Article

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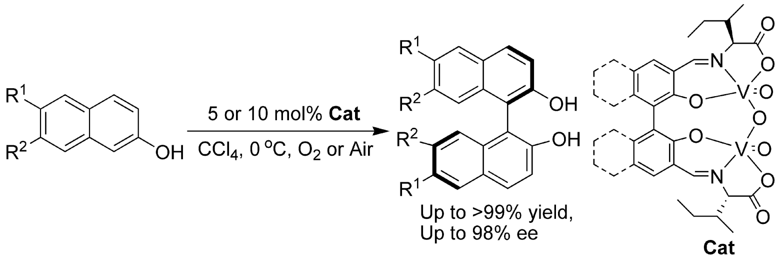

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Highly Enantioselective Oxidative Couplings of 2-Naphthols Catalyzed by Chiral Bimetallic Oxovanadium Complexes with Either Oxygen or Air as Oxidant

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Abstract: The chiral bimetallic oxovanadium complexes have been designed for the enantioselective oxidative coupling of 2-naphthols bearing various substituents at C6 and/or C7. The chirality transferring from the amino acid to the axis of the biphenyl in oxovanadium complexes **2** was found to occur with the use of UV and CD spectra and DFT calculation. The homo-coupling reaction with oxygen as the oxidant was promoted by 5 mol % of an oxovanadium complex derived from L-isoleucine and achiral biphenol to afford binaphthols in nearly quantitative yields with high enantioselectivities of up to 98% ee. An oxovanadium complex derived from L-isoleucine and H_8-binaphthol is highly efficient at catalyzing the air-oxidized coupling of 2-naphthols with excellent enantioselectivities of up to 97% ee. ^{51}V NMR study shows that the oxovanadium complexes have two vanadium(V) species. Kinetic studies, the cross-coupling reaction, and HRMS spectral studies on the reaction have been carried out and illustrate that two vanadium(V) species are both involved in catalysis and that the coupling reaction undergoes a radical−radical mechanism in an intramolecular manner. Quantum mechanical calculations rationalize the importance of the cooperative effects of the axial chirality matching *S*-amino acids on the stereocontrol of the oxidative coupling reaction. The application of the transformation in the preparation of chiral ligands and conjugated polymers confirms the importance of the current process in organic synthesis.

Introduction

Axially chiral compounds play very important roles in the history of asymmetric synthesis, in particular, asymmetric catalysis.[1] Optically pure 1,1′-binaphthol and its derivatives have been evaluated as versatile chiral auxiliaries and ligands in asymmetric transformations.[2] Many biologically active natural products, for example, bioxanthracene (−)-ES-242-4, cercosporin and calphostins A−D contain the binaphthol backbone.[3] More importantly, optically pure binaphthyl-based small molecules and polymers have also been extensively applied to the preparation of organic materials such as second nonlinear optics, organic light-emitting devices (OLED), and chiral sensers.[4] The wide scope of applications of such compounds in organic synthesis request efficient methods for their preparation. The oxidative coupling of 2-naphthols is a straightforward pathway to approach the binaphthols. Consequently, a large number of transition metal-based homogeneous[5] and heterogeneous[6] catalysts have been discovered for the oxidative coupling reactions to access racemic BINOL derivatives. As for the synthesis of optically active binaphthols, optical resolution of

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racemic binaphthols is a conventional method and has been used for the scalemic preparation of optically pure BINOL.[7] Kinetic resolution of BINOL derivatives by palladium-catalyzed alcoholysis has very recently been developed as an alternative method to approach optically active binaphthols and biphenols.[8] The use of a chiral pool method to prepare optically active BINOLs has also been investigated; however, it suffers from the stoichiometric amounts of chiral sources as chiral resolution does.[9] In sharp contrast to well-developed catalytic synthesis of racemic BINOLs, the asymmetric catalytic preparation of chiral binaphthols develops much more slowly. The oxidative couplings of 2-naphthols in the presence of catalytic amounts of copper complexes of chiral amines have provided several promising results,[10] and their applications to the synthesis of various poly(2,3-dihydroxy-1,4-naphthylene) derivatives with main-chain chirality have been attempted.[11] Very recently, Kozlowski and co-workers disclosed a general approach to optically active perylenequinones via an enantioselective oxidative coupling reaction catalyzed by the complex of CuI and (*S*,*S*)-1,5-diaza-cis-decalin.[12] However, the copper-catalyzed asymmetric oxidative biaryl coupling reaction cannot provide the high enantioselectivity for 2-naphthols without a coordinating functional group to copper. A photoactivated chiral (NO)-Ru^{II}−salen complex catalyzes the aerobic oxidative coupling of 2-naphthols with 33−71% ee.[13] Chiral vanadyl complexes are another class of promising catalysts for the oxidative coupling of 2-naphthols. The studies in this area started with similar works from Chen[14] and Uang[15] whose groups independently designed similar oxovanadium complexes of chiral Schiff bases for the asymmetric oxidative coupling of 2-naphthols with moderate enantioselectivities. Subsequently, oxovanadium complexes prepared from chiral Schiff bases with an additional stereogenic center close to the reactive site were discovered with an improved enantioselectivity over that observed with the catalyst containing a single stereogenic center.[16] Very recently, chiral self-dimerized vanadium complexes on SiO_2 were developed for the oxidative coupling of 2-naphthols with a maximum enantioselectivity of 90% ee.[17]

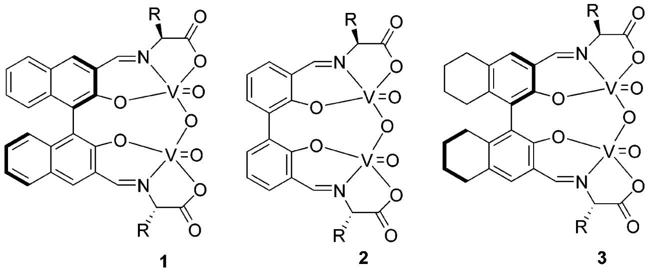

Figure 1. The oxovanadium complexes evaluated in this study.

The known monometallic chiral vanadyl complexes always provided moderate enantioselectivity for the oxidative coupling of most 2-naphthols. To overcome the low stereocontrol inherent in these monovanadyl complexes, we have designed bimetallic oxovanadium complexes **1** with multiple stereogenic centers, which catalyzed the oxidative coupling of 2-naphthols and derivatives with excellent enantioselectivity (up to 98% ee).[18] In our further development, achiral biphenol-derived diastereomeric oxovanadium complexes **2** with an induced axial chirality have been disclosed for the reaction also with excellent enantioselectivity.[19] In this contribution, we report the full results of these studies, together with the discovery of new chiral catalysts **3** with improved catalytic performance and their applications in an efficient air-oxidized coupling of 2-naphthols (Figure 1).

Results and Discussion

Binaphthol-Based Bimetallic Chiral Oxovanadium Complexes. In the catalyst system based on monometallic oxovanadium complexes of chiral Schiff bases, the stereochemical discrimination just depended on the chirality in the amino acid. We initially reasoned that the stereocontrol would be improved by introducing another suitable chiral center close to the naphthoxy or phenoxy in the complex **4**.[14,15] On the basis of this idea, we have designed novel oxovandium complexes **1** and **5**, which contain two chiral centers in amino acids and an axial chirality in the binaphthyl unit (Figure 2). The complexes **1** and **5** differ in the absolute configuration of the axial chirality of the binaphthyl moiety. In principle, the catalysts with matched chirality show better catalytic performance than those with

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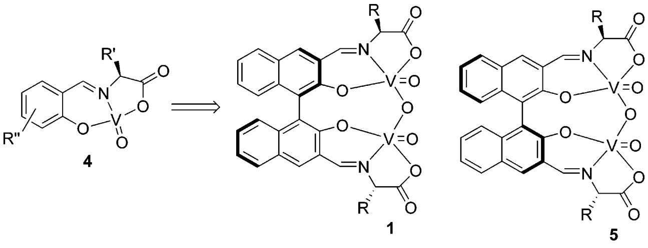
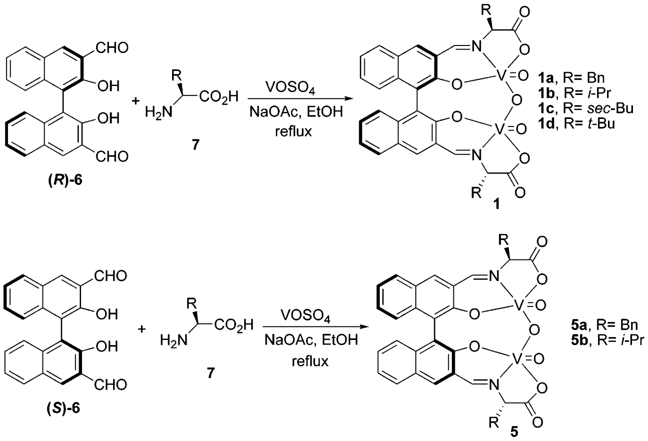


Figure 2. General strategy for the design of bimetallic oxovanadium complexes with multiple stable stereogenic centers.

Scheme 1. Preparation of Bimetallic Oxovanadium Complexes



mismatched chirality. Thus, complexes **1** and **5** must exhibit different abilities at catalyzing the oxidative coupling of 2-naphthols.

Oxovanadium complexes **1** are prepared by condensations of (*R*)-3,3′-diformyl-2,2′-dihydroxy-1,1-binaphthol[20] with (*S*)-amino acids (**7**) and vanadyl sulfate according to the previous procedure[21] (Scheme 1). The condensations proceeded smoothly to provide crude complexes **1** as a dark-green solid. Oxovanadium complexes **5** were prepared from (*S*)-3,3′-diformyl-2,2′-dihydroxy-1,1-binaphthol through the same procedure as that for the preparation of **1**. However, the reaction took a prolonged time and gave the target complexes in comparably low yields. Oxovandium complexes **1** and **5** were identified by high-resolution mass spectra (HRMS) and FT-IR. In HRMS spectra, the observed exact molecular weight of either of **1a**−**d** or **5a,b** is consistent with the calculated one and thus suggests that the structures shown in **1** and **5a,b** are most likely correct.

^{51}V NMR spectroscopy has been a powerful probe for studies of complexes in solution, and the vanadium nucleus is particularly suitable for studies of vanadium (V) complexes.[22] The ^{51}V NMR spectrum of oxovanadium complex **1c** was measured with $VOCl_3$ as a standard in DMSO. A strong signal at −584 ppm was observed (Figure 3), indicating that the vanadium is vanadium (V) and the structures shown in the oxovanadium complexes **1** are most reasonable.

In our preliminary studies, we have observed a remarkable dependence of the enantioselectivity on the reaction temperature and found that 0 °C is an optimal reaction temperature in terms of reactivity and enantioselectivity.[18] Therefore, the oxidative coupling reaction of 2-naphthol was conducted with 10 mol % of either oxovanadium complexes **1** or **5** at 0 °C using carbon tetrachloride as a solvent with an intension to clarify the effect of the substituent of the vanadyl catalyst on enantioselectivity and the contribution of the axial chirality to stereoselection (Table 1). Catalysts bearing aliphatic substituents such as **1b**−**d** exhibit higher catalytic activity and enantioselectivity than their benzyl-substituted counterpart **1a**. Catalyst **1c** with a *sec*-butyl substituent provided the best result.

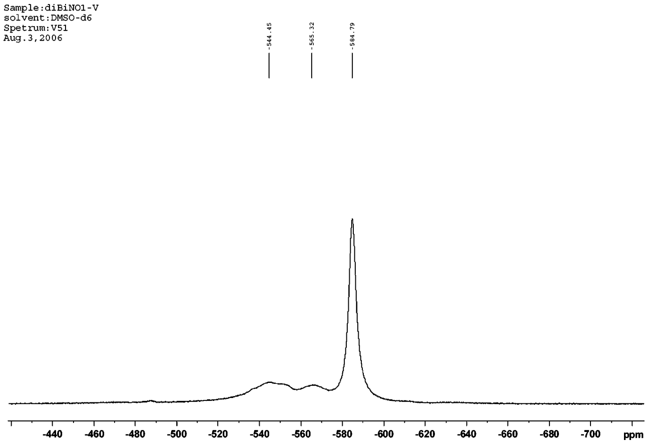
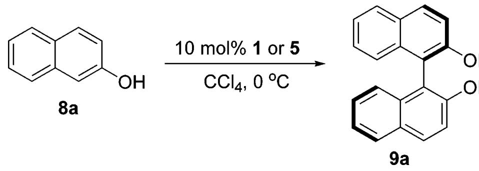


Figure 3. ^{51}V NMR spectrum of **1c**.

Table 1. Oxidative Coupling of 2-Naphthol with Bimetallic Oxovanadium Complexes **1a**−**d** and **5a,b**



entry	catalyst	time (days)	yield (%)[b]	ee (%)[c]
1	**1a**	5	<20	50
2	**1b**	8	70	81
3	**1c**	6	93	83
4	**1d**	8	63	71
5	**5a**	5	70	6[d]
6	**5b**	5	75	10[d]

[a] The reaction was carried out in CCl_4. [b] Isolated yield. [c] The ee values were determined by HPLC on a Kromasil CHI-TBB column, and the absolute configuration is *R*. [d] Reactions were conducted at RT.

A significant decrease in the enantioselectivity was observed in the reaction catalyzed by complexes **5a,b** in comparison with the reaction catalyzed by their related diastereomers **1a,b** (entries 1−2 and 5−6), demonstrating that the (*R*)-configuration of the axial chirality matches (*S*)-amino acids to favor the stereocontrol of the oxovanadium complex.

The use of **1c** to catalyze the oxidative coupling of 7-substituted-2-naphthol derivatives was investigated. The reaction was performed under 1 atm oxygen with 10 mol % of the oxovanadium complex **1c**, and proceeded after 7 days to give the homo-coupling product in high yields. Excellent enantioselectivities ranging from 92% to 98% ee were observed for all of the 7-substituted-2-naphthols tested (Table 2). In general, the stereochemical outcome does not rely on the size of the substituents. Variation of the substituent at C7 from methoxy

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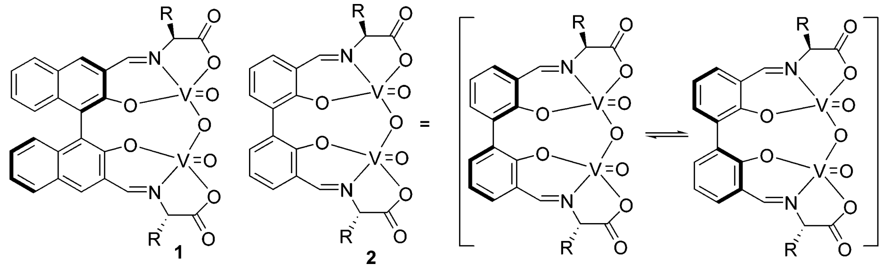
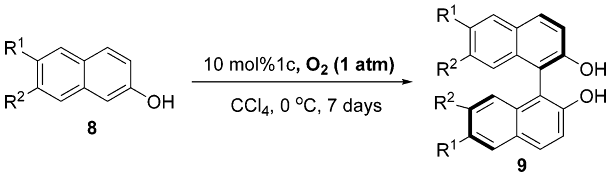


Figure 4. General strategy for the design of bimetallic chiral oxovanadium complexes with flexible axial chirality.

Table 2. Oxidative Coupling of 2-Naphthols Catalyzed by Oxovanadium Complex **1c**[a]



entry	products	R_1	R_2	yield (%)[b]	ee (%)[c]
1	**9b**	H	$OCH_2CH{=}CH_2$	98	95
2	**9c**	H	OMe	88	98
3	**9d**	H	OEt	99	93
4	**9e**	H	O^nBu	95	96
5	**9f**	H	$O^nC_8H_{17}$	93	94
6	**9g**	H	$O^nC_{12}H_{25}$	91	92
7	**9h**	H	OBn	96	96

[a] The reactions are carried out at 0 °C in the presence of 10 mol % of catalyst **1c** using CCl_4 as solvent. [b] Isolated yields. [c] The ee values are determined by HPLC on a Kromasil CHI-TBB or Chiralpak AD column.

to other alkoxy's does not lead to much change in the enantioselectivity.

Achiral Biphenol-Based Bimetallic Chiral Oxovanadium Complexes. An achiral ligand with a biphenyl backbone, once coordinated to a chiral transition-metal complex, will become axially chiral and thus lead to the formation of a chiral catalyst with the amplified chiral environment. Such a strategy is called "asymmetric activation" and becomes a powerful platform for discovering new and efficient chiral catalysts.[23] The utility of this method to evaluate an efficient chiral catalyst with a conformationally flexible biphenyl moiety has been demonstrated by a large number of successful examples.[24]

Oxovanadium complexes **2** are structurally similar to **1** except that the binaphthyl unit of **1** is replaced with a conformationally flexible biphenyl unit (Figure 4). In principle, diastereomeric complexes will be generated when 3,3′-diformyl-2,2′-dihydroxy-1,1′-phenol (**10**) is condensed with (*S*)-amino acids (**7**) and vanadyl sulfate because of the increased rotation barrier in **2** (Figure 4). The diastereomers with matching chirality between the chiral centers of the amino acid units and the induced axially chiral biphenyl unit should provide high enantioselectivity for the oxidative coupling; otherwise low enantioselectivity will result.

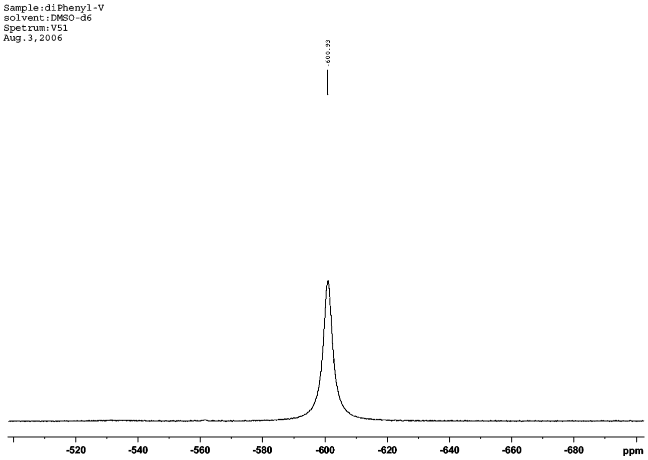
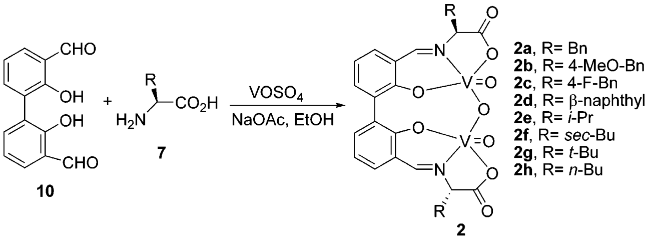


Figure 5. ^{51}V NMR spectrum of oxovanadium complex **2f**.

Scheme 2. Preparation of Oxovanadium Complexes 2



Oxovanadium complexes **2** were prepared by condensations of 3,3′-diformyl-2,2′-dihydroxy-2-phenol (**10**)[20b] with (*S*)-amino acids (**7**) and vanadyl sulfate following a similar procedure for the preparation of **1** (Scheme 2). All the complexes **2** obtained are dark-green. As with the vanadium complexes **1**, it is difficult to obtain pure samples for most of complexes **2** for the NMR measurement; thus, these were preliminarily characterized by HRMS and IR. Fortunately, the complex **2f** was obtained in an analytically pure form. The ^1H NMR and ^{13}C NMR spectra of **2f** are in agreement with those of the structure of **2f** (See Supporting Information). The ^{51}V NMR spectrum of **2f** was also measured with $VOCl_3$ as a standard (Figure 5). A signal at −600 ppm is assigned to vanadium(V).

The use of circular dichroism (CD) to investigate the axial chirality of the biaryl compounds has been extensively studied.[25] To estimate the flexible propagated chirality that exists in vanadium complexes **2**, optical spectroscopy studies on **2f** and their analogues **1c**, **2f′**, **3**, and **11** were carried out. Vanadium complexes **2f′**, **3**, and **11** were synthesized in a manner similar to that for the synthesis of **1a**−**d** and **2a**−**h**. The UV−vis

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(23) (a) Mikami, K.; Terada, M.; Korenaga, T.; Matsumoto, Y.; Ueki, M.; Angelaud, R. *Angew. Chem., Int. Ed.* **2000**, *39*, 3532. (b) Mikami, K.; Terada, M.; Korenaga, T.; Matsumoto, Y.; Matsukawa, S. *Acc. Chem. Res.* **2000**, *33*, 391. (c) Mikami, K.; Yamanaka, M. *Chem. Rev.* **2003**, *103*, 3369. (d) Faller, J. W.; Lavoie, A. R.; Parr, J. *Chem. Rev.* **2003**, *103*, 3345. (e) Ding, K.; Du, H.; Yuan, Y.; Long, J. *Chem. Eur. J.* **2004**, *10*, 2872.

(24) Walsh, P. J.; Lurain, A. E.; Balsells, J. *Chem. Rev.* **2003**, *103*, 3297.

(25) Berova, N., Nakanishi, K., Woody, R. W., Eds. *Circular Dichroism: Principles and Applications*; Wiley-VCH: New York, 2000.

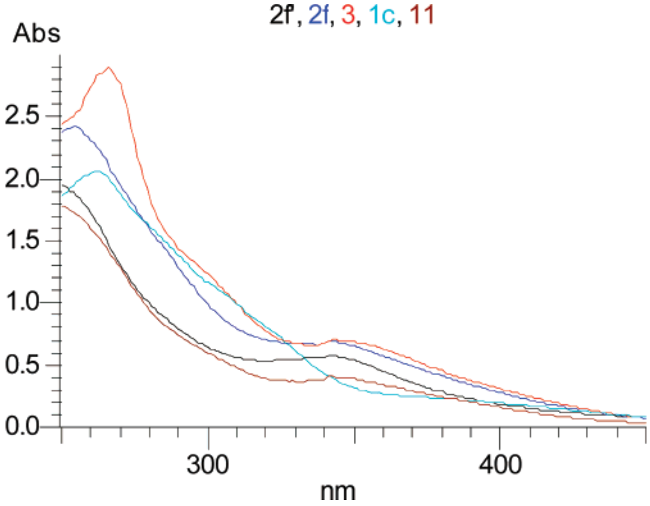


Figure 6. UV−vis spectra of vanadium complexes; (blue line) with **1c**; (black line) with **2f′**; (red line) with **3**; (red/yellow double line) with **11**; (dark blue line) with **2f**.

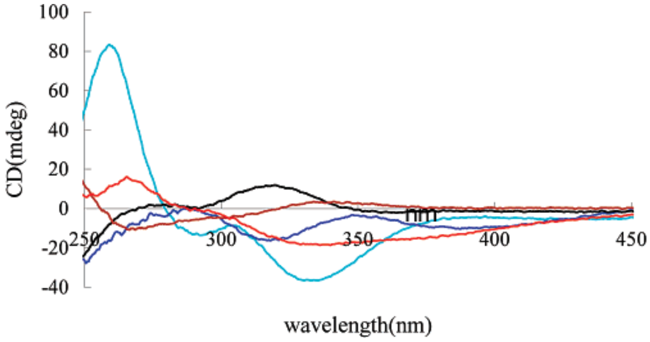
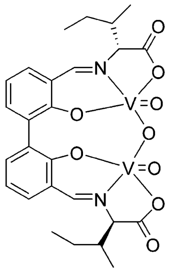
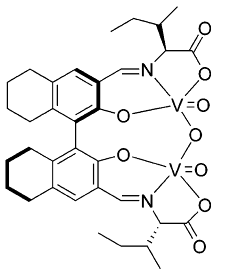


Figure 7. CD spectra of vanadium complexes; (blue line) with **1c**; (black line) with **2f′**; (red line) with **3**; (red/yellow double line) with **11**; (dark blue line) with **2f**.

absorption spectra of **1c**, **2f, 2f′**, **3**, and **11** were obtained with a concentration of the complexes at 1.0 × 10^{-5} M in CH_2Cl_2, which are shown in Figure 6. Two absorption bands were observed in spectra of the complexes. One strong band is around 250−320 nm, which arises from the phenylene. The other one is around 320−420 nm, which stems from the conjugated double bonds in the azomethyne and phenylene in the complexes.[26]



2f′



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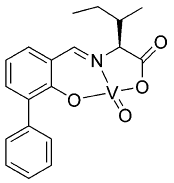

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Figure 7 shows the circular dichroism (CD) of the vanadium complexes. The CD maxima at 320−340 nm, which are correlated with the absorptions of the conjugated double bonds in the azomethyne of the vanadium complexes and thus reflect the absolute configuration of the axis bond, were observed. The complexes **2f** and **2f′** were prepared from L- and D-isoleucines, respectively. A clearly negative Cotton effect was seen at 320 nm in the spectrum of **2f**. In contrast to this, a positive Cotton effect was observed at 320 nm in the spectrum of **2f′**. These CD spectra indicate that complexes **2f** and **2f′** are mirror images and the chirality does transfer from D- or L-isoleucines to axis of the biphenyl moiety. No Cotton effect was found at the similar absorption area in the CD spectrum of **11**, indicating no or very little occurrence of the chirality transfer from L-isoleucine due to the free rotation of the axis bond. A negative Cotton effect was also seen at 340 nm, tailed toward 450 nm in the CD spectrum of **3**. Comparison of the CD spectra of **3** and **2f** implies that the absolute configuration of the axis bond in **3** seems the same as that arising from the chirality transfer from L-isoleucine in **2f**.

The complexes **2a−h** possibly exist as diastereomeric mixtures in solution, of which, as indicated by the CD study, (*S*,*R*)-diastereomers might be predominant. Although it is difficult to separate these diastereomers, these diastereomeric mixtures are found to be efficient for the asymmetric oxidative coupling of 2-naphthols. The oxidative coupling of 2-naphthol is employed as a model reaction to investigate the effects of the substituents of amino acids and the catalyst loading on the reactivity and enantioselectivity (Table 3). It is found that both the reactivity and enantioselectivity are dependent on the substituent R of the amino acids. Complex **2a**, derived from (*S*)-phenylalanine gives a high yield of 77% and a fairly good enantioselectivity of 80% ee (entry 1). However, catalysts **2b** and **2c** that were prepared from 4-methoxyphenylalanine and 4-fluorophenylalanine, respectively, exhibit much lower enantioselectivities (entries 2 and 3) compared to that of their structural analogue **2a** (entry 1). The complex **2d** with a *β*-naphthyl group shows the lowest enantioselectivity (entry 4). The highest yield of 89% and enantioselectivity of 89% ee are observed with catalyst **2f** that contains two *sec*-butyl substituents (entry 6). A decrease in enantioselectivity was found upon replacement of the *sec*-butyl group with other alkyl substituents (entries 5, 7, and 8).

Even though employed as diastereomeric mixtures, **2e−g** still give higher or comparable enantioselectivities in comparison with their 1,1′-binaphthyl analogues **1b−d**. These results, together with the CD study, indicate that the major diastereomers in **2** might have an axial chirality similar to that of the 1,1′-binaphthyl unit of (*R*,*S*)-**1**, which matches the chirality of the (*S*)-amino acid unit to be responsible for the high enantioselectivity.

The generality of the process catalyzed by **2f** was then examined. A wide range of 2-naphthols was coupled in the presence of 5 mol % of **2f** under the optimized conditions with oxygen as oxidant. Table 4 shows the results. The reaction is quite sensitive to the substituent position on the 2-naphthols. Generally, much higher enantioselectivities for 7-substituted 2-naphthols (94−97% ees, entries 1−7) than those for the 2-naphthols with similar substituents at C6 (36% and 44% ees, entries 10 and 11) were observed. The enantioselectivity does not depend on the size of the substituent. Thus, variation of the substituent at C7 from methoxy to other alkoxy groups hardly changed the enantioselectivities (entries 1−7). However, the electron nature of the substituent impinges to some degree on the enantioselectivity. In the cases of 2-naphthols substituted

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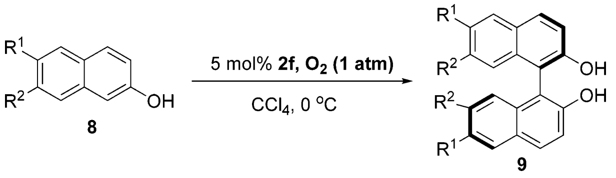
[26] (a) Tada, M.; Kojima, N.; Izumi, Y.; Taniike, T.; Iwasawa, Y. *J. Phys. Chem. B* **2005**, *109*, 9905. (b) Pessoa, J. C.; Cavaco, I.; Correia, I.; Duarte, M. T.; Gillard, R. D.; Henriques, R. T.; Higes, F. J.; Madeira, C.; Tomaz, I. *Inorg. Chim. Acta* **1999**, *293*, 1.

Table 3. Oxidative Coupling of 2-Naphthol with Oxovanadium Complexes **2**

entry	catalyst	R	yield (%)[a]	ee (%)[b]
1	**2a**	Bn	77	80
2	**2b**	4-MeOC$_6$H$_4$CH$_2$	38	51
3	**2c**	4-FC$_6$H$_4$CH$_2$	64	67
4	**2d**	β-naphthyl	69	50
5	**2e**	*i*-Pr	42	79
6	**2f**	*sec*-Bu	89	89
7	**2g**	*t*-Bu	56	79
8	**2h**	*n*-Bu	73	70

[a] isolated yield. [c] The *ee* values were determined by HPLC on a Kromasil CHI−TBB column, and the absolute configuration is *R*.

Table 4. Oxidative Coupling of 2-Naphthols in the Presence of 5 mol % **2f**[a]



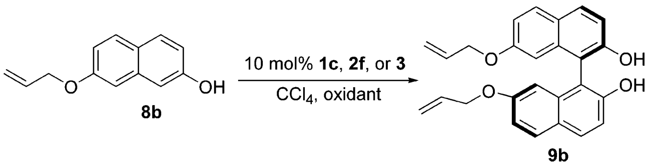
entry	products	R^1	R^2	time (days)	yield (%)[b]	ee (%)[c]
1	**9b**	H	OCH$_2$CH=CH$_2$	4	99	95
2	**9c**	H	OMe	7	95	95
3	**9d**	H	OEt	4	99	96
4	**9e**	H	O^{n}Bu	4	99	94
5	**9f**	H	O^{n}C$_8$H$_{17}$	4	99	94
6	**9g**	H	O^{n}C$_{12}$H$_{25}$	4	94	97
7	**9h**	H	OBn	6	80	95
8	**9i**	H	Ph	6	92	86
9	**9j**	H	4-FC$_6$H$_4$	6	>99	85
10	**9k**	OCH$_2$CH=CH$_2$	H	5	>99	36
11	**9l**	O^{n}Pr	H	5	93	44
12	**9m**	Br	H	4	98	90
13	**9n**	Br	OMe	6	97	96
14	**9o**	Br	OEt	6	95	97
15	**9p**	Br	OCH$_2$CH=CH$_2$	6	>99	98
16	**9q**	Br	*O*^{n}Bu	6	>99	98
17	**9r**	Br	O^{n}C$_5$H$_{11}$	6	96	89
18	**9s**	Br	O^{n}C$_6$H$_{13}$	6	97	91
19	**9t**	Br	O^{n}C$_8$H$_{17}$	6	95	90
20	**9u**	Br	OBn	6	96	96[d]
21	**9v**	4-FC$_6$H$_4$	O^{n}Bu	6	96	48

[a] The reactions are carried out under 1 atm oxygen. [b] Isolated yields. [c] The ee values are determined by HPLC on a Kromasil CHI-TBB or Chiralpak AD column, the configurations of products are *R*. [d] Using toluene/CCl$_4$ = 1:3 as the solvent.

with an aromatic group at C7, much decreased enantioselectivites were provided (entries 8 and 9). The best result for the oxidative coupling of 6-substitued 2-naphthols was seen in the case of 6-bromo-2-naphthol, which gave rise to the product with 90% ee (entry 12).

Also conducted were symmetric oxidative couplings of 2-naphthols bearing two substituents at C6 and C7, respectively-(entries 13−21). The size of the substituent at C7 somewhat affects the enantioselectivity. The increase in the size of substituent at C7 by varying that from hydrogen to *n*-butoxy leads to a slightly improved enantioselectivity (entries 12−16). However, the enantioselectivity gradually drops by a small amount as the substituent size at C7 increases. Very high enantioselectivities were observed for **9p** and **9q**, which bear two butoxy and allyloxy substituents, respectively (entries 15 and 16). A much lower enantioselectivity but a high yield were provided for **9v** that has two 4-fluorophenyl substituents, a much bulkier group than bromide, at C6 and C6′. These results, in the combination with those for 6-substituted binaphthols **9k** and **9l**, suggest that the C6 substituent of 2-naphthols has a remarkable impact on the stereochemistry, but has little influence on the reactivity.

Table 5. Comparison of the Ability of **3**, **1c**, and **2f** at Catalyzing the Oxidative Coupling of **8b**



entry	catalyst	oxidant	time (days)	yield (%)[a]	TOF (d^{-1})	ee (%)[b]
1	3	O$_2$	1.5	92	6.1	91
2	**3**	**Air**	**2**	**99**	5.0	**93**
3	**1c**	Air	2	51	2.5	96
4	**2f**	Air	2	25	1.3	89

[a] Isolated yields. [b] The ee values are determined by HPLC on a Kromasil CHI-TBB or Chiralpak AD column, the configurations of products are *R*.

H$_8$-BINOL-Based Bimetallic Chiral Oxovanadium Complexes and Oxidative Coupling Using *Air* as Oxidant. Our interest to investigate the ability of the H$_8$-BINOL-based vanadium complexes for catalyzing the oxidative coupling of 2-naphthols stemmed from the fact that most chiral ligands with a H$_8$-binaphthyl backbone show higher efficiencies and enantioselectivities than those with binaphthyl in many cases.[1,2k,27] The complex **3**, which was synthesized by a similar procedure for the preparation of **1** and **2**, was also characterized by IR and HRMS. It did not give an improved enantioselectivity for the coupling of **8b** compared with its structural analogues **1c** and **2f**. However, upon using air as the oxidant, the vanadium complex **3** is much more efficient than both **1c** and **2f** (Table 5, entries 2−4). Interestingly, faster reaction and higher enantioselectivity were seen by using **3** as a catalyst under 1 atm air (Table 5).

This result is very important because air is the most plentiful oxidant source and is safe and environmentally benign. The air-oxidized homocouplings of 2-naphthols in the presence of transition-metal complexes in either asymmetric or racemic manner were attempted;[6b,10a] however, the reactions proceeded with unsatisfactory results. Although the asymmetric oxidative coupling of 2-naphthols using air as oxidant catalyzed by a bimetallic vanadium complex in chloroform solvent proceeded successfully to give the product in high yield, a lower enantioselectivity relative to the reaction using molecular oxygen in CCl$_4$ was observed.[28] So far, there is no efficient chiral catalyst, which shows high catalytic activity and enantioselectivity for the oxidative coupling of 2-naphthols with air as the oxidant.

The ability of vanadium complex **3** at catalyzing the oxidative coupling of various 2-naphthols bearing a substituent at C7 or two substituents at both C6 and C7 using air as oxidant was examined (Table 6). The reaction was performed following a

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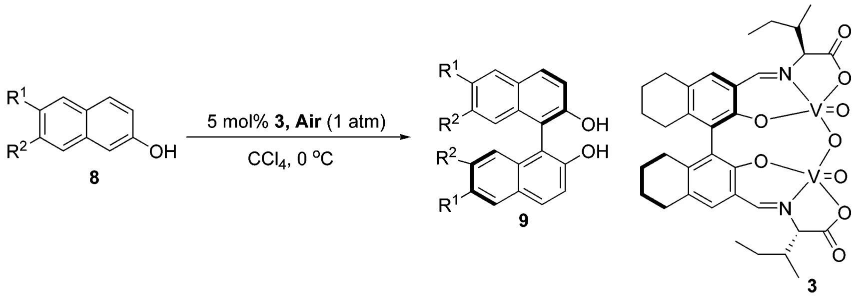
(27) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029.
(28) Somei, H.; Asano, Y.; Yoshida, T.; Takizawa, S.; Yamataka, H.; Sasai, H. *Tetrahedron Lett.* **2004**, *45*, 1841.

Table 6. Oxidative Coupling of 2-Naphthols with Air as Oxidant in the Presence of **3**[a]



entry	products	R^1	R^2	time (days)	yield (%)[b]	ee (%)[c]
1	**9a**	H	H	4	58	60
2	**9c**	H	OMe	2	94	92
3	**9d**	H	OEt	1.5	99	93
4	**9e**	H	O^nBu	1.5	97	93
5	**9g**	H	$OC_{12}H_{25}$	2	85	89
6	**9o**	Br	OEt	2	96	97
7	**9p**	Br	$OCH_2CH_2{=}CH_2$	2	92	95
8	**9q**	Br	O^nBu	2	90	97
9	**9r**	Br	$O^nC_5H_{11}$	2	90	96
10	**9s**	Br	$O^nC_6H_{13}$	2	89	93
11	**9t**	Br	$O^nC_8H_{17}$	2	88	96
12	**9m**	Br	H	2	82	86

[a] The reactions are carried out under 1 atm air. [b] Isolated yields. [c] The ee values are determined by HPLC on a Kromasil CHI-TBB or Chiralpak AD column.

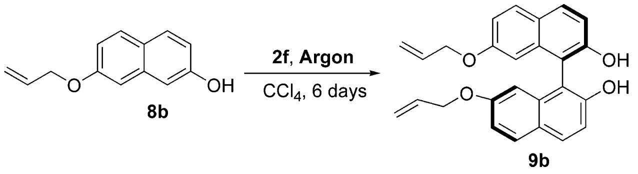
procedure similar to that for a coupling reaction catalyzed by **2f** with the exception of using air to replace oxygen as the oxidant. Most of reactions proceeded to completion within 2 days even though the oxidative couplings were catalyzed by 5 mol % of **3** under 1 atm air. In most cases (entries 2−8, 12), the enantioselectivities that were obtained were comparable with those observed for the similar **2f**-catalyzed reactions with molecular oxygen as the oxidant (entries 2−4, 6, 12, and 14−16, Table 4). However, the air-oxidative coupling of 2-naphthol afforded a moderate yield and enantioselectivity (entry 1). It is noteworthy that the coupling reactions proceeded to generate **9r**−**t** with higher enantioselectivities (entries 9−11) than those observed with **2f** (Table 4, entries 17−19). This process represents the most efficient and enantioselective oxidative coupling of 2-naphthols with air as oxidant.

Mechanistic Aspect. It has been reported that the oxidative coupling generally proceeds via three possible mechanisms: (1) the radical−radical coupling, (2) the radical−anion coupling, and (3) the heterolytic coupling of cationic species with 2-naphthol. The ruthenium-[6h] and copper-[10d]catalyzed oxidative coupling reactions of 2-naphthols have been proven to possibly proceed through a radical−radical coupling pathway. To make clear the exact mechanism for the present reaction, a cross-coupling of 6-bromo-2-naphthol (**8m**) and 6-methoxy-2-naphthol (**8w**) was attempted in the presence of **2f** (Scheme 3). In principle, a radical−radical coupling should give a mixture of products, and the ratios of these compounds should be in agreement with the relative reactivities. Because the redox potential of **8m** is higher than that of **8w**, the 6,6′-dimethoxy-2,2′-binaphthol (**9x**) will be produced in the majority. Theoretically, the radical−anion coupling will preferentially form a cross-coupling product since the radical would form from a more oxidizable **8w** and then attack a more stable anion generated from **8m**. In the heterolytic coupling, the electron-richer 6-methoxy-2-naphthol (**8w**) would be oxidized to a cation, which attacks another molecule of more nucleophilic **8w**, giving **9x** as a major product. Since **8m** is much less nucleophilic and more difficult to be oxidized than 6-methoxy-2-naphthol, **9m** and the cross-coupled **9w** would be generated the least.

In the presence of 5 mol % of **2f**, the competitive coupling reaction proceeded to give a mixture of cross-coupled **9w**, homocoupled **9m**, and **9x**. The ratio of **9m**/**9w**/**9x** is 1:2.2:5.2, which is statistically in agreement with the radical−radical coupling mechanism.[6h,10d]

A kinetic study was carried out on the oxidative coupling of 7-allyloxy-2-naphthol (**8b**) in the presence of 10 mol % of either of these catalysts, **11**, **2f**, **1c**, and **3**, with molecular oxygen as oxidant. As shown in Figure 8, these catalysts exhibit dramatically different catalytic activity. Of them, **3** is the most catalytically active and provided an 8 times faster reaction than **11**. The catalytic activity of these vanadium complexes decreases in an order of **3** > **1c** > **2f** ≫ **11**. The monovanadium complex **11** is much less catalytically active than the bis-vanadium ones. Recently, Sasai and co-workers also observed a similar tendency in this issue.[28]

The oxidative coupling of 7-allyloxy-2-naphthol (**8b**) in the presence of various amounts of vanadium complex **2f** *under argon* were carried out. As shown in Figure 9, the conversion



is linearly correlated to the amount of the vanadium complex **2f**. The observed data are consistent with the calculated ones in that one molecule of bimetallic vanadium complex **2f** can

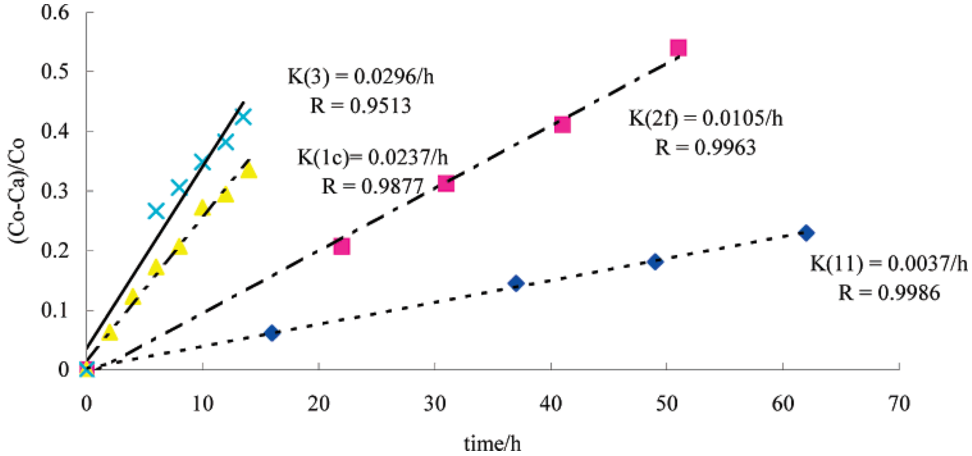


Figure 8. Kinetic studies on the oxidative coupling of 7-allyloxy-2-naphthol. (blue ×) with **11**. (red ■) with **2f**. (yellow ▲) with **1c**. (dark blue ■) with **3**.

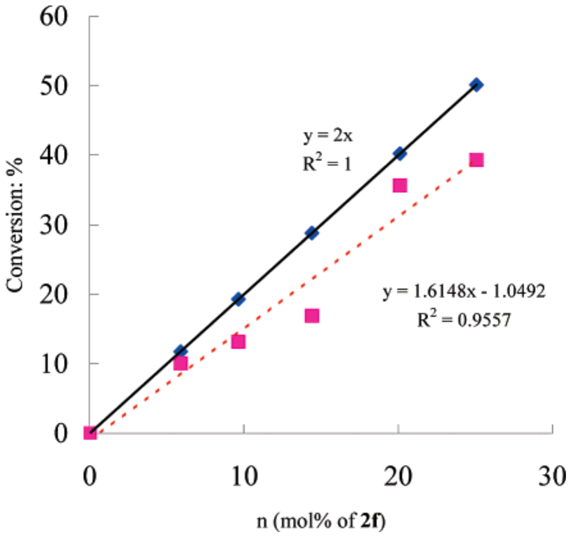
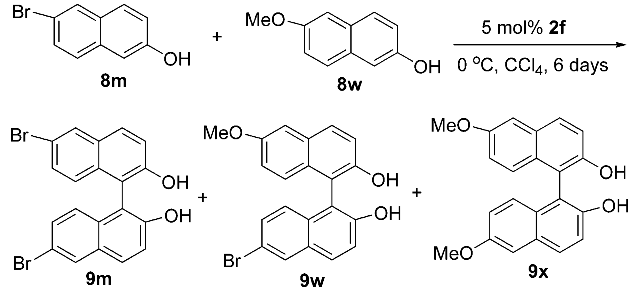


Figure 9. Oxidative coupling of **8b** with various amounts of **2f** under argon. (black ■) Theoretical data; (red ■) experimental data.

Scheme 3. Catalytic Cross-Coupling of 6-Bromo-2-naphthol and 6-Methoxy-2-naphthol



9m: **9w**: **9x**= 1: 2.2: 5.2

oxidize two 7-allyloxy-2-naphthol (**8b**) to generate the coupling product. These results indicate that both vanadiums(V) of **2f** are involved in simultaneous oxidative coupling.[29]

On the basis of the experimental data and literatures, a reaction mechanism has been proposed (Scheme 4). The bimetallic vanadium complex **2f** first reacts with one molecule of 2-naphthol to generate a complex **I**, which reacts with another molecule of 2-naphthol to give a complex **II** and to release one molecule of water. Two intramolecular oxidations take place in **II** to form a double-free radical species **III**, and vanadium(V) is reduced into vanadium(IV). The intermediate **III** proceeds an enantioselective intramolecular radical−radical coupling reaction to give **IV**, which undergoes an isomerization to afford an intermediate **V**. After a decoordination and subsequent oxidation with molecular oxygen, (*R*)-BINOL was released, and the vanadium catalyst **2f** was regenerated from the intermediate **V**. In these steps, the intramolecular radical−radical coupling reaction is aggregately supported by the results of kinetic study, the oxidative coupling of **8b** under argon, and cross-coupling between **8m** and **8w**. The proposed mechanism is therefore reasonable to account for the observed results.

The reaction mechanism was further studied by high-resolution mass spectroscopy (HRMS) with ESI source (Figure 10). The coupling reaction catalyzed by **2f** was monitored off-line in negative ion mode. Surprisingly, the radical anion $[\mathbf{2f}]^{\bullet-}$ (*m*/*z* 614) of the catalyst was observed. It has been reported that ESI is able to directly transfer ions from solution to gas phase;[30] thereby the radical anion (*m*/*z* 614) of the catalyst is another piece of evidence to support the radical reaction mechanism that we propose (Scheme 4). After 5 h, we observed four peaks at *m*/*z* 757, 780, 884, and 907, of which the peaks at *m*/*z* 884, 907 are assigned to the intermediates $[\mathbf{II}]^{\bullet-}$ and $[\mathbf{II} + \mathbf{Na}]^{\bullet-}$, respectively, and those at *m*/*z* 757 $[\mathbf{I}\text{-}2\mathrm{H}]^{-}$ and 780 $[\mathbf{I}\text{-}\mathrm{H}+\mathrm{Na}]^{\bullet-}$ are assigned to the intermediate **I** formed by the coordination of the catalyst **2f** with one molecule of 2-naphthol. The intermediate **I** reacts with another molecule of 2-naphthol to release one molecule of H_2O, generating the intermediate **II**. After the reaction has performed for 23 h, the peaks at *m*/*z* 882 and 883 are observed, which are probably formed through losing H atoms from the intermediate **V**. Meanwhile, the peak at *m*/*z* 285 that is assigned to the product BINOL was also detected (see Supporting Information for the whole spectra). The relative intensity of the peak at *m*/*z* 884 vs that at *m*/*z* 882 became weaker gradually as the reaction proceeded (Figure 10). After 154 h, all intermediates could not be detected, indicating the reaction proceeded completely. All these observed MS data,

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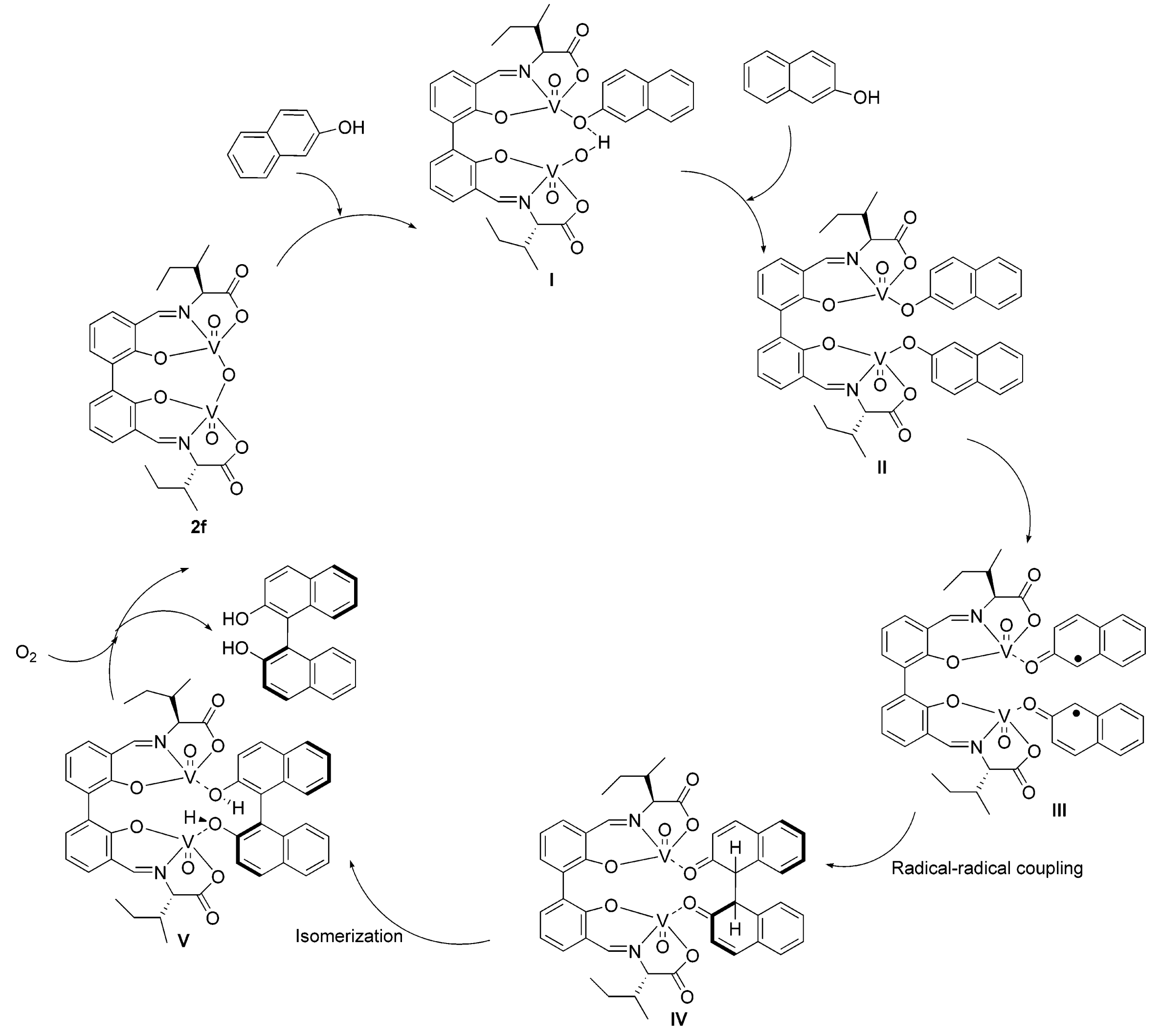
(29) The oxidation reaction of stoichiometic amounts of homochiral chlorovanadate with (*S*)-ethyl mandelate under unaerobic conditions has been used for the mechanistic investigation, see: Radosevich, A. T.; Musich, C.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 1090.

(30) de la Mora, J. F.; Van Berkel, G. J.; Enke, C. G.; Cole, R. B.; Martinez-Sanchez, M.; Fenn, J. B. *J. Mass Spectrom.* **2000**, *35*, 939.

Scheme 4. Proposed Mechanism for the Oxidative Coupling of 2-Naphthol Catalyzed by Bimetallic Vanadium Complexes



together with precedent experiments, are consistent with the proposed mechanism.

Theoretical Studies on the Stereochemistry. Theoretical calculations were performed to explore the intrinsic factors for the asymmetric oxidative coupling of 2-naphthol catalyzed by the oxovanadium complex **2f**. All the structures were completely optimized by using the gradient-corrected hybrid density function theory B3LYP method as implemented in the G03 program package.[31] A basis set of valence double-ξ quality was used. Relativistic effects were addressed implicitly by the use of relativistic effective core potentials (RECPs) for V. The standard Dunning−Hay D95V basis was used for C, H, O, and N atoms. This basis set/RECP combination is commonly denoted by the acronym "LANL2DZ".[32]

Oxovanadium complexes **2f** have a conformationally flexible biphenyl unit, leading to the existence of diastereomers (*R*,*S*)-**2f** and (*S*,*S*)-**2f**. The catalytic results and CD studies indicated that (*R*,*S*)-**2f** is possibly predominant. To further estimate the flexible propagated chirality that exists in vanadium complex **2f**, theoretical calculations were first performed on (*R*,*S*)-**2f** and (*S*,*S*)-**2f**. The calculated most stable structures are shown in Figure 11. The parameters of bond length involving vanadium of (*R*,*S*)-**2f** and (*S*,*S*)-**2f** obtained from the DFT modeled structures are in agreement with the crystallographic structural data (Table 7).[33]

The most stable structure of (*R*,*S*)-**2f** was predicted to be much more favorable than that of (*S*,*S*)-**2f** by a calculated energy of 4.43 kcal/mol, indicating that the diastereomer (*R*,*S*)-**2f** is easier to be formed than (*S*,*S*)-**2f**. The greater stability of the (*R*,*S*)-diastereomer of the oxovanadium complex **2f** results from the (*R*)-axial chirality of biphenyl matching the (*S*)-configuration of α-amino acids because the *sec*-butyl group is perpendicular to the azomethyne of the complex. However, in (*S*,*S*)-**2f**, the (*S*)-axial chirality of biphenyl makes the *sec*-butyl group of the (*S*)-α-amino acid take a coplanar orientation with the azomethyne. This eclipsed conformation of *sec*-butyl group causes a significantly repulsive interaction between H^1-H^3 with a

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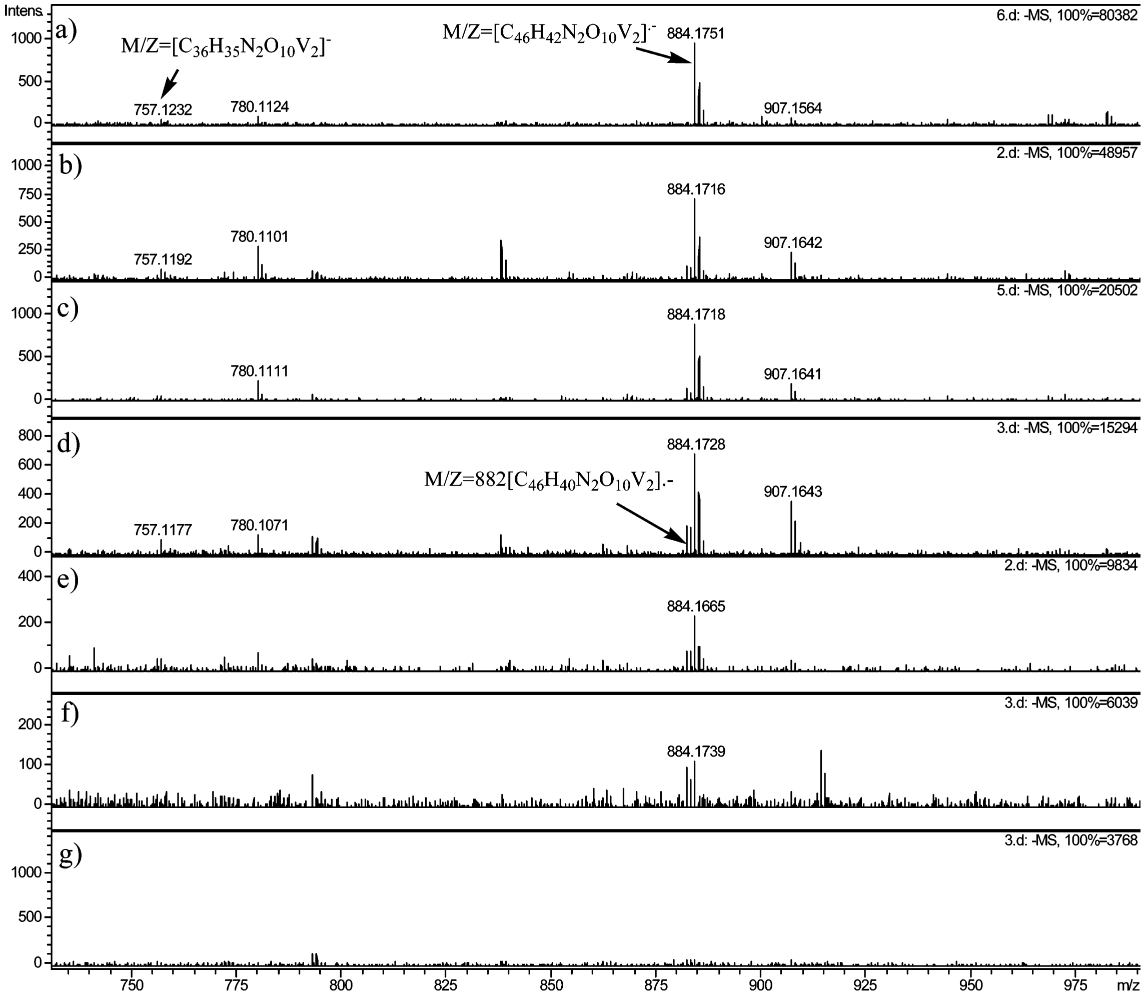


Figure 10. Reaction process detected by ESI-MS. (a) ESI-MS spectrum was obtained after the reaction was performed after 5 h; (b) after 23 h; (c) after 34 h; (d) after 80 h; (e) after 106 h; (f) after 130 h; (g) after 154 h.

Table 7. Parameters of Bond Length Involving Metal Vanadium by DFT Calculations and X-ray Crystallography of ref 33 (in Å)

shell	(*R*,*S*)-**2f**	(*S*,*S*)-**2f**	X-ray[a]
V═O	1.589	1.588	1.589
V−N	2.117	2.126	2.043
V−O	1.775	1.775	2.008
V−OCO	1.863	1.861	1.975
V−Oph	1.851	1.847	1.921

[a] The bond lengths are from X-ray crystallography of ref 33.

distance of about 1.987 Å in (*S*,*S*)-**2f** (Figure 11). The calculation once again proved that (*R*,*S*)-**2f** is the predominant diastereomer.

To gain insights into the origin of the enantioselectivity of the oxidative coupling, further calculations were undertaken on the catalytic performance of the asymmetric oxidative coupling of 2-naphthol in the presence of (*R*,*S*)-**2f**. The four possible structures of the intermediate **IV**, which principally offer the final products, were successfully modeled by DFT calculations as shown in Figure 12. The two 2-naphtholates respectively coordinated to vanadiums can take an orientation either of two naphthyl rings parallel to each other or of a crosswise section with the top coordinated 2-naphtholate pointing down and the bottom one stretching up. While the coupling reaction takes place, the H atoms connected to two carbon atoms where the coupling takes place can take an orientation either toward or away from the central vanadium.

Among the four structures of the intermediate **IV** formed from the (*R*,*S*)-**2f**-catalyzed coupling of 2-naphthols (Figure 12), the most favorable one was predicted to be (*R*,*S*,*R*)-**IV-1**, which corresponds to the experimental major product. (*R*,*S*,*R*)-**IV-2**, an alternative assembly to give (*R*)-BINOL, was predicted to be much less stable than (*R*,*S*,*R*)-**IV-1** by about 4.28 kcal/mol due to the different arrangement of the two coordinated 2-naphtholates. In (*R*,*S*,*R*)-**IV-1**, the two naphthyl rings take a parallel orientation and are away from the metal centers with an *anti*-conformation. The (VO)C−C−C−C(OV) dihedral angle (along with the forming C−C bond) was predicted to be about 141° to minimize the sterical repulsion during the whole coupling procedure, whereas in (*R*,*S*,*R*)-**IV-2**, the crosswise section of two naphthyl rings with a perpendicular $\pi-\pi$ stacking makes the structure distorted, leading to an eclipsed conformation. The (VO)C−C−C−C(OV) dihedral angle was predicted to be about 26° so that the steric strength was significantly enhanced as the located 1H−8′H distance is about 2.04 Å in (*R*,*S*,*R*)-**IV-2**. Both (*R*,*S*,*S*)-**IV-1** and (*R*,*S*,*S*)-**IV-2**, which will give the (*S*)-BINOL, were predicted to be much less stable than (*R*,*S*,*R*)-**IV-1** by about 13 kcal/mol. The destabilization resulted from the peculiar arrangement of two naphthyl rings, which took a crosswise configuration with the top pointing down and the bottom stretching up so that the steric interaction was increased. Thus, the coupling reaction catalyzed by **2f** occurred through

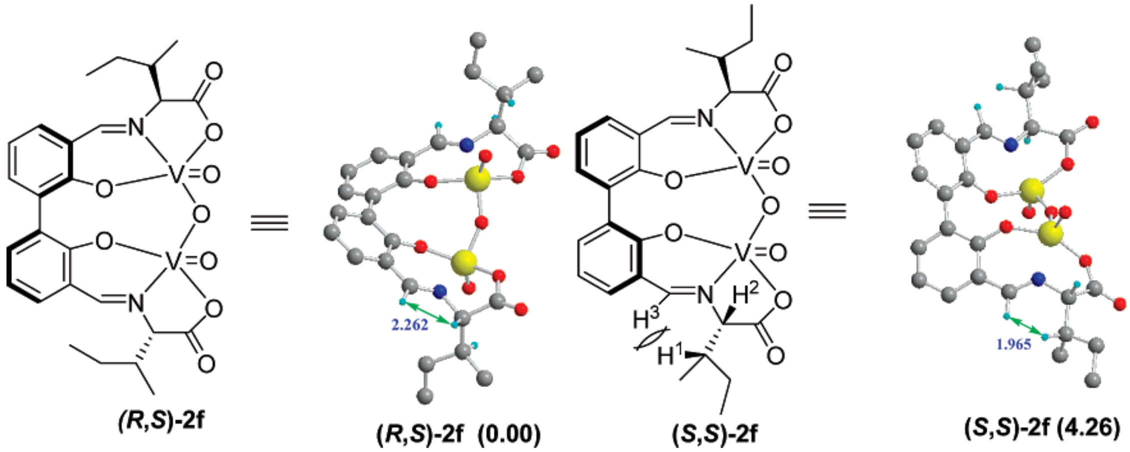


Figure 11. Structures of oxovanadium complex **2f** modeled by DFT, relative enthalpy in kcal/mol. Legend is as follows: (yellow) vanadium; (gray) carbon; (red) oxygen; (blue) nitrogen; (cyan) hydrogen. For clarity just key hydrogen atoms are shown.

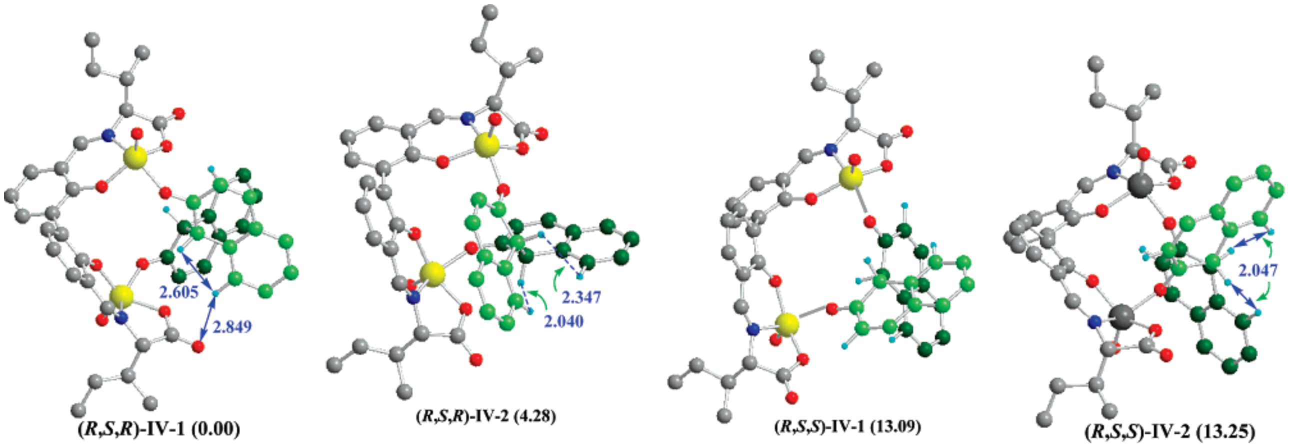
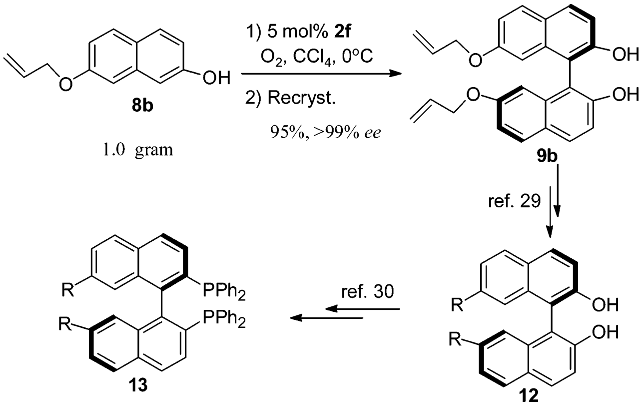


Figure 12. Structures of intermediate **IV** modeled by DFT, relative enthalpy in kcal/mol and H−H distance in Å. Legend is as follows: (yellow) vanadium; (gray) carbon; (red) oxygen; (blue) nitrogen; (cyan) hydrogen; (light green) top naphthyl of BINOL; (dark green) down naphthyl of BINOL. For clarity just key hydrogen atoms are shown.

Scheme 5. Preparation of 7,7′-Disubstituted BINOLs and BINAPs Based on the Oxidative Coupling



the most favorable intermediate (*R*,*S*,*R*)-**IV-1** to predominantly give (*R*)-BINOL.

Application of Oxidative Coupling Reactions. The current process is quite synthetically useful. The oxidative coupling of **8b** to generate **9b** is very reproducible and can be easily scaled up with no loss of the enantioselectivity. After several convenient synthetic steps, **9b** was transformed into a family of 7,7′-disubstituted 2,2′-binaphthols (**12**), which were used in the titanium-catalyzed phenylacetylene addition to aldehydes with excellent enantioselectivity.[34] Referring to the general procedure for the preparation of BINAP and related chiral ligands, compounds **12** were transformed into 7,7′-disubstituted BINAP **13** (Scheme 5). The rhodium complexes of **13** have been used to catalyze the conjugated addition of arylboronic acids to unsaturated ketones with high enantioselectivity.[35]

Optically active binaphthol-based conjugated polymers have extensive application in asymmetric catalysis[2] and in the creation of organic materials.[4a,b] An optically active conjugated polymer **17** was readily prepared starting with an oxidative coupling of **8q**, which furnished **9q** in quantitative yield with 98% ee (Scheme 6). Protection of **9q** by treatment with methoxymethylchloride (MOMCl) and sodium hydride (NaH) afforded **14** in more than 95% yield. After a Suzuki coupling with **15** and a subsequent hydrolysis, chiral conjugated polymer **17** was obtained in 80% yield. Compared with similar polymers reported previously,[4a,b] this polymer has a substituent at C7 of its binaphthol repeating unit, and thus its dihedral angle is tunable. The effect of the dihedral angle on the secondary structure and optical properties of the polymer could be investigated further.

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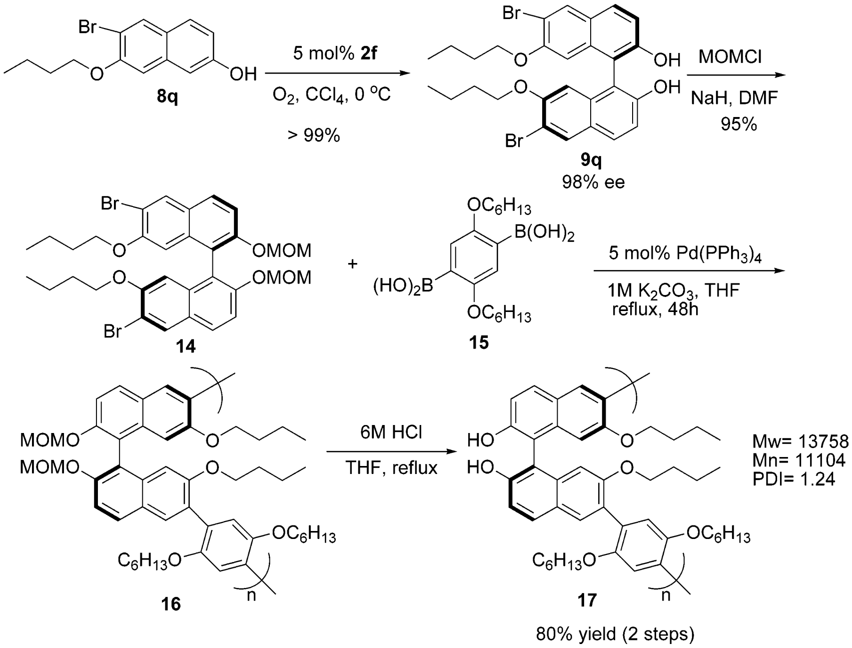
Scheme 6. Preparation of Chiral Conjugated Polymer Based on Oxidative Coupling



Conclusion

Chiral, bimetallic vanadium complexes derived from optically pure binaphthol, H$_8$-binaphthol, and achiral biphenol were prepared and evaluated for catalyzing the enantioselective catalytic oxidative coupling of 2-naphthols. In the oxovanadium complexes derived from binaphthol, the *R*-configuration of the axial chirality matches *S*-amino acids to favor stereocontrol. Spectral and experimental studies demonstrated that the axial chirality of the vanadium complex that is derived from biphenol is transferred from the amino acids and is crucial for the stereocontrol. Excellent enantioselectivities of 90−97% ee, and almost perfect yields are provided by the presence of 5 mol % of the optimal catalyst **2f** for a large number of monosubstituted and bisubstituted 2-naphthols. Oxidative coupling of 2-naphthols catalyzed by the H$_8$-binaphthol-based oxovanadium complex with air as the oxidant proceeded smoothly to give homo-coupling products in nearly quantitative yields with very high enantioselectivities. Kinetic studies, cross-coupling experiments, and HRMS spectral studies on the reaction all indicate that the radical−radical coupling reaction takes place in an intramolecular manner. Theoretical studies on the intermediates of the reaction revealed the origin of the stereochemistry and suggested that the cooperative effects of the axial chirality and the matching *S*-amino acids would have stereocontrol of the catalytic oxidative coupling of 2-naphthols. The usefulness of this efficient oxidative coupling reaction has been demonstrated by the synthesis of chiral ligands and conjugated polymers.

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Supporting Information Available: Experimental details and characterization of new compounds, calculated energies and Cartesian coordinates of the calculated structures, and complete ref 31. This material is available free of charge via the Internet at http://pubs.acs.org.

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