Communication

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Efficient Enantioselective Synthesis of Oxahelicenes Using Redox/Acid Cooperative Catalysts

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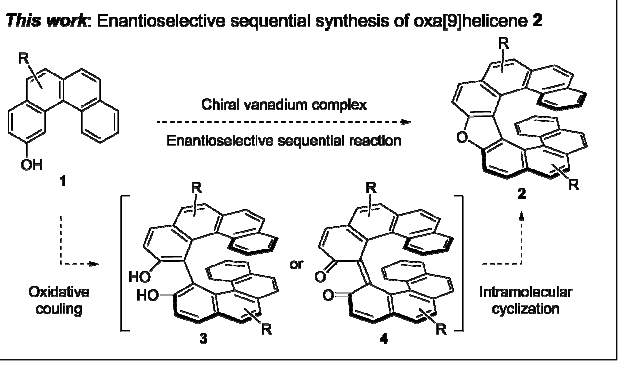
Supporting Information Placeholder

ABSTRACT: An efficient and enantioselective synthesis of oxa[9]helicenes has been established via vanadium(V)-catalyzed oxidative coupling/intramolecular cyclization of polycyclic phenols. A newly developed vanadium complex cooperatively functions as both a redox and Lewis acid catalyst to promote the present sequential reaction and afford oxa[9]helicenes in good yields with up to 94% ee.

Helicenes are polycyclic aromatic compounds with nonplanar screw-shaped skeletons formed from ortho-fused benzene or other aromatic rings. Optically active helicenes and other related helical molecules have received considerable attention as a result of their high potential[1] as chiral ligands,[1a] auxiliaries,[1b] organocatalysts,[1c] liquid crystals,[1d,e] and molecular motors.[1f] Helicene derivatives have classically been synthesized via photocyclization of stilbene units followed by dehydrogenation.[1g,2] This method generally affords *trans*/*cis* isomers and is difficult to apply to the asymmetric synthesis of helicene derivatives. Since Starý and Stará reported a synthesis of helicene-like molecules using the transition metal-catalyzed [2+2+2] cycloadditions of alkynes,[3a] cycloaddition methodologies are principally utilized for the construction of helicene and helicene-like molecules;[3] however, syntheses of heterohelicenes, which have at least one heteroaromatic ring in the helical chain, and oxahelicenes based on furan rings in particular, are still scarce. In 2005, Nozaki reported the preparation of an optically active oxa[7]helicene via the oxidative coupling of phenol derivatives catalyzed by an achiral Cu complex followed by the optical resolution of the coupling product and Pd-catalyzed intramolecular cyclization.[4] Recently, Karikomi[5] and Bedekar[6] independently reported that oxa[9 or 11]helicene derivatives could be synthesized from π-expanded phenol derivatives in a few steps. Although the construction of oxahelicenes *via* oxidative coupling has been achieved, there is no report detailing a catalytic and enantioselective preparation of their derivatives to the best of our knowledge.

Vanadium catalysis is intriguing from an environmental viewpoint because of the abundant natural availability of vanadium as well as the relatively low toxicity of this metal compared with other heavy metals.[7] The redox characteristics of vanadium complexes have been utilized for asymmetric reactions[8] including, for example, epoxidation,[8f] sulfoxidation,[8g] the oxidative coupling of 2-naphthols,[8h-i] and the oxidation of α-hydroxy carbonyl compounds.[8j] In addition, the Lewis acidity of vanadium complexes[9] can be used to promote Diels–Alder reactions,[9a] cyanations,[9b] the ring-opening of *meso*-epoxides,[9c] and Friedel–Crafts-type reactions.[9d] However, there are few reports describing the cooperative effect of these two properties in vanadium-catalyzed sequential reactions.[10] The enantioselective sequential reaction using a chiral vanadium complex with *tert*-butylhydroperoxide as the primary oxidant was first reported by Toste[10a] in 2006 with further contributions by Liu[10b] and You.[10b,c] These groups succeeded in the development of both epoxidation reactions and ring-opening cascades. As part of our effort to explore chiral vanadium catalysis,[9d,11] we were interested in designing novel vanadium-mediated sequential reactions to access important structural motifs. We assumed that if the chiral vanadium complex functioned as both a redox and Lewis acid catalyst for the coupling of 2-hydroxybenzo[*c*]phenanthrenes (**1**), oxa[9]helicenes (**2**) would be obtained in a single operation *via* aerobic oxidative coupling and subsequent Lewis acid-mediated intramolecular cyclization (Scheme 1).

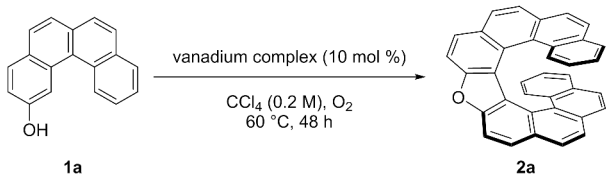
Scheme 1. Synthesis of oxahelicenes



We initially tested the reaction of **1a** (R = H)[12] with the chiral dinuclear vanadium complex (*R*a,*S*,*S*)-**5**, which efficiently catalyzes the enantioselective oxidative coupling reaction of 2-naphthols.[11b] Among the reaction conditions screened (solvent, temperature, and co-oxidant; see Table S1, ESI), we found that the desired oxa[9]helicene **2a** was formed in 81% yield with 58% ee at 60 °C in CCl_4 under a molecular oxygen atmosphere (Table

1, entry 1). Some starting material **1a** remained after the reaction period but no diol **3a** and/or quinone **4a** was detected. During further investigation of suitable vanadium complexes, we found that the mononuclear vanadium complex (*S*)-**6** also promoted this sequential process. The reaction employing catalyst (*S*)-**6**, which possesses a naphthyl skeleton, yielded **2a** in 61% yield with 19% ee (entry 2); catalysts (R_a,*S*)-**7** and (R_a,*S*)-**8**, which both bear a binaphthyl unit, resulted in an improved yield and ee of helicene **2a** (entries 3 and 4). Catalyst (R_a,*S*)-**9**, which has a free hydroxy group on the binaphthyl unit, increased the chemical yield of **2a** without a decrease in the ee (87% yield, 58% ee, entry 5). The phenolic hydroxy group in the catalyst could cooperatively activate of **1a** with the vanadium metal to accelerate the present sequential reaction.[13] The diastereomeric complex (S_a,*S*)-**9** was found to be a mismatched catalyst, affording **2a** with lower enantioselectivity (entry 6). Catalyst (R_a,*S*)-**10**, having a benzyl group instead of a *tert*-butyl group on the amino acid unit, did not show any improvement (entry 7). Among the catalysts that were screened, the presence of a substituent at the 3' position of the binaphthyl unit proved effective for the improvement of enantioselectivity. The phenyl-substituted catalyst (R_a,*S*)-**11** afforded **2a** in 86% yield with 66% ee (entry 8). This result prompted us to examine the effect of substituents at the 3' position of the binaphthyl moiety. The 3,5-dimethylphenyl-substituted catalyst (R_a,*S*)-**12** increased the chemical yield and ee to 95% and 75%, respectively, (entry 9), while the 9-anthryl-substituted catalyst (R_a,*S*)-**13** resulted in a decreased yield and ee, probably as the result of steric hindrance between the substituents (entry 10). When the 3,5-diphenylphenyl-substituted catalyst (R_a,*S*)-**14** was employed, **2a** was obtained in quantitative yield with 75% ee (entry 11). Finally, **2a** was obtained in 95% yield with 78% ee in the reaction that employed 10 mol% of catalyst (R_a,*S*)-**14** at 50 °C (entry 12). Furthermore, optically pure **2a** was readily accessible by single recrystallization of the enantioenriched product from CH_2Cl_2 and hexane. The optical rotation value of optically pure **2a** showed a characteristic value, $[\alpha]_D^{19} = -2647$ (*c* 0.32, $CHCl_3$). X-ray crystallographic analysis of **2a** unambiguously demonstrated its helical structure, and the absolute configuration of **2a** was definitely determined to be *M* based on the Flack parameter (Figure 1).

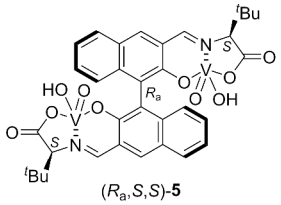
Table 1. Screening of chiral vanadium complexes[a]

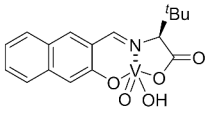


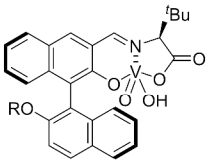
1a **2a**

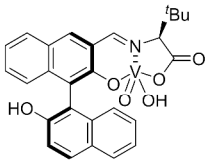
entry	Catalyst	yield (%)[b]	ee (%)[c]
1[d]	(R_a,*S*,*S*)-**5**	81	58
2	(*S*)-**6**	61	19
3	(R_a,*S*)-**7**	71	60
4	(R_a,*S*)-**8**	72	58
5	(R_a,*S*)-**9**	87	58
6	(S_a,*S*)-**9**	91	41
7	(R_a,*S*)-**10**	90	41
8	(R_a,*S*)-**11**	86	66
9	(R_a,*S*)-**12**	95	75
10	(R_a,*S*)-**13**	52	42
11	(R_a,*S*)-**14**	99	75
12[e]	(R_a,*S*)-**14**	95	78 (99)[f]

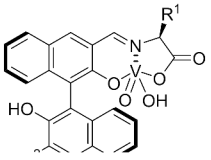
[a]The reaction of **1a** (0.04 mmol) with 10 mol% of vanadium complex (0.004 mmol) was carried out in CCl_4 (0.2 mL) at 60 °C under O_2 (1 atm). [b]Yields were determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. [c]ees were determined using HPLC (DAICEL CHIRALPAK AD-H). [d]5 mol% of (R_a,*S*,*S*)-**5** (0.002 mmol) for 72 h. [e]At 50 °C. [f]After a single recrystallization.


(R_a,*S*,*S*)-**5**


(*S*)-**6**


(R_a,*S*)-**7** (R = Me)
(R_a,*S*)-**8** (R = ^{i}Pr)
(R_a,*S*)-**9** (R = OH)


(S_a,*S*)-**9**


(R_a,*S*)-**10** (R^1 = Bn, R^2 = H)
(R_a,*S*)-**11** (R^1 = ^{t}Bu, R^2 = Ph)
(R_a,*S*)-**12** (R^1 = ^{t}Bu, R^2 = 3,5-$Me_2C_6H_3$)
(R_a,*S*)-**13** (R^1 = ^{t}Bu, R^2 = 9-anthryl)
(R_a,*S*)-**14** (R^1 = ^{t}Bu, R^2 = 3,5-$Ph_2C_6H_3$)

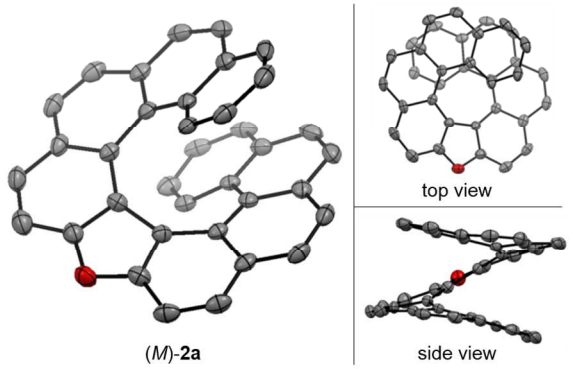
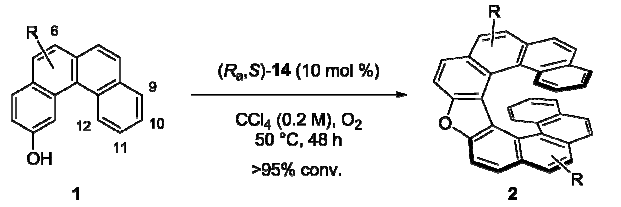
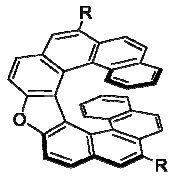


Figure 1. X-ray structure of (*M*)-oxa[9]helicene (**2a**) with thermal ellipsoids at the 50% probability level. Hydrogen atoms are omitted for clarity. Only one of the two independent molecules present in the unit cell is shown.

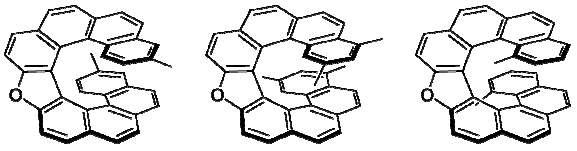
Table 2. Substrate scope and limitations[a]



2	R	yield, ee[b]
2a	H	86%, 78% ee
2b	Ph	72%, 45% ee
2c	*p*-tolyl	61%, 44% ee
2d	*p*-FC_6H_4	68%, 50% ee[c]
2e	Me	70%, 88% ee[d]
2f	hexyl	72%, 76% ee
2g	Br	56%, 94% ee[e,f]



2a-g

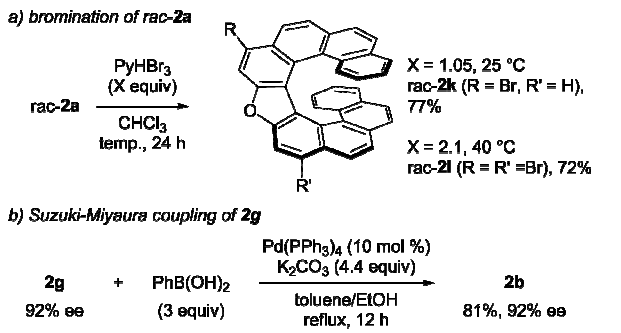


2h 68%, 80% ee | 2i 84%, 60% ee[g] | 2j trace[g]

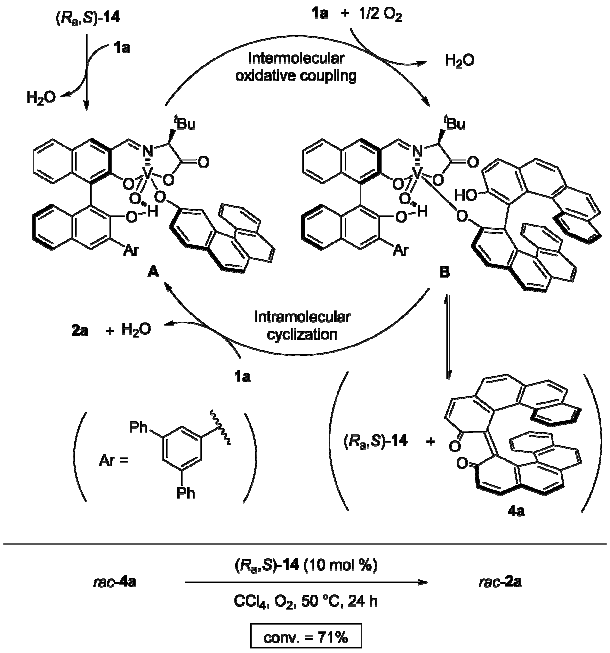
[a]The reaction of **1** (0.04 mmol) with 10 mol% of catalyst (R_a,*S*)-**14** (0.004 mmol) was carried out in CCl_4 (0.2 mL) at 50 °C under O_2 (1 atm) for 48 h. [b]Yield of isolated product. ees were determined by HPLC (DAICEL CHIRALPAK AD-H). [c]For 72 h. [d]94% NMR yield. [e]At 60 °C for 72 h. [f]61% NMR yield. [g]At 60 °C with 10 mol% of TMSCl.

With the optimal conditions in hand, the substrate scope and limitations of the reaction were investigated using analogs of **1** containing various substituents (Table 2). Phenyl-, *p*-tolyl-, and *p*-fluorophenyl-substituted substrates (**1b**, **1c**, and **1d**, respectively) were converted to the corresponding products **2b**, **2c**, and **2d** in good yields with ca. 50% ee. Alkyl-substituted substrates, such as those with methyl or hexyl groups at the 6 position, afforded coupling products **2e** and **2f** in moderate yields with 88% and 76% ee, respectively. In the coupling reaction of the bromo-substituted substrate **1g** at 60 °C for 72 h, the desired dibrominated helicene **2g** was obtained in 56% yield with 94% ee. We next examined the effect of a substitution at the 9 to 12 positions on the terminal aromatic ring. The reaction of **1h** smoothly proceeded to provide **2h** in 68% yield with 80% ee. In contrast, substrate **1i** showed low reactivity, affording **2i** in only 32% yield with 30% ee. When 10 mol % of TMSCl[8i] was added to the reaction of **1i** at 60 °C, an improvement in both the yield and ee of **2i** was observed (84% yield, 60% ee). The reaction of **1j**, with a methyl group at the 12 position, did not form the desired product probably as a result of steric hindrance during the coupling.

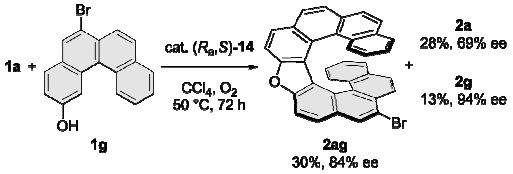
Scheme 2. Synthetic transformations



Scheme 3. Plausible catalytic cycle



Scheme 4. Oxidative hetero-coupling of **1a** with **1g**[a]



[a]The reaction of **1a** (0.02 mmol) and **1g** (0.02 mmol) with catalyst (R_a,*S*)-**14** (0.004 mmol) was carried out in CCl_4 (0.2 mL) at 50 °C under O_2 (1 atm) for 72 h.

To further demonstrate the introduction of substituents on oxa[9]helicenes **2**, several transformations were carried out (Scheme 2). Oxa[9]helicene (**2a**) could be further modified by regioselective bromination; bromination was conducted using 1.05 or 2.1 equivalents of pyridinium tribromide ($PyHBr_3$) to yield mono- and dibrominated oxa[9]helicene **2k** and **2l**, respectively, in good yields (Scheme 2a). Pd-catalyzed Suzuki-Miyaura coupling of dibrominated oxa[9]helicene **2g** with phenylboronic acid ($PhB(OH)_2$) smoothly proceeded to give **2b** in 81% yield with a retention of the enantiomeric excess (Scheme 2b).

To gain an insight into the reaction mechanism, the reaction order with respect to the vanadium catalyst was investigated by calculating the initial rate of the reaction using 5, 10, or 15 mol% catalyst loading; the reaction was found to be that of the first order in catalyst (R_a,*S*)-**14** (see ESI). This result rules out a dual activation mechanism involving radical–radical coupling mediated by two molecules of the vanadium complex.[11,14] The present oxidative coupling likely occurred through a radical–anion coupling with one molecule of the vanadium complex.[15] A plausible catalytic cycle for the sequential synthesis of oxa[9]helicenes is shown in Scheme 3. The reaction of the mononuclear vanadium(V) complex (R_a,*S*)-**14** with substrate **1a** generates an intermediate **A**. **A** then undergoes an intermolecular coupling with another molecule of **1a** after a single electron

transfer to a vanadium(V) species. This is followed by oxidation of vanadium(IV) by O_2 to form an intermediate **B**. Finally, intramolecular cyclization assisted by the Lewis acidity of vanadium(V) affords the desired product **2a** and the intermediate **A** is regenerated. It is likely that the hydroxy group on the binaphthyl ligand in the vanadium complex increased the Lewis acidity of vanadium metal through an intramolecular hydrogen bond in intermediates **A** and **B**. When a racemic quinone derivative **4a**[5a] was treated with 10 mol% of catalyst (R_a,*S*)-**14**, **2a** was produced in racemic form with 71% conversion; the remaining **4a** was also racemic (Scheme 3). Kinetic resolution was not observed in the reaction of **4a** to yield **2a**, which implies that the enantio-determining step is the oxidative coupling step of intermediate **A** to intermediate **B**. The quinone **4a** might be outside of the catalytic cycle and in an equilibrium with the intermediate **B**. The radical-anion coupling mechanism is also supported by the fact that the treatment of both of electron-rich **1a** (0.02 mmol) and -poor **1g** (0.02 mmol) by (R_a,*S*)-**14** (0.004 mmol) afforded a mixture of the oxa[9]helicenes (Scheme 4); hetero-coupling product **2ag** (30% yield, 84% ee) and the homo-coupling products **2a** (28% yield, 69% ee) and **2g** (13% yield, 94% ee) (Scheme 4) though the radical–radical coupling would preferentially form homo-coupling product **2a**.[14-16]

In conclusion, we have developed an efficient and enantioselective sequential synthesis of oxa[9]helicenes catalyzed by a newly developed chiral vanadium complex. In this process, the vanadium complex works as both a redox and a Lewis acid catalyst, allowing the sequential reaction *via* an oxidative coupling/intramolecular cyclization sequence. Additional investigations into the reaction mechanism and the substrate generality in other hetero-couplings are now in progress. Furthermore, synthetic studies on other heterohelicenes containing nitrogen, silicon, and/or sulfur are in process in our laboratory.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

Experimental procedures, spectroscopic data

X-ray crystallographic data for (*M*)-**2a** (CCDC 1493624)

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Notes

The authors declare no competing financial interests.

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