazoles and bihydroxycarbazoles.

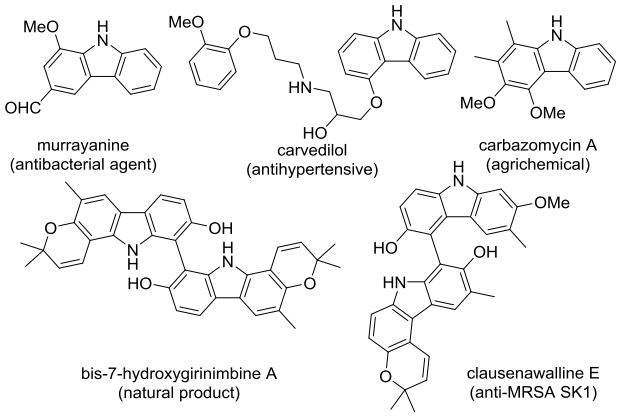
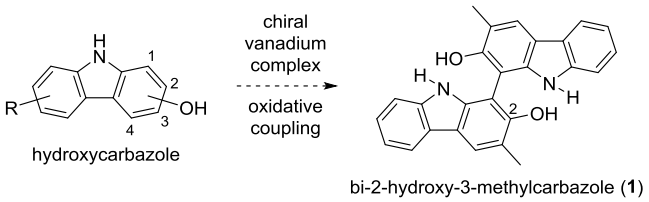


Fig. 1. Hydroxycarbazoles and bihydroxycarbazoles as natural products.

In this study, we report on the highly enantioselective coupling of hydroxycarbazoles to produce bihydroxycarbazole derivatives. We have found that a chiral dinuclear vanadium complex that can be used to mediate the oxidative coupling of polycyclic phenols[4] also works as a chiral catalyst for 3-hydroxycarbazoles to produce the corresponding coupling products with up to 80% ee. To demonstrate the utility of this synthesis method, we have employed it for the facile preparation

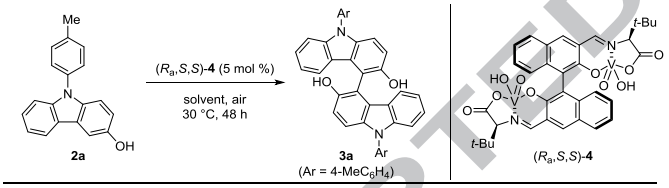
of bi-2-hydroxy-3-methylcarbazole (**1**) through the condensation of cyclohexanone and commercially available aniline, followed by Pd(II)-catalyzed dehydrogenative aromatization/intramolecular C−C bond coupling and deprotection. We used a chiral vanadium complex to mediate the oxidative coupling of hydroxycarbazole derivatives to afford (+)-**1** with acceptable enantioselectivity (Scheme 1).



Scheme 1. Enantioselective synthesis of bihydroxycarbazoles *via* chiral vanadium catalyzed coupling of hydroxycarbazoles.

We began the screening of reaction conditions for enantioselective oxidative coupling using *N*-*p*-tolyl-3-hydroxycarbazole (**2a**) as a model starting material, with 5 mol % (R_a,*S*,*S*)-**4**[4a] (Table 1). Among the solvents we tested (entries 1–5), the reaction in CCl_4 at 30 °C gave the product **3a** preferentially coupled at position C4 with a 65% NMR yield and 80% ee (entry 5). A change in the ambient atmosphere from air to O_2 decreased the yield of **3a** probably owing to side reactions, such as ortho-benzoquinone formation and over-oxidative couplings of **3a** (entry 6). Although the reaction was performed at low and high temperatures (10 °C or 50 °C), no improvement in the yields or enantioselectivities was obtained (entries 7 and 8).

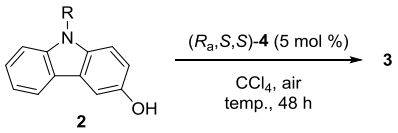
Table 1. Screening of reaction conditions for 3-hydroxycarbazoles using (R_a,*S*,*S*)-**4**



Entry	Solvent	Conv. of **2a** (%)	Yield (%)[a]	Ee (%)[b]
1	Toluene	80	45	79
2	1,2-$Cl_2C_6H_4$	94	44	74
3	CH_2Cl_2	74	55	70
4	$(Cl_2CH)_2$	87	56	62
5	CCl_4	85	65	80
6[c]	CCl_4	>95	43	79
7[d]	CCl_4	28	24	76
8[e]	CCl_4	87	56	69

[a]Determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. [b]Determined by HPLC (CHIRAL ART Cellulose-SB). [c]Under O_2 (balloon) instead of air. [d]At 10 °C for 72 h. [e]At 50 °C for 24 h.

Table 2. Substrate scope and limitations



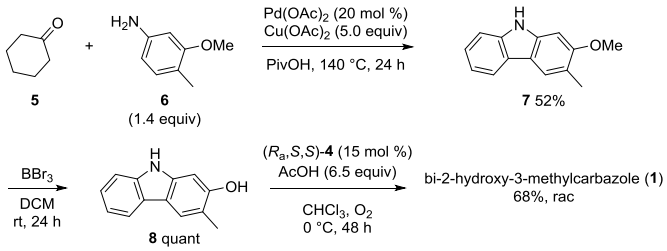
Entry	**2**, R	Temp. (°C)	Yield (%)[a]	Ee (%)[b]
1	**2a**, 4-MeC_6H_4	30	**3a**, 65	80
2	**2b**, Ph	30	**3b**, 55	80
3	**2c**, 4-ClC_6H_4	30	**3c**, 44	75
4	**2d**, Me	50	**3d**, 20	65
5	**2e**, Ac	50	**3e**, NR[c]	—

[a]Isolated yield. [b]Determined by HPLC (CHIRAL ART Cellulose-SB). [c]No reaction.

Considering the optimized reaction conditions, we investigated the scope and limitations of the substrates (Table 2). Phenyl- and 4-ClC_6H_4-substituted substrates (**2b** and **2c**) were converted to the corresponding products **3b** and **3c** with a moderate yield with 80% ee and 75% ee, respectively (entries 2 and 3). *N*-Me-3-hydroxycarbazole (**2d**) underwent a coupling reaction at 50 °C to give **3d** with 65% ee, but with only a 20% yield owing to the low reactivity of **2d**. The reaction of **2e**, which has an acetyl group on the nitrogen, did not proceed at all (entry 5), thus indicating that the oxidative coupling depends greatly on the electronic nature of the starting materials. The absolute configuration of **3** was assigned as *R* by comparison with an optical rotation of synthetic 9*H*,9'*H*-[4,4'-bicarbazole]-3,3'-diol (BACOL)[5] (**3f**: R = H) by (R_a,*S*,*S*)-**4**.

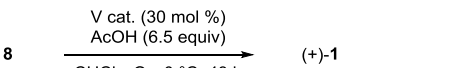
Since (R_a,*S*,*S*)-**4** proved to be effective for the oxidative coupling of 3-hydroxycarbazoles **3**, we focused on the enantioselective oxidative coupling of 2-hydroxycarbazole. Recently, Kozlowski has reported on the enantioselective oxidative coupling of *N*-protected-2-hydroxycarbazole derivatives,[3] while we have investigated the coupling of *N*-H-2-hydroxycarbazoles for the facile synthesis of bi-2-hydroxy-3-methylcarbazole (**1**), which is isolated from the roots of *Murraya koenigii*.[6,7] We synthesized the coupling precursors *via* a one-pot reaction of cyclohexanone (**5**) and the commercially available aniline derivative **6,** with 20 mol % of $Pd(OAc)_2$ and $Cu(OAc)_2$ (5.0 equiv) as a co-oxidant in PivOH[8], followed by the deprotection of the methyl group (Scheme 2). After sequential reactions, we obtained 2-hydroxy-3-methylcarbazole (**8**) in two steps, with a 52% overall yield. Considering the coupling precursor **8**, we performed the initial coupling reaction of **8** using 15 mol % of (R_a,*S*,*S*)-**4** in the presence of AcOH[3] in chloroform at 0 °C. Although we obtained bi-2-hydroxy-3-methylcarbazole (**1**) with a 68% yield, we did not observe asymmetric induction.

Scheme 2. Synthesis of 2-hydroxy-3-methylcarbazole (**8**) and an



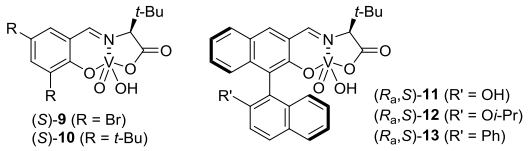
oxidative coupling of **8**

Table 3. Screening of reaction conditions in an enantioselective oxidative coupling of **8** using chiral mononuclear vanadium complexes



Entry	V cat.	Conv. of **8** (%)	Yield (%)[a]	Ee (%)[b]
1	(*S*)-**9**	>95	59	Rac
2	(*S*)-**10**	64	43	15
3	(R_a,*S*)-**11**	93	63	18
4	(S_a,*S*)-**11**	>95	78	9
5	(R_a,*S*)-**12**	90	44	21
6	(R_a,*S*)-**13**	>95	70	16

[a]Determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. [b]Determined by HPLC (DAICEL CHRALPAK IA).



During screening of the vanadium complexes, we found that mononuclear vanadium complexes also promoted the present reaction. The results obtained using chiral mononuclear vanadium complexes are shown in Table 3. Using 30 mol % of (*S*)-**9** led to **1** with a 59% yield, but it was in the form of a racemic mixture (entry 1). The vanadium catalyst (*S*)-**10**, which bears bulky *tert*-butyl groups, showed an asymmetric induction with 15% ee (entry 2). The use of other mononuclear vanadium complexes that possess a chiral binaphthyl backbone **11**–**13** resulted in the formation of **1** in moderate yields with ca. 20% ees (entries 3–6). Further investigation of the reaction conditions (vanadium catalysts, reaction solvents, and temperature; see supplementary material) revealed no improvement in the enantioselectivity. One reason responsible for the low enantioselectivity is the low rotation barrier of the aryl–aryl bond that leads to the racemization of the coupling product **1**. To demonstrate the easy racemization of **1**, we performed an optical resolution of **1** (>95% ee) with chiral high performance liquid chromatography, using a preparative DAICEL CHIRALPAK IC column. After the separation, followed by the removal of the solvent using a rotary evaporator at room temperature, the enantioselectivity had decreased to ca. 80% ee from an optically pure form in a few minutes. The enantioselectivity of **1** dropped further to less than 20% after 3 days at room temperature in the solution. Thus, the coupling product **1** was found to be easily racemized in a solution even at room temperature.[9]

In summary, we have performed enantioselective oxidative coupling of hydroxycarbazole derivatives using chiral vanadium complexes. By using the proposed protocol, we have demonstrated the short step asymmetric synthesis of bi-2-hydroxy-3-methylcarbazole, but with up to 21% ee owing to ready racemization.

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9. The easy racemization of **1** is probably due to less configurational stability of Aryl-Aryl bond, see ref 2d.

Supplementary Material

Supplementary material that may be helpful in the review process should be prepared and provided as a separate electronic file. That file can then be transformed into PDF format and submitted along with the manuscript and graphic files to the appropriate editorial office.

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