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ARTICLE

Chemo- and enantioselective hetero-coupling of hydroxycarbazoles catalyzed by a chiral vanadium(v) complex

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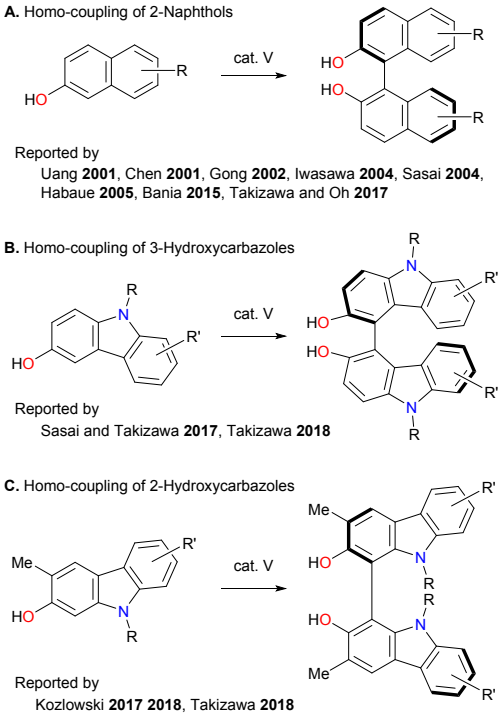
The catalytic enantioselective oxidative hetero-coupling of arenols using a chiral vanadium(v) complex has been developed. The coupling of hydroxycarbazole derivatives with various arenols provided axially chiral biarenols in high chemo-, regio-, and enantioselectivities. The reaction took place under mild conditions and exhibited satisfactory functional group tolerance. Aerobic oxidative hetero-coupling with β-ketoesters also proceeded in high chemo- and stereoselectivities under the slightly modified reaction conditions.

Introduction

Optically pure biarenol derivatives have played a significant role in organic chemistry due to their considerable utilization as chiral reagents, ligands, and building blocks.[1] To date, transition-metal-catalyzed cross-couplings is one of the most fundamental approaches to access the axially chiral molecules[2] through a carbon-carbon (C–C) bond formation.[2b,2c,3] An important issue in recent synthetic chemistry is to provide efficient methods to perform chemo-, regio-, and enantioselective C–C bond formations avoiding or minimizing undesired side-products and toxic wastes, leading to environmentally benign chemical syntheses.[4] Compared with well-established enantioselective oxidative homo-couplings to afford C_2-symmetric biarenols[5], hetero-couplings have the advantage to create C_1-symmetric[6] biarenols. Several enantioselective oxidative hetero-couplings of mainly 2-naphthol derivatives via radical-radical and radical-anion pathways, have so far been reported [Cu: Smrčina and Kočovský 1993[7], Kozlowski 2003[8], Habaue 2005[9], Tu and Tian 2019, 2021[10]; Fe: Katsuki 2010[11], Pappo 2016[12]; Ru: Uchida 2020[13]]. Although remarkable work has been conducted in this area, suppressing homo-couplings and the application of various arenols still remain a challenge.



Scheme 1. Reported Chiral Vanadium(v)-catalyzed Oxidative Homo-coupling of 2-Naphthols and 3-, 2-Hydroxycarbazoles.

Over the past few decades, chiral vanadium catalysts[14,15] were utilized in oxidative homo-couplings of 2-naphthols under the mild reaction conditions (Scheme 1A).[15a,16] Recently, our group and Kozlowski group independently extended chiral vanadium(v) complexes to the enantioselective oxidative homo-couplings of various arenols[17,18] such as polycyclic phenols,[17d,17e] resorcinols,[17a,18] 2- and 3-hydroxycarbazoles[17b,17c,18b,18c] (Scheme 1B, 1C), that have not been used in the other metal complexes because of their high catalyst activities leading to over-oxidation and side-reaction of starting material and/or coupling products.[19] Despite a

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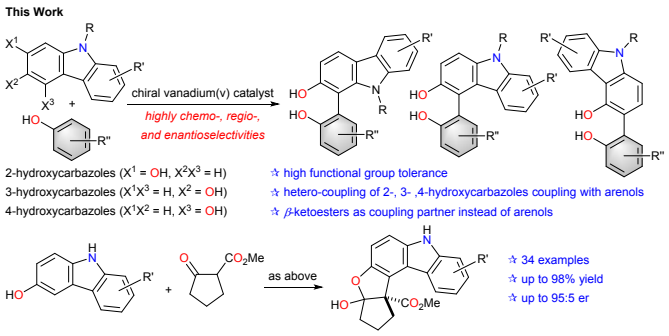
†Electronic supplementary information (ESI) available. X-ray crystallographic data for **3ga** (CCDC 1966275) and **8e** (CCDC 2025416). See DOI: 10.1039/x0xx00000x

potential abilities of vanadium(v) catalysts, no efficient enantioselective oxidative hetero-coupling of arenols has been reported to date. As part of our ongoing research with chiral vanadium(v) catalysis,[20] we herein disclose the chemo-, regio-, and enantioselective catalytic oxidative hetero-coupling of hydroxycarbazoles mediated by chiral vanadium(v) complexes, producing unsymmetrical carbazole-based biaryl derivatives that can be applied in functional materials and are also found in natural products (Scheme 2).[21] Additionally, *β*-ketoesters could be utilized as a coupling partner in the aerobic oxidative hetero-coupling.



Scheme 2. Oxidative Hetero-coupling of Hydroxycarbazoles with Various Arenols and *β*-Ketoester.

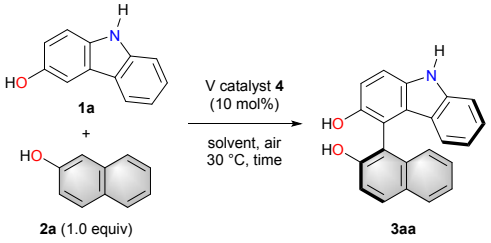
Results and discussion

Reaction optimization and substrate scope

Initially, chiral vanadium(v) catalysts were screened for the oxidative hetero-coupling employing a 1:1 molar ratio of 3-hydroxycarbazole (**1a**) and 2-naphthol (**2a**) under air (Table 1). The catalyst (R_a,*S*)-**4a** having a (*R*)-BINOL skeleton and a *tert*-leucine moiety[17b] afforded the axially chiral hetero-coupling product **3aa** in good yield (81%) with a moderate enantiomeric ratio (69:31 er) (Entry 1). Homo-coupling products **5a** and **6a** as well as other regioisomers were observed in less than 5% yield.[22] The diastereomeric catalyst (S_a,*S*)-**4a** had a catalytic activity comparable to that of (R_a,*S*)-**4a** to generate **3aa** in 75% yield with 61:39 er (Entry 2). During the catalyst screening, bulky substituents at the 3'-position on the binaphthyl skeleton of the catalyst were crucial for the high enantioselectivity. The vanadium(v) catalysts (R_a,*S*)-**4b** (R = Me) and (R_a,*S*)-**4c** (R = I) yielded **3aa** in 75:25 er and 72:28 er, respectively (Entries 3 and 4). Among the more sterically bulky aryl-substituted vanadium(v) catalysts (Entries 5–7), (R_a,*S*)-**4f** containing a 2,6-dimethylphenyl group afforded **3aa** in 92% yield with 82:18 er (Entry 7). Eventually, 1,4-dioxane proved to be a suitable solvent, furnishing **3aa** in 40% yield along with the unreacted starting materials **1a** and **2a** (Entry 11). In the presence of lithium chloride (LiCl) as an additive[18c,23] **3aa** was isolated in 84% yield with 94:6 er (Entry 13).

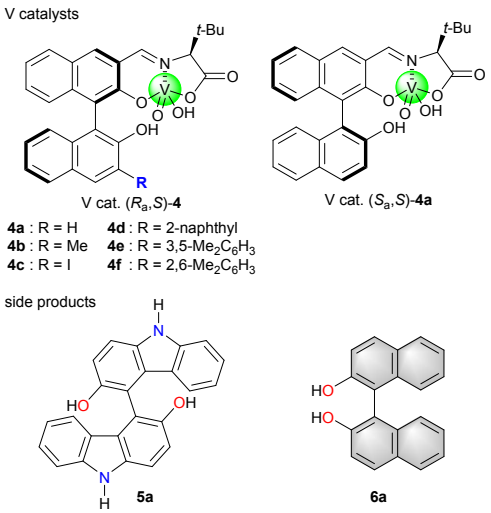
With the optimal reaction conditions in hand, the scope and limitations of the substrates were investigated (Scheme 3). A series of 3-hydroxycarbazoles containing a methyl (**1b**), aryl (**1c–e**), and bromo (**1f**) substituents efficiently reacted with **2a** to the corresponding products **3aa-3fa** (63–85% yields and 89:11–94:6 er).

Table 1. Optimization of the Reaction Conditions[a].



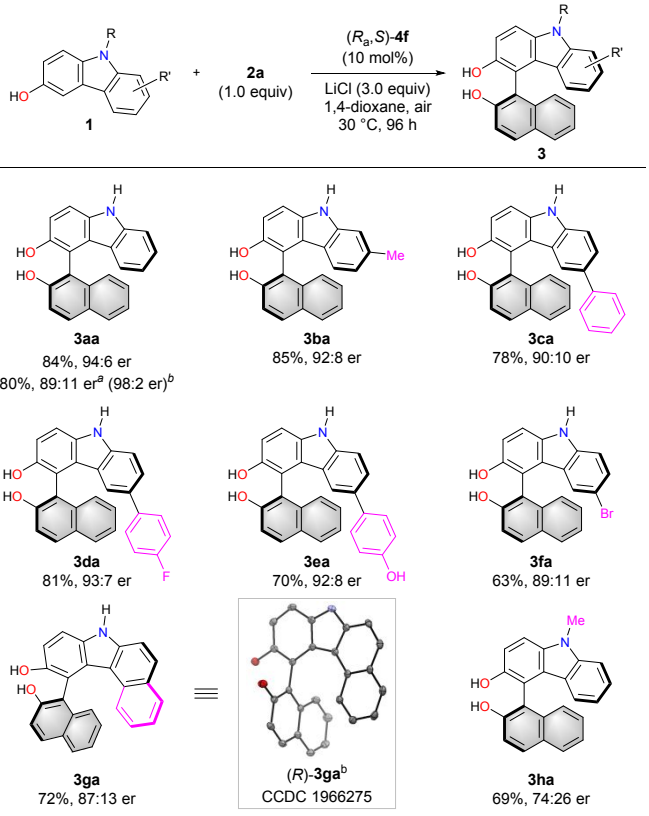
Entry	**4**	Solvent	Time (h)	Yield (%)[b]	Er[c]
1	(R_a,*S*)-**4a**	TCE	24	81	69:31
2	(S_a,*S*)-**4a**	TCE	24	75	61:39
3	(R_a,*S*)-**4b**	TCE	24	>95	75:25
4	(R_a,*S*)-**4c**	TCE	24	73	72:28
5	(R_a,*S*)-**4d**	TCE	24	84	71:29
6	(R_a,*S*)-**4e**	TCE	24	76	73:27
7	(R_a,*S*)-**4f**	TCE	24	92	82:18
8	(R_a,*S*)-**4f**	toluene	24	79	79:21
9	(R_a,*S*)-**4f**	diethyl ether	48	49	74:26
10	(R_a,*S*)-**4f**	THF	48	20	88:12
11	(R_a,*S*)-**4f**	1,4-dioxane	48	40	92:8
12[d]	(R_a,*S*)-**4f**	1,4-dioxane	96	74	91:9
13[e]	(R_a,*S*)-**4f**	1,4-dioxane	96	85 (84)	94:6

[a]The reaction of **1a** (1.0 equiv) and **2a** (1.0 equiv) using the vanadium(v) complex **4** (10 mol%) was conducted in a solvent (0.1 M for **1a**) at 30 °C under ambient conditions (1 atm). [b]Yields were determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard. [c]Enantiomeric ratios (ers) were determined using HPLC (DAICEL CHIRALPAK IA). [d]Conducted for 96 h [e]LiCl (3.0 equiv) was added. [f]Isolated product yield in parentheses. TCE = 1,1,2,2-tetrachloroethane. THF = tetrahydrofuran



The π-expanded hydroxycarbazole, 7*H*-benzo[*c*]carbazol-10-ol (**1g**), produced the coupling product **3ga** in 72% yield with 87:13 er. The absolute configuration of **3ga** was determined as *R* through X-ray crystallographic analysis. Moderate enantioselectivity was observed for 3-hydroxycarbazole **1h**, having a methyl group on the nitrogen atom. The coupling reaction of **1a** with **2a** in a 1.0 mmol scale also proceeded

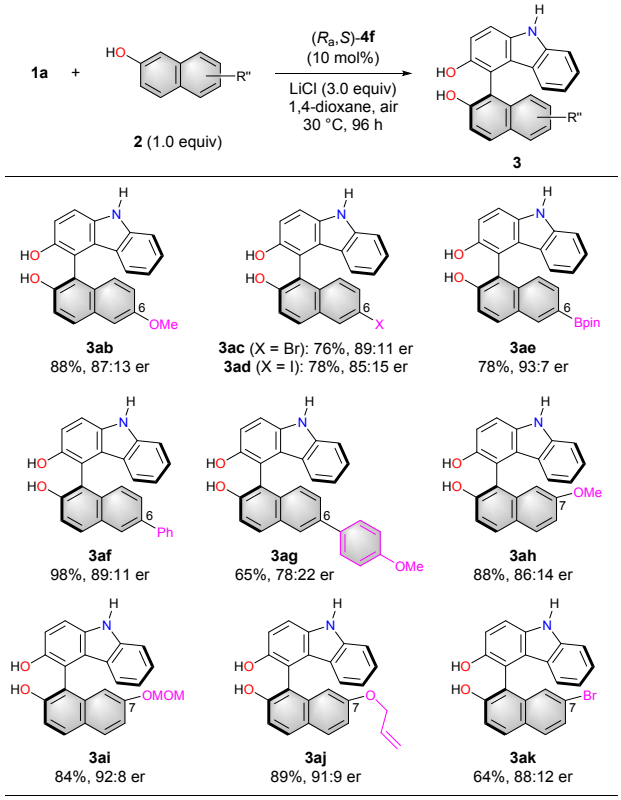
smoothly to give **3aa** in 80% yield with 89:11 er and **3aa** with high optical purity (98:2 er) was readily obtained after a single recrystallization.



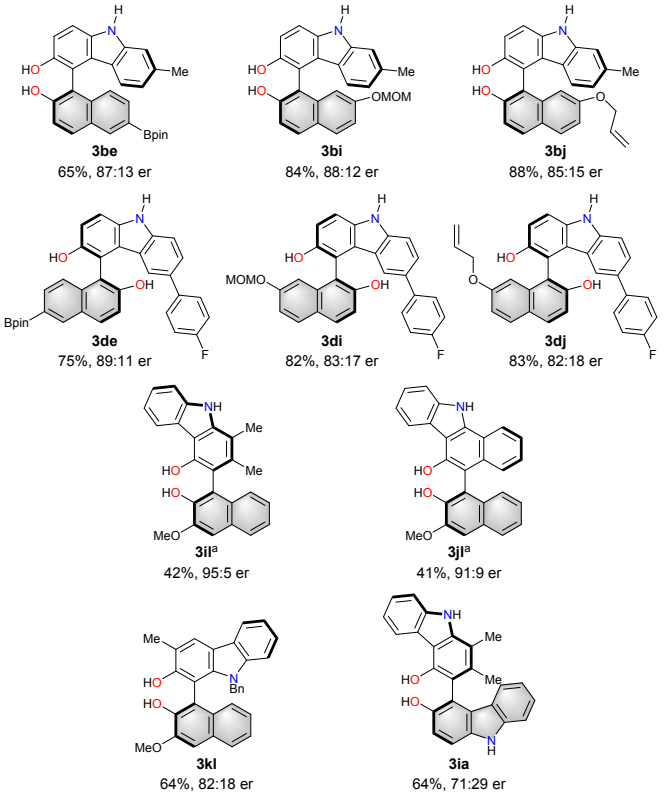
[a]Results on 1.0 mmol of **1**. [b]After a single recrystallization. X-ray structure of (*R*)-**3ga** with ellipsoids at 50% probability (H atoms and ethyl acetate were omitted for clarity).

Scheme 3. Substrate Scope of 3-Hydroxycarbazoles **1**[a].

Subsequently, various 2-naphthol derivatives **2** were examined in the coupling (Scheme 4). The reactions of electron-rich 6-methoxy- (**2b**), electron-deficient 6-bromo- (**2c**), or 6-iodo-2-naphthol (**2d**) with **1a** provided the desired products **3ab**–**3ad** in 76–88% yields with good enantioselectivities (85:15–89:11 er). Furthermore, 2-naphthols with (pinacolate)boryl and phenyl groups at the 6-position efficiently produced **3ae** and **3af** in 78% yield with 93:7 er and in 98% yield with 89:11 er, respectively. The reactions with 2-naphthol having a 4-MeO-C_6H_4 substituent at 6-position provided **3ag** in moderate yield and enantioselectivity. The use of 7-substituted 2-naphthols **2h**–**2k** afforded **3ah**–**3ak** in acceptable yields and enantioselectivities. The present catalytic system exhibited adequate tolerance towards functional groups such as halogens [Br (**3fa**, **3ac**, and **3ak**) and I (**3ad**)] and (pinacolate)boryl (**3ae**, **3be**, and **3de**) groups. Moreover, various combinations of coupling precursors **1** with **2** led to the formation of products **3be**, **3bi**, **3bj**, **3de**, **3di**, and **3dj** (Scheme 5). 4-Hydroxycarbazoles (**1i-j**) and 3-hydorxycarbazole (**1k**) were also found to be appropriate substrates for the hetero-coupling with 2-naphthol



Scheme 4. Substrate Scope of 2-Naphthols **2**.



[a]2.0 equiv of **2l** was used.

Scheme 5. Various Combinations of **1** with **2**

derivative (**2l**), providing C_1-symmetric biaryls **3il**, **3jl**, and **3kl** respectively, with up to 95:5 er. It was noted that considerable chemoselectivity was achieved in the reaction using a 1:1 molar ratio of 2-hydroxycarbazole (**2a**) and 4-hydroxycarbazole (**2i**) to afford the corresponding hydroxycarbazole dimer (**3ia**) in 64% yield with 71:29 er.

Mechanistic studies toward an extension to the other hetero-coupling

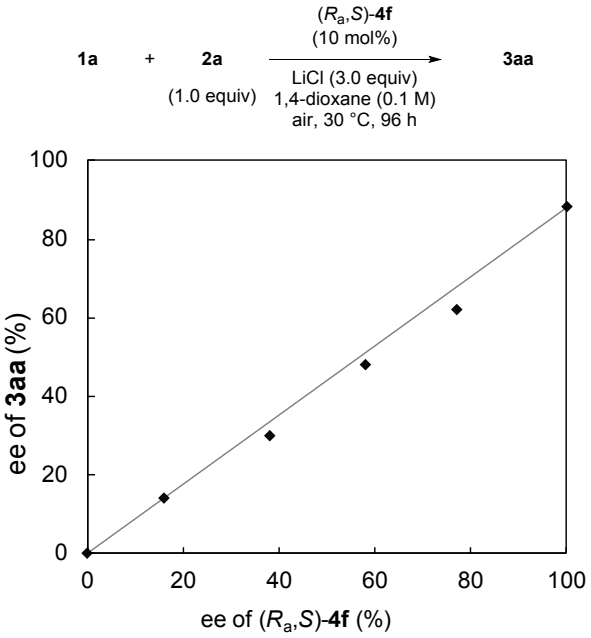
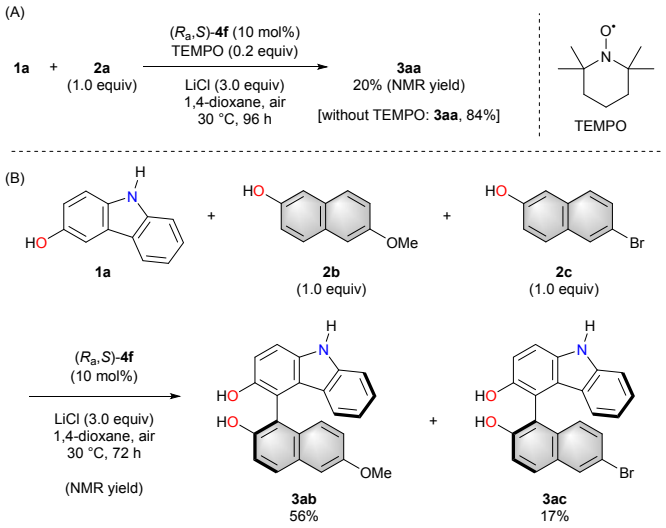


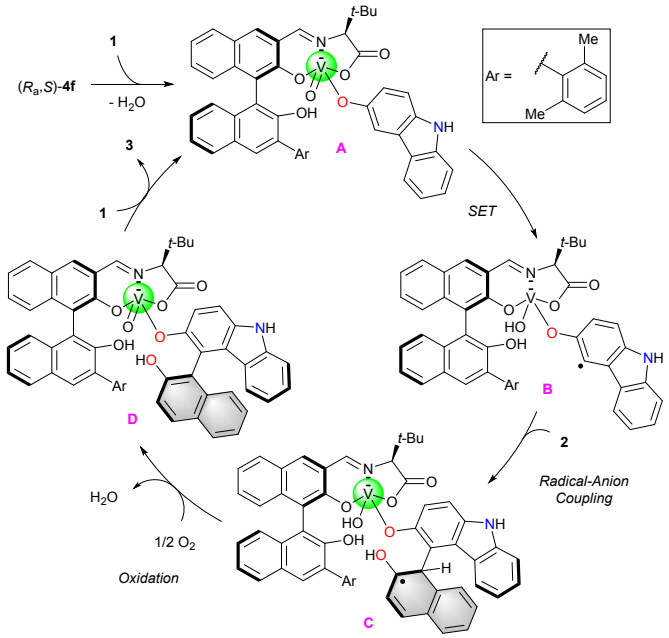
Figure 1. Ee of **3aa** as a Function of Ee of (R_a,*S*)-**4**.

In 2018, Kozlowski and co-workers reported mechanistic studies on vanadium(v)-catalyzed enantioselective oxidative radical-radical coupling of phenol derivatives based on a positive non-linear effect,[24] and proposed the formation of a dimeric cluster that included a vanadium(v) complex in the C–C bond forming step.[18b] In our catalytic system, the nonlinear effect experiment exhibited the linear correlation of the enantiomeric excess (ee) of the catalyst with the ee of the product (Figure 1). Therefore, our hetero-coupling might proceed through a different activation mode compared to Kozlowski's system. The addition of 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) to the present reaction inhibited the formation of **3aa** (20% NMR yield) (Scheme 6A). Additionally, when a competing reaction of **1a** with **2b** having a MeO group and **2c** containing a Br group was examined, **3ab** (56% NMR yield) was preferentially formed rather than **3ac** (17% NMR yield) (Scheme 6B). These outcomes might support the nucleophilic attack of **2** on radical cations arisen form **1** because the more electron-rich nucleophile **2b** showed a higher reaction rate than that of **2c**.[25]



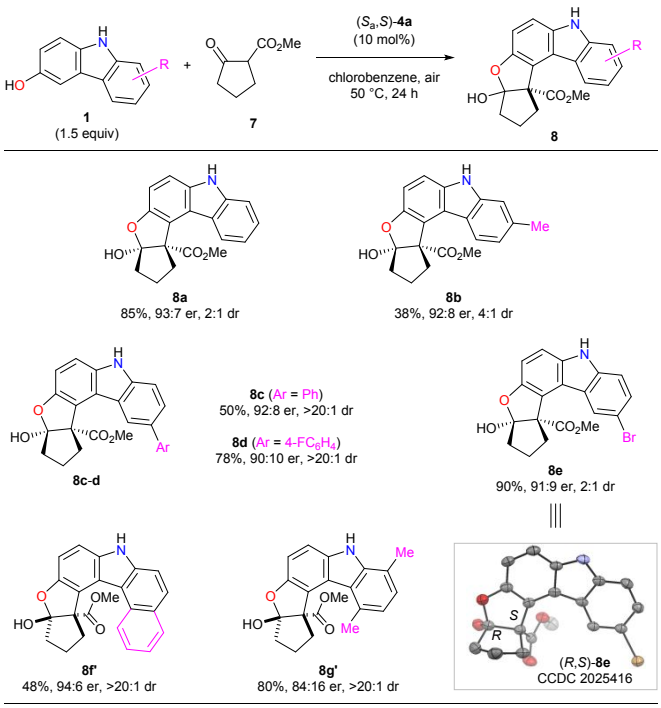
Scheme 6. Control Experiments.

A plausible catalytic cycle for the oxidative hetero-coupling of hydroxycarbazoles **1** with 2-naphthols **2** is illustrated in Scheme 7. The condensation of the mononuclear vanadium(v) complex (R_a,*S*)-**4f** with **1** generates intermediate **A**. Then, intermediate **A** undergoes a single electron transfer (SET) from the carbazole moiety to vanadium(v) to generate conceivable electrophilic radical intermediate **B**, since **1a** is more easily oxidized than **2a**.[26] This is followed by an intermolecular radical-anion coupling to afford intermediate **C** with the formation of a new carbon-carbon bond through the nucleophilic attack of 2-naphthols. Re-oxidation of vanadium(iv) to vanadium(v) proceeds by molecular oxygen in air to give intermediate **D**. After subsequent exchange with **1**, hetero-coupling product **3** is obtained and intermediate **A** is regenerated.



Scheme 7. Plausible Reaction Mechanism for the Oxidative Hetero-coupling of 3-Hydroxycarbazoles **1** with 2-Naphthols **2**.

Encouraged by these obtained results, we further investigated the effects of different nucleophiles[27] on the vanadium(v)-catalyzed oxidative hetero-couplings. In 2017, Pappo and co-workers reported an asymmetric coupling of 2-naphthols and *β*-ketoesters which have a chiral auxiliary catalyzed by iron phosphate complexes *via* a radical-anion coupling mechanism.[27b] Hence, *β*-ketoester **7** was employed as a coupling partner for 3-hydroxycarbazoles **1** with a vanadium(v) catalyst (Scheme 8). Under the slightly modified reaction conditions (see Table S6 in SI), the enantioselective oxidative hetero-coupling of **1a** with **7** using (S_a,*S*)-**4a** in chlorobenzene successfully provided cyclic hemiacetal product *cis*-**8a** having an all-carbon chiral quaternary center[28] in 85% yield with 93:7 er and 2:1 diastereomeric ratio (dr). A series of hydroxycarbazoles were converted into the *cis*-products **8b**-**d**, **8e** in moderate to good yields with up to 92:8 er and >20:1 dr.[29] Hetero-coupling products **8f'** and **8g'** were obtained as *trans*-form (>20:1 dr) due to steric hindrance effect of the substituent at 5-position of **1**. The absolute configuration of **8e** was determined as (*R*,*S*) through X-ray crystallographic analysis.



X-ray structure of (*R*,*S*)-**8f** with ellipsoids at 50% probability (H atoms and ethyl acetate were omitted for clarity).

Scheme 8. Oxidative Hetero-coupling of 3-Hydroxycarbazoles **1** with *β*-Ketoester **7**.

Conclusions

In summary, we have developed a highly enantioselective and catalytic oxidative hetero-coupling of 3-hydroxycarbazoles **1** with 2-naphthols **2** using a newly developed mononuclear vanadium(v) complex (R_a,*S*)-**4f**. With a 1:1 molar ratio of the two starting materials, this catalytic system successfully and efficiently produced hetero-coupling products **3** with up to 98% yield and 95:5 er. 4-, 3-Hydorxycarbazoles **1i-k** and *β*-ketoester **7** were also found to be appropriate substrates for the chiral vanadium(v)-catalyzed oxidative hetero-coupling. Further mechanistic studies and applications of the biarenol products as chiral catalysts or ligands are ongoing in our laboratory.

Author contributions

M. S., S. T. and H. S. designed the study and managed manuscript preparation. M. S., K. H., A. K., G. T. K., Y. H. performed the reactions. D.-Y. Z. and T. S. performed X-ray analysis. M. R., and T. M. investigated the reaction mechanism and assisted with manuscript preparation.

Conflicts of interest

There are no conflicts to declare.

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