JOC The Journal of Organic Chemistry

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Resolution of Vaulted Biaryl Ligands via Borate Esters of Quinine and Quinidine

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Cite This: https://dx.doi.org/10.1021/acs.joc.0c00494 Read Online

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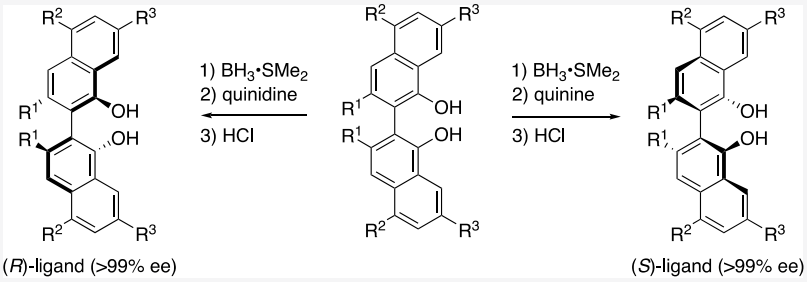


ABSTRACT: Given the sudden and unexplained rise in the cost of (+)- and (−)-sparteine, an alternative method for the resolution of vaulted biaryls has been developed. This method involves the reaction of a racemic vaulted biaryl ligand with one equivalent of BH_3·SMe_2 and one equivalent of either quinine or quinidine. A precipitate then forms from the resulting mixture of diastereomeric borates as a result of differential solubilities. Hydrolysis of the precipitate then liberates the (*S*)-ligand in the case of quinine and the (*R*)-ligand in the case of quinidine, both with >99% ee. This method has been applied to 16 different vaulted biaryl ligands, including 10 whose preparation is described here for the first time. In addition, proof of principle has been demonstrated for the dynamic thermodynamic resolution of the vaulted biaryl ligands with this method in combination with a nonchiral copper(II) complex that can racemize the ligand.

1. INTRODUCTION

The vaulted biaryl ligands VANOL **1** (vaulted binaphthol) and VAPOL **2** (vaulted biphenanthryl) and their derivatives have proven to be uniquely valuable in a variety of catalytic asymmetric processes.[1] The original method that was developed for the resolution of VANOL and VAPOL was via their hydrogen phosphate esters **3** and **4** (Scheme 1). This method is a three-step process that involves the synthesis of their corresponding hydrogen phosphate esters, salt formation with a chiral base (brucine for VANOL and cinchonidine for VAPOL), separation of the salts by crystallization, and then reduction of the phosphate esters to give the (*R*)- and (*S*)-ligands in high optically purity (>99% ee).[2] Although three chemical transformations are involved, this resolution method is suitable for large scale synthesis. A method more convenient for small scale synthesis is deracemization with a copper(II) complex of sparteine.[3] This method converts both enantiomers of the racemic ligand to a single enantiomer in high yield and with greater than 99% ee for both VANOL and VAPOL. The (*S*)-enantiomers are formed with the copper complex of (−)-sparteine **5** and the (*R*)-enantiomers with the complex with (+)-sparteine **5** or O'Brien's diamine **6**.[3,4] However, in the past few years, the price of both (+)- and (−)-sparteine have become prohibitively expensive.[5]

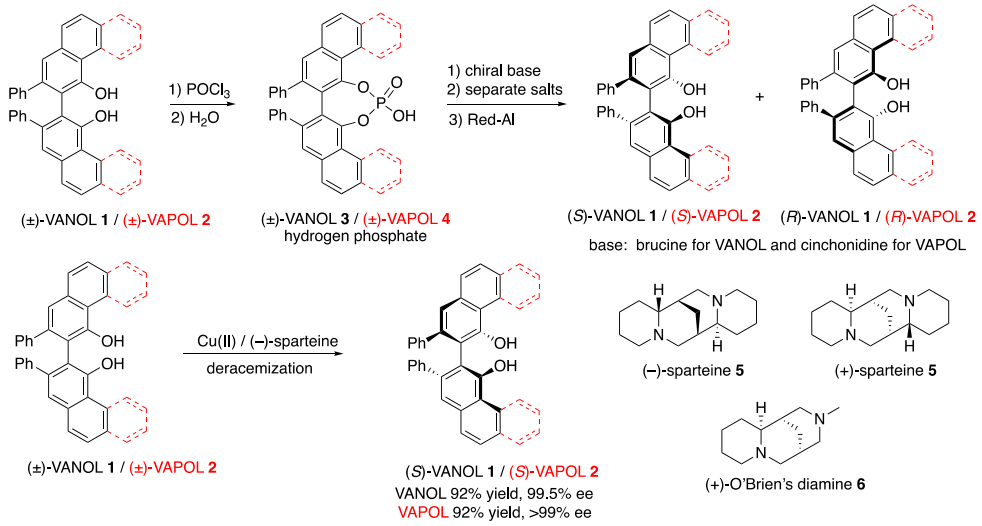
As a result of the increase in cost of both enantiomers of sparteine, we sought an alternative method for small scale resolution and also for a method that could be applied to a range of VANOL and VAPOL derivatives. We took note of a report by Shan and coworkers who showed that BINOL **7** could be resolved by forming borate esters of BINOL and quinine and separating the diastereomers by crystallization (Scheme 2).[6a] Hydrolysis of the solid that separated provided optically pure (*S*)-BINOL. In the following year, Shan and coworkers reported that (*R*)-BINOL could be obtained in highly enantiomerically pure form from the precipitate of a borate complex with cinchonine which was proposed to have the structure **8b**.[6b] It was not determined which diastereomer of **8b** preferentially formed a solid. Although the details of the structure of **8b** were not provided, it is considered likely that the boron is four coordinate with an internal Lewis acid−Lewis base complex with the 3° amine.[6]

The subject of the present work was to develop a new method for the resolution of vaulted biaryls based on the success observed for the linear biaryl BINOL. This method

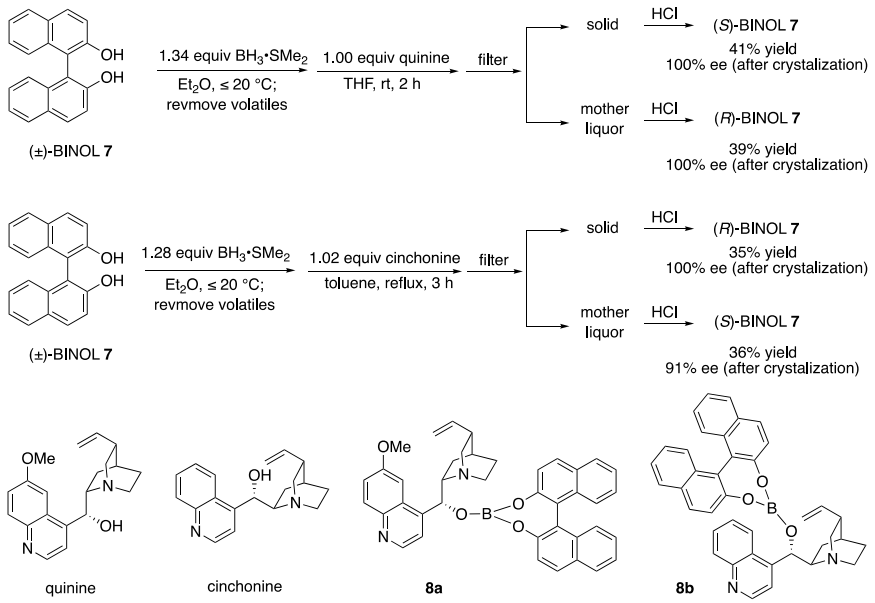
Received: March 23, 2020
Published: July 21, 2020

https://dx.doi.org/10.1021/acs.joc.0c00494
J. Org. Chem. XXXX, XXX, XXX−XXX

Scheme 1. Vaulted Biaryl Ligands and Previous Methods for Their Resolution



Scheme 2. Shan's Method for the Resolution of BINOL



involves borate esters of the vaulted biaryls with quinine and quinidine. This work also presents the synthesis and resolution of several new VANOL derivatives, including 3,3′-disubstituted aryl VANOL derivatives **11a** to **11c**, the 5,5′-disubstituted VANOL ligands **12a** to **12e**, and the 7,7′-disubstituted VANOL ligands **13d** and **13e** (Scheme 3).

2. RESULTS AND DISCUSSION

We were delighted to find that application of the Shan procedure to racemic VANOL with quinine lead to the isolation of a solid which upon hydrolysis gave pure (*S*)-VANOL in 46% yield and ≥99% ee (Table 1, entry 1). Concentration of the mother liquor and hydrolysis gave a residue that was largely (*R*)-VANOL in 64% yield and 69% ee. However, it was disappointing that an effort to find a resolution procedure that would afford (*R*)-VANOL in high optical purity was not as forthcoming. The use of quinidine as the chiral alkaloid gave a solid which upon hydrolysis gave (*R*)-VANOL in 31% yield but in only 66% ee (entry 2). The use of either cinchonidine or cinchonine each gave solids but the VANOL liberated from them was nearly racemic in each case (entries 3 and 4). It was at this point that it was recalled that Shan was able to effect the resolution of BINOL to give the (*R*)-Enantiomer with cinchonine as the alkaloid, however, only if toluene was used as the crystallization solvent.[6b] Unfortunately, no improvement in the resolution of either (*R*)- or (*S*)-VANOL could be realized with any of the four cinchona alkaloids with toluene as the crystallization solvent (Table 1, entries 5–8).

The racemic VANOL ligand can be resolved to the (*S*)-enantiomer with >99% ee with quinine, as indicated in Table 1, and thus, it was decided to determine whether this success could be extended to other VANOL derivatives and other vaulted biaryls. The set of 5,5-disubstituted VANOL ligands **12a** to **12e** has not been prepared before and would be of interest because they could be used to vary the electron density on the phenol functions while at the same time not sterically impeding any reaction occurring in the active site of a catalyst

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Scheme 3. Biaryl Ligands to Be the Subject of the Present Resolution Method

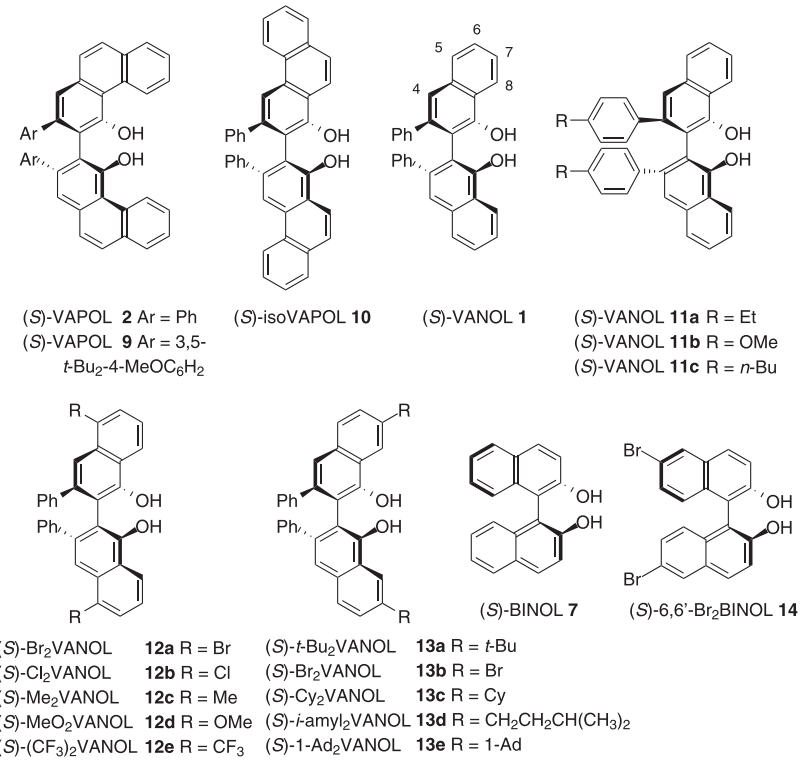
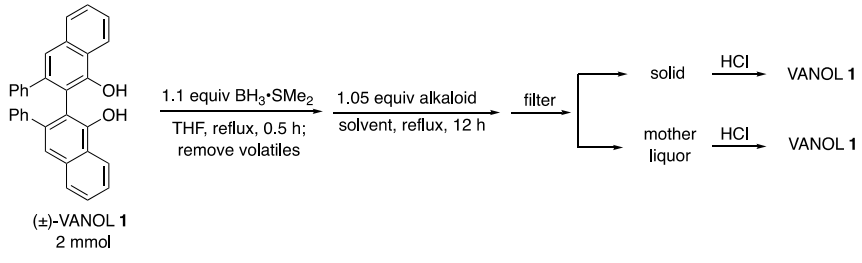
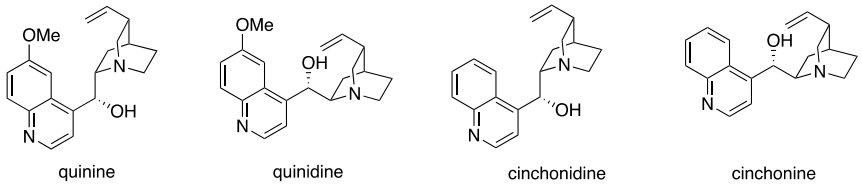


Table 1. Resolution of (±)-VANOL with Various chinchona Alkaloids



entry	alkaloid	solvent (mL)	% yield **1** from solid	% ee **1** from solid	% yield **1** from solution	% ee **1** from solution
1	quinine	THF (6)	46	>99 (*S*)	64	69 (*R*)
2	quinidine	THF (8)/hexanes (8)	31	66 (*R*)	70	23 (*S*)
3	cinchonidine	THF (8)/hexanes (12)	28	3 (*R*)		
4	cinchonine	THF (8)/hexanes (12)	35	7 (*R*)		
5	quinine	toluene (8)	37	94 (*S*)	64	61 (*R*)
6	quinidine	toluene (8)	30	70 (*R*)	65	44 (*S*)
7	cinchonidine	toluene (8)/hexanes (4)	35	0		
8	cinchonine	toluene (8)/hexanes (4)	24	1 (*R*)		

a



that was anchored to the phenol functions. The synthesis of **12a**–**12e** shown in Table 2 involves a cycloaddition/electrocyclization cascade (CAEC) that was developed for the synthesis of VANOL.[2b] This reaction involves the formation of a ketene which undergoes a [2 + 2] cycloaddition with the alkyne followed by an electrocyclic ring opening of the cyclobutenone and finally a 6 e^- electrocyclic ring closure of the aryl vinyl ketene to give the phenol **19** after tautomerization. The purpose of the anhydride is to trap the phenol and prevent it from reacting with the ketene, which can dramatically reduce the yield. All five of the ortho-substituted phenyl acetic acids **15** are commercially available and, on a 100

https://dx.doi.org/10.1021/acs.joc.0c00494
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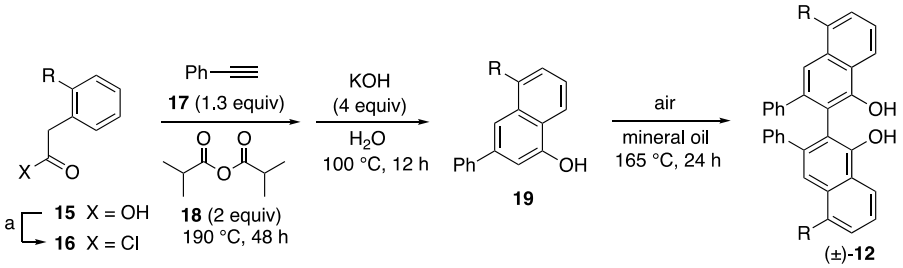
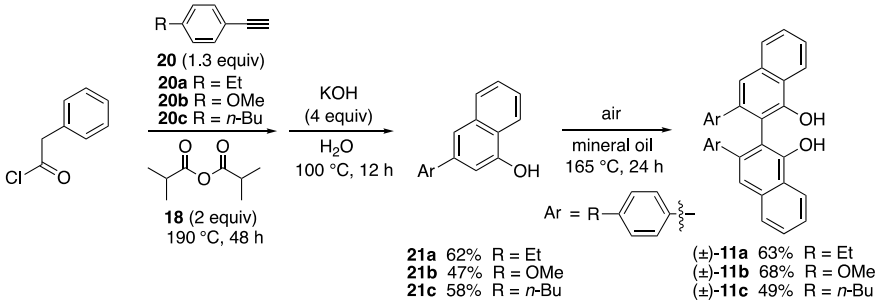
Table 2. Preparation of the Racemic 5,5′-Substituted Ligands 12[b]



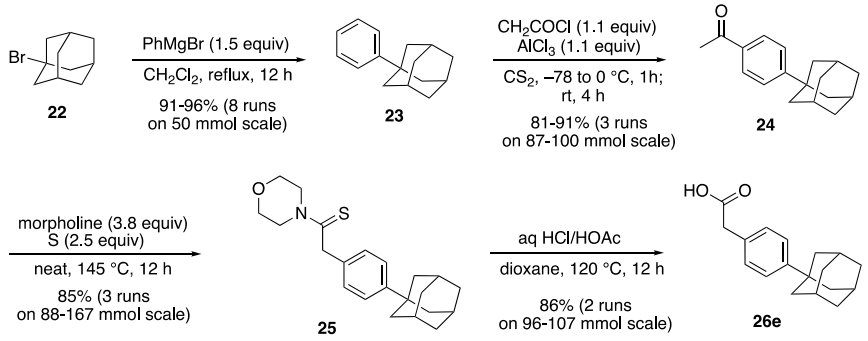
entry	series	R	% yield 19[c]	% yield (±)-12
1	a	Br	67	92[d]
2	b	Cl	71	75
3	c	Me	52	72
4	d	OMe	52	72
5	e	CF_3	66	65

[a]$SOCl_2$ (2 equiv), 70 °C, 1 h. [b]All reactions were carried out on 100 mmol of **15** and 50 mmol of **19**. [c]Yield from **15**. Combined yield of two crops after crystallization. [d]36 h.

Scheme 4. Preparation of Racemic 3,3′-Disubstituted Ligands 11a to 11c



Scheme 5. Preparation of the 1-Adamantyl Substituted Phenyl Acetic Acid 26e



mmol scale, gave the substituted naphthols **19a** to **19e** in 52 to 71% yield. The oxidative coupling of these 1-naphthols was effected by heating in the presence of air at 165 °C in mineral oil to give the racemic VANOL derivatives **12a** to **12e** in 65 to 92% yield all on a 50 mmol scale.

The 3,3′-disubstituted VANOL ligands **11a** to **11c** were also prepared by the cycloaddition/electrocyclization cascade (CAEC) as shown in Scheme 4.[2b] These syntheses begin with the reaction of the 4-substituted phenyl acetylenes **20a** to **20c** with phenylacetyl chloride on a 100 mmol scale and gave the naphthols **21a**, **21b**, and **21c** in 62, 47, and 58% yields, respectively. The subsequent phenol coupling reactions were carried out on 50 mmol scale to give the racemic ligands **11a** in 63% yield, **11b** in 68% yield, and **11c** in 49% yield.

We had previously observed the superior performance of boroxinate catalyst generated from the 7,7′-di-*t*-butyl substituted VANOL ligand **13a** in the catalytic asymmetric aziridination reaction of imines with ethyl diazoacetate,[4,7] and thus, we became interested as to how the catalyst prepared from the 7,7′-di-1-adamantylVANOL ligand **13e** would compare. Access to this ligand required the preparation of the 4-(1-adamantyl)phenylacetic acid **26e**, which was achieved in four steps, as outlined in Scheme 5. After exploring several different coupling reactions, the best method for the introduction of a phenyl group at the 1-position of adamantane was found to involve the simple coupling of 1-bromoadamantane **22** with phenylmagnesium bromide. This method developed by Eguchi and coworkers does not require a transition metal catalyst and gives good yields for the direct coupling of Grignard reagents with *t*-halides if the solvent is methylene chloride, which is thought to enhance the Lewis acidity of the Grignard and in turn aid in carbenium in

https://dx.doi.org/10.1021/acs.joc.0c00494
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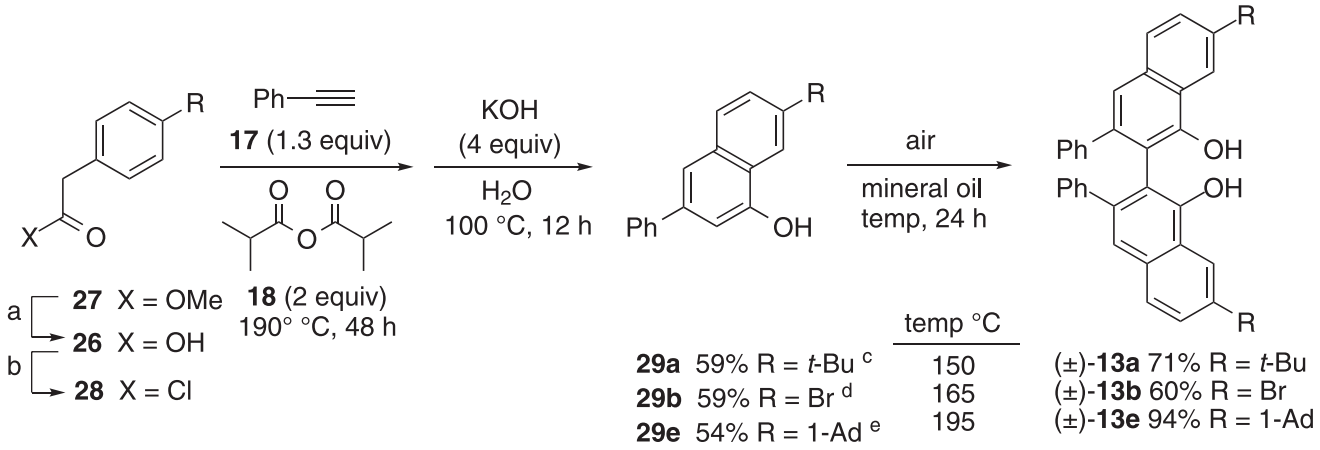
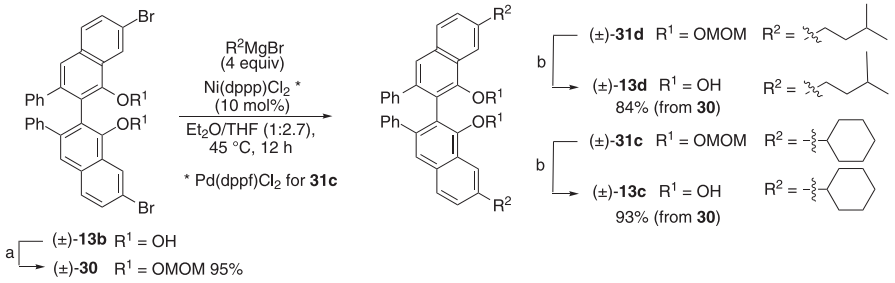
Scheme 6. Preparation of Racemic 7,7′-Disubstituted Ligands 13a, 13b, and 13e



[a]6 M NaOH, MeOH/H_2O (1:1), rt, 12 h, 100%. [b]$(COCl)_2$ (2.5 equiv), DMF (cat), CH_2Cl_2, rt, 2 h. [c]Yield from **26a**. [d]Yield from **26b**. [e]Yield from **26e**.

Scheme 7. Kumada Coupling in the Synthesis of Racemic Ligands 13d and 13c



[a](i) NaH (2.5 equiv), 0 °C; (ii) CH_3OCH_2Cl (2.5 equiv), THF, rt; 12 h, 95%. [b]Amberlyst 15, THF/MeOH (1:1), 65 °C, 15 h.

formation.[8] This coupling reaction gave 1-phenyladamantane **23** in 91−96% yield over 8 runs, each on a 50 mmol scale. The Friedel−Crafts acylation of **23** with acetyl chloride proceeded smoothly to give the acetophenone derivative **24** as one regioisomer in 81−91% yield (3 runs) on 96−100 mmol scale. Migration of the carbonyl group was effected by the Willgerodt−Kindler reaction,[9] which gave the thioamide **25** in 85% yield over 3 runs. Hydrolysis of the thioamide unit with aqueous hydrogen chloride and acetic acid in dioxane gave the desired acid **26e** in 86% yield.

The preparations of the 7,7′-substituted VANOL ligands **13a** and **13e** are presented in Scheme 6. The preparation of the 7,7′-di-*t*-butylVANOL **13a** has been described before[4] but is slightly different here as it begins with the commercially available methyl ester **27a**. Hydrolysis gives the acid **26a** in quantitative yield, which then is incorporated into the CAEC cascade, as indicated in Scheme 6, to give the naphthol **29a** in 59% yield from the acid **26a** on a 241 mmol scale. Oxidative coupling in air gives the racemic 7,7-di-*t*-butylVANOL **13a** in 71% yield on a 100 mmol scale. The preparation of racemic **13b** has also been reported before[4] but is reported here on a much large scale (150 mmol). The CAEC cascade with the 4-(1-adamantyl)phenylacetic acid **26e** gives the naphthol **29e** in 52−54% yield (2 runs) on a 100 mmol scale. Remarkably, the oxidative phenol coupling of naphthaol **29e** give the racemic 7,7′-di-1-adamantylVANOL **13e** in 94% yield, an unusually high yield for this naphthol coupling step.

Access to the 7,7′-dialkyl substituted VANOL derivatives can be achieved by Kumada coupling with the 7,7′-dibromoVANOL **13b** with the proper alkyl Grignard.[4] This is illustrated in the synthesis of the 7,7′-*i*-amyl$_2$VANOL **13d** and **13c** shown in Scheme 7, which was carried out on racemic **13b**. The (±)-dibromoVANOL **13b** first had its phenol units protected with MOM groups and then subjected to a nickel catalyzed coupling with an alkylmagnesium bromide. Removal of the MOM groups from the intermediate **31d** was aided by Amerlyst-15 to give the desired bisisoamyl VANOL derivative (±)-**13d** in 80% yield for the three steps from (±)-**13b**. The synthesis of the 7,7′-dicyclohexylVANOL derivative **13c** was achieved in a similar manner in 93% overall yield from the MOM protected VANOL **30**. This is a higher yield than was previously reported for **13c** (71%) starting from the bis-methylated VANOL corresponding to **30**.[4] This synthesis of 7,7′-dialkyl substituted VANOL derivatives would be much more convergent if the coupling reaction could be carried out on optically pure 7,7′-dibromoVANOL **13b**. That is why we were very eager to see if the present resolution method with borate esters of chinchona alkaloids would be applicable to the VANOL derivative **13b**.

In the past, we have not observed any vaulted biaryl ligand to undergo racemization during routine preparation, isolation, or purification. We have previously reported that VANOL **1** will undergo thermal racemization in octane at 200 °C to the extent of 10% after 3 h and 30% after 30 h.[2a] Both VANOL and VAPOL can be deracemized with a copper diamine complex, which is the basis of a synthetically useful method for preparing optically pure (>99% ee) VANOL or VAPOL (Scheme 1).[3] In the course of the present work, it was found

https://dx.doi.org/10.1021/acs.joc.0c00494
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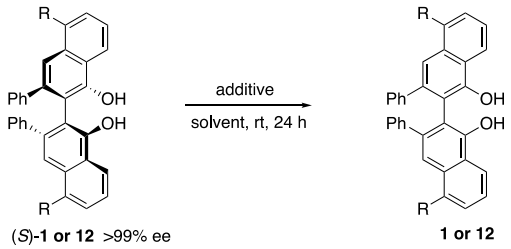
that during the isolation of the 5,5′-disubstituted ligands **12c** and **12e**, we encountered variation in the percent ee of these ligands. To further investigate this observation, a set of four optically pure (>99% ee) 5,5′-disubstituted VANOL ligands was tested for configurational stability along with VANOL itself (Table 3). In the first set of experiments, each ligand (15 mg) was allowed in stand as a solution in methylene chloride (1 mL) for 24 h (entries 1−5). After this time, the optical purity of the methyl substituted and trifluoromethyl substituted ligands **12c** and **12e** dropped from >99% ee to 74 and 22% ee, respectively (entries 2 and 5). The other two ligands with methoxy- and bromo-substituted in the 5,5′-positions as a well as VANOL were unchanged. The solvent had a big effect on the racemization. The bis-trifluoromethyl substituted ligand **12e** remained optically pure in ethyl acetate after 24 h. Regarding other biaryl ligands, Cram et al. have reported that BINOL can be racemized in either acid or base.[10] Given Cram's observations, we decided to examine the effect of various additives on the racemization (Table 3). All of the ligands were racemized by the addition of 10 mg of quinine (60−94% ee) except for VANOL, which remained optically pure. The addition of 2 M aq HCl had less effect on the racemization than quinine with only the trifluoromethyl substituted ligand **12e** being affected (93% ee). The mechanism for this racemization of 5,5′-disubstituted VANOL ligands was not further pursued but may be related to those proposed by Cram for BINOL.[10] In light of these findings regarding racemization, the protocols for the workup of the resolutions reactions (Tables 4 and 5) were modified to use ethyl acetate instead of methylene chloride in hydrolysis, extraction, and purification as well as to decrease hydrolysis time to 1 h and then to directly purify the product by chromatography to remove the quinine or quinidine from the mixture. The present resolution process became more consistent and reproducible after these modifications, as indicated by the data in Tables 4 and 5.

Table 3. Racemization of Ligands 12 and 1[a]



(*S*)-**1 or 12** >99% ee — **1 or 12**

entry	ligand	R	solvent	additive[b]	% ee **12**/**1**[c]
1	**12d**	OMe	CH_2Cl_2	none	>99
2	**12c**	Me	CH_2Cl_2	none	74
3	**1**	H	CH_2Cl_2	none	>99
4	**12a**	Br	CH_2Cl_2	none	>99
5	**12e**	CF_3	CH_2Cl_2	none	22
6	**12e**	CF_3	EtOAc	none	>99
7[d]	**12d**	OMe	CH_2Cl_2	quinine	82
8	**12c**	Me	CH_2Cl_2	quinine	60
9[d]	**1**	H	CH_2Cl_2	quinine	>99
10[d]	**12a**	Br	CH_2Cl_2	quinine	80
11[d]	**12e**	CF_3	CH_2Cl_2	quinine	94
12	**12d**	OMe	CH_2Cl_2	2 M HCl	>99
13	**12c**	Me	CH_2Cl_2	2 M HCl	>99
14	**1**	H	CH_2Cl_2	2 M HCl	>99
15	**12d**	Br	CH_2Cl_2	2 M HCl	>99
16	**12e**	CF_3	CH_2Cl_2	2 M HCl	93

[a]Unless otherwise specified, all reactions were carried out on 15 mg of ligand in 1 mL of solvent at rt for 24 h. [b]10 mg of quinine and 0.5 mL of 2 M aq HCl were used. [c]Determined by HPLC. [d]36 h.

The generality of the ability of a borane/quinine complex to resolve various ligands was examined by screening with 18 different biaryl ligands, and the results are presented in Table 4. In the case of BINOL, a solid precipitated from THF, which upon hydrolysis with aq HCl gave (*S*)-BINOL in 46% yield with 91% ee (entry 18). Hydrolysis of the material remaining in the mother liquor gave (*R*)-BINOL in 47% yield with 85% ee. The yields of the (*R*)- and (*S*)-isomers indicated in Table 4 are after purification on silica gel and after solvent removal, which in some cases includes one or two molecules of the solvent in the solid product. Attempted resolution of 6,6′-dibromoBINOL failed in that no solid was formed from a (1:2) mixture of THF and hexanes (entry 19). Incredibly, all 16 of the vaulted biaryls that were screened gave initial solids from which the free (*S*)-ligands could be liberated in >99% ee in each case. This includes VAPOL **2** and *iso*-VAPOL **10** as well as 14 different VANOL derivatives. The quinine/borane/ligands from all of the VANOL derivatives gave adducts that precipitated in all cases from THF or mixtures of THF and hexanes to give, after hydrolysis, the optically pure (*S*)-ligand in >99% ee. The exception was with 7,7′-dibromoVANOL **13b**, which gave a solid from THF, but hydrolysis gave the racemic ligand (entry 16). However, we were very gratified to find that a quinine/borane complex of 7,7′-dibromoVANOL **13b** could be precipitated from toluene and upon hydrolysis gave a 32% yield of (*S*)-7,7-dibromoVANOL with >99% ee (entries 17 vs 16).

Because it had been previously observed that a borane/quinidine complex of VANOL gave a solid from which (*R*)-VANOL could only be obtained with 66% ee (Table 1), it was a surprise to find that nearly all of the other vaulted biaryl ligands screened in this work could be obtained as optically pure (*R*)-enantiomers in >99% ee via a borane/quinidine complex (Table 5). The exception was the 7,7′-*t*-Bu_2VANOL ligand **13a**, which would not give a solid with the borane/quinidine complex (entry 11). However, optically pure ligand (*R*)-**13a** could easily be obtained from the mother liquor from the borane/quinine complex (see Scheme 8). It was quite surprising to find that while the optically pure 7,7′-Ad_2VANOL ligand **13e** could be obtained from the borane/quinidine complex, it was found to be the (*S*)-enantiomer, the same as was isolated from the borane/quinine complex. Also, as was the case of the resolution of the 7,7′-dibromoVANOL **13b** with quinine (Table 4), racemic ligand was obtained from the solid precipitated from THF, but optically pure (*R*)-ligand could be obtained from the solid precipitated from toluene in 35% yield in >99% ee (entry 16). It is also to be noted that entry 4 in Table 5 employs a sample of ligand **11b** that is enriched in the (*R*)-enantiomer (79% ee) that was taken from the mother liquor from the resolution of the racemic ligand **11b** with quinine. In this case the precipitate from the borate complex with quinidine gave upon hydrolysis pure (*R*)-**11b** in 76% yield and >99% ee.

The only two vaulted biaryls that could not be resolved to give pure (*R*)-enantiomers with quinidine (Table 5) are VANOL **1** and 7,7′-*t*-Bu_2VANOL **13a**. VANOL can be resolved on a large scale via its hydrogen phosphate **3**

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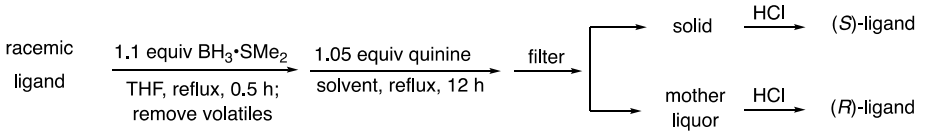
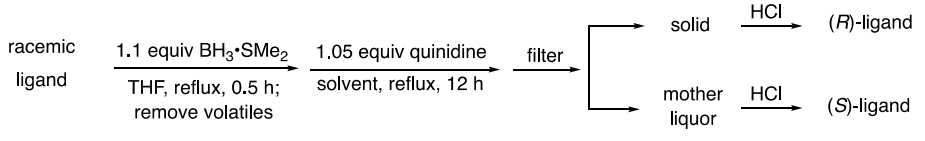
Table 4. Resolution of Vaulted Biaryl Ligands with Quinine



entry	ligand number	ligand[a]	solvent (mL/mmol)	% yield of (*S*)[b]	% ee of (*S*)	% yield of (*R*)[b]	% ee of (*R*)
1	**2**	VAPOL	THF (3)	44	>99	56	68
2	**10**	*iso*-VAPOL	THF (4)/hexanes (2)	33	>99	68	45
3	**1**	VANOL	THF (3)	46	>99	64	69
4	**11b**	3,3′-(4-MeOC$_6$H$_4$)$_2$VANOL	THF (3)/hexanes (3)	34	>99	50	59
5	**11a**	3,3′-(4-EtC$_6$H$_4$)$_2$VANOL	THF (3)/hexanes (3)	36	>99	69	60
6	**11c**	3,3′-(4-*n*-BuC$_6$H$_4$)$_2$VANOL	THF (3)/hexanes (4)	17	>99	79	24
7	**12a**	5,5′-Br$_2$VANOL	THF (4.5)	46	>99	69	72
8	**12b**	5,5′-Cl$_2$VANOL	THF (4.5)	45	>99	54	76
9	**12c**	5,5′-Me$_2$VANOL	THF (4.5)	44	>99	58	75
10	**12d**	5,5-(OMe)$_2$VANOL	THF (4)/hexanes (2)	47	>99	60	80
11	**12e**	5,5′-(CF$_3$)$_2$VANOL	THF (4)/hexanes (2)	39	>99	69	12[c]
12	**13a**	7,7′-*t*-Bu$_2$VANOL	THF (4)	35	>99	48	77
13	**13c**	7,7′-Cy$_2$VANOL	THF (8)	26	>99	80	20
14	**13d**	7,7′-*i*-amyl$_2$VANOL	THF (3)/hexanes (3)	23	>99	76	19
15	**13e**	7,7′-Ad$_2$VANOL	THF (4)	41	99	56	67
16	**13b**	7,7′-Br$_2$VANOL	THF (3)	46	0	nd	nd
17	**13b**	7,7′-Br$_2$VANOL	toluene (4)	32	>99	69	54
18	**7**	BINOL	THF (2.5)	46	91	47	85
19	**14**	6,6′-Br$_2$BINOL	THF (3)/hexanes (6)	0		nd	nd

[a]Unless otherwise specified, all resolutions were carried out on 2 mmol ligand. [b]Yields of isolated material after purification on silica gel. [c]Racemization occurs, see Table 4.

Table 5. Resolution of Vaulted Biaryl Ligands with Quinidine



entry	ligand number	ligand[a]	solvent (mL/mmol)	% yield of (*R*)[b]	% ee of (*R*)	% yield of (*S*)[b]	% ee of (*S*)
1	**2**	VAPOL	THF (3)	28	>99	68	31
2	**10**	*iso*-VAPOL	THF (7)/hexanes (3)	26	>99	70	35
3	**1**	VANOL	THF (4)/hexanes (4)	31	66	70	23
4	**11b**	3,3′-(4-MeOC$_6$H$_4$)$_2$VANOL[c]	THF (3)/hexanes (3)	76	>99	18	89
5	**11a**	3,3′-(4-EtC$_B$H$_4$)$_2$VANOL	THF (3)/hexanes (6)	45	>99	60	78
6	**12a**	5,5′-Br$_2$VANOL	THF (8)	32	>99	65	84
7	**12b**	5,5′-Cl$_2$VANOL	THF (8)	41	>99	55	84
8	**12c**	5,5′-Me$_2$VANOL	THF (8)/hexanes (4)	39	>99	60	71
9	**12d**	5,5-(OMe)$_2$VANOL	THF (8)/hexanes (4)	46	>99	63	81
10	**12e**	5,5′-(CF$_3$)$_2$VANOL	THF (8)/hexanes (4)	13	>99	87	16
11	**13a**	7,7′-*t*-Bu$_2$VANOL	THF (4)	0		nd	nd
12	**13c**	7,7′-Cy$_2$VANOL	THF (4)/hexanes (4)	24	>99	79	20
13	**13d**	7,7′-*i*-amyl$_2$VANOL	THF (3)/hexanes (3)	20	>99	81	18
14	**13e**	7,7′-Ad$_2$VANOL	THF (4)	35	99[d]	64	59[e]
15	**13b**	7,7′-Br$_2$VANOL	THF (3)	52	0	nd	nd
16	**13b**	7,7′-Br$_2$VANOL	toluene (4)	35	>99	60	57
17	**7**	BINOL	THF (2.5)	39	94	61	57
18	**14**	6,6′-Br$_2$BINOL	THF (3)/hexanes (1.5)	48	>99	55	88

[a]2 mmol ligand. [b]Yields of isolated material after purification on silica gel. [c]Starting with ligand of 79% ee. [d]The (*S*)-enantiomer is produced. [e]The (*R*)-enantiomer is produced.

(Scheme 1) as a salt with brucine,[2b] but attempts to resolve 7,7′-*t*-Bu$_2$VANOL hydrogen phosphate did not identify any chiral base that would give a solid precipitate. While the screening of other chiral bases has not been exhausted, we were able to develop a convenient route to (*R*)-7,7′-*t*-Bu$_2$VANOL by taking advantage of the observation that most other vaulted biaryl VANOL and VAPOL derivatives are much less soluble in their racemic form than their pure enantiomers.[2a]

The resolution of 7,7′-*t*-Bu$_2$VANOL into its pure (*R*)- and (*S*)-enantiomers was carried out on an 8-fold increased scale

https://dx.doi.org/10.1021/acs.joc.0c00494
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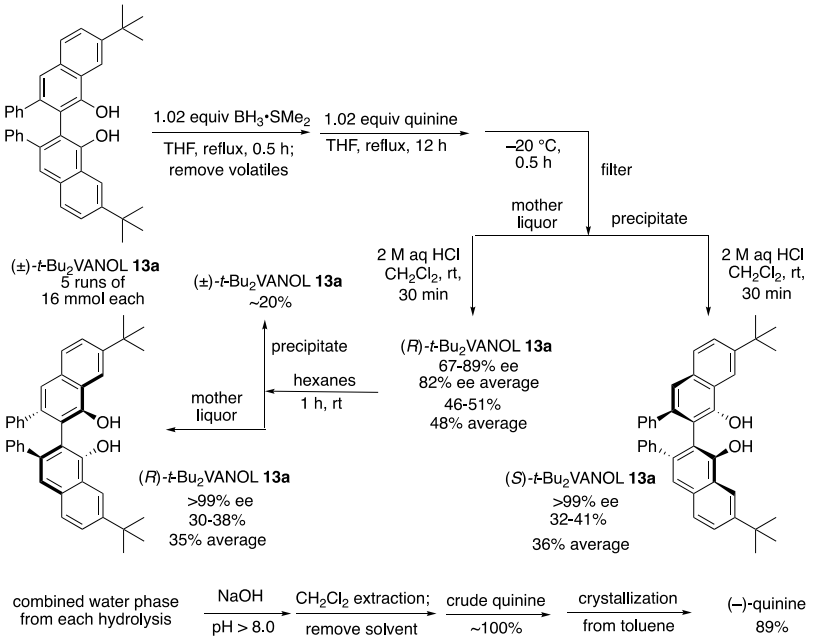
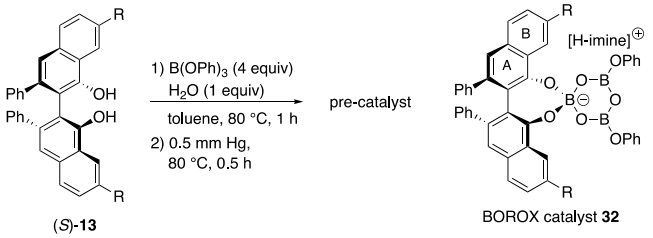
Scheme 8. Large Scale Resolution of 7,7′-Di-*t*-butylVANOL 13a with Quinine to Give (*S*)-13a and Enhancement of the Optical Purity of (*R*)-13a



over that used in Table 4 (5 independent runs on a 16 mmol scale), and the results are summarized in Scheme 8. Thus, upon generating the borane/quinine complex with racemic 7,7′-*t*-Bu$_2$VANOL, the precipitate was separated to give after hydrolysis (*S*)-7,7′-*t*-Bu$_2$VANOL **13a** in >99% ee in 36% yield averaged over 5 runs. The mother liquor was hydrolyzed to give scalemic 7,7′-*t*-Bu$_2$VANOL that was enriched in the (*R*)-enantiomer to the extent of 67−89% ee over 5 runs in 48% average yield. Because the formation of the (*R*)-enantiomer **13a** did not work with quinidine (Table 5), this material was allowed to stand in hexanes at rt for 1 h. The solution phase was separated and solvent removed to give (*R*)-7,7′-*t*-Bu$_2$VANOL in >99% ee in 35% overall yield from racemic **13a** (average over five runs). In addition, recovery of quinine was achieved by combining the two different aqueous phases from hydrolysis with HCl and, after treatment with aqueous sodium hydroxide and then extraction into methylene chloride, the crude quinine was obtained, which could be crystallized from toluene to give pure (−)-quinine in 89% yield.

In the catalytic asymmetric aziridination of imines with diazo compounds that we developed with VANOL and VAPOL ligands and their derivatives, a BOROX catalyst derived from the 7,7′-*t*-Bu$_2$VANOL ligand **13a** gave the highest induction.[4] The catalyst was generated by treatment of ligand **13a** with triphenylborate and water at 80 °C for 1 h and then removal of all volatiles to leave a precatalyst (Scheme 9). Upon exposure of the precatalyst to the imine substrate, the BOROX catalyst **32** is generated,[11] which then catalyzes the reaction of the imine and diazo ester **34** to give an aziridine with high yields, diastereoselectivities, and enantioselectivities.[12] The catalyst generated from the 7,7′-*t*-Bu$_2$VANOL ligand **13a** gives the aziridine **35a** in 89% yield and 95% ee as only the *cis*-diastereomer from the benzhydryl imine of benzaldehyde and the aziridine **35b** in 88% yield and 94% ee as only the *cis*-diastereomer from the benzhydryl imine of cyclohexane carboxaldehyde (Scheme 9).[4] By comparison, a catalyst generated from the 7,7′-Ad$_2$VANOL ligand **13e**, which is

Scheme 9. Comparison of the Aziridination of Imines 33a and 33b with BOROX Catalysts Generated from 7,7′-Disubstituted Ligands 13a and 13e



ligand	R	35a R^1 = Ph % Yield	35a R^1 = Ph %ee	35b R^1 = Cy % Yield	35b R^1 = Cy %ee
13a	*t*-butyl	89	95	88 [a]	94 [a]
13e	1-adamantyl	88	96	75	93

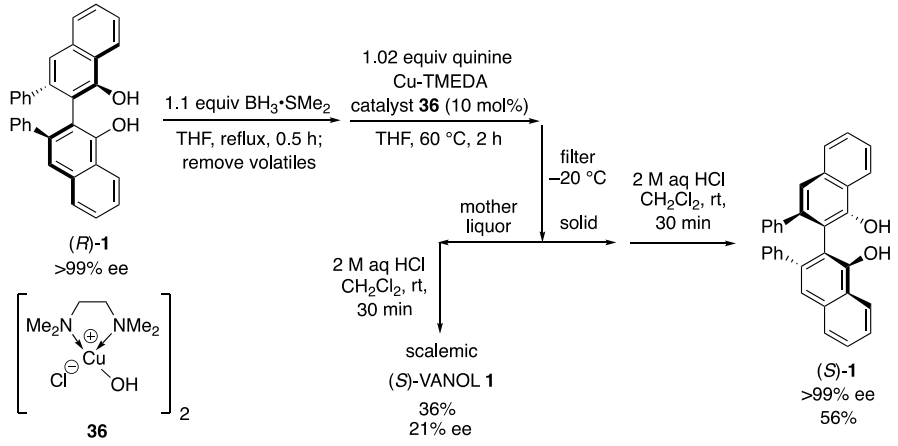
[a]Reference 4.

described here for the first time, gave the aziridines **35a** in 88% yield and 96% ee as only the *cis*-diastereomer and the aziridine **35b** in 75% yield and 93% ee as only the *cis*-diastereomer (Scheme 9). Although these asymmetric inductions for these two ligands are within experimental error, it is interesting that the presence of the adamantyl groups does not impede the reaction and still gives excellent inductions. Therefore, the adamantyl VANOL ligand **13e** will be among those considered in screening borate catalysts for other reactions.

Previously, the best method[3] for the resolution of vaulted biaryl ligands, on a small scale at least, was the deracemization with a stoichiometric copper complex of sparteine in a dynamic

https://dx.doi.org/10.1021/acs.joc.0c00494
J. Org. Chem. XXXX, XXX, XXX−XXX

Scheme 10. Proof-of-Principle for a Catalytic Dynamic Thermodynamic Resolution of VANOL with Copper Diamine Complex 36 and Quinine



thermodynamic resolution (Scheme 1).[13] This involved a copper(II) species of the racemic VANOL or VAPOL ligand which was complexed with the diamine unit in either (−)- or (+)-sparteine. The resulting mixture of diastereomeric complexes undergo epimerization at the ligand to give the most thermodynamically stable diastereomer from which optically pure ligand can be liberated from the stoichiometric copper complex. In the present method a borane complex of VANOL or VAPOL is treated with an alkaloid base that binds to the boron and one of the resulting diastereomers selectively precipitates from solution. It would be of interest to couple these two methods where the copper causes epimerization of the vaulted biaryl ligand and the nature of the alkaloid base that is used would determine which diastereomeric complex precipitated from solution. In such a scenario, the copper could be used in substoichiometric amount because it would not be the stability of a copper(II) sparteine complex that shifts the equilibrium. In a proof-of-principal experiment the commercially available achiral copper complex of TMEDA **36** (10 mol %) was added to a mixture of optically pure (*R*)-VANOL/borane complex and along with 1.02 equiv of quinine (Scheme 10). This mixture was heated in THF at 60 °C for 2 h, and then the precipitate was filtered and hydrolyzed to give (*S*)-VANOL in 56% yield that was >99% ee. The mother liquor was hydrolyzed to give an additional 36% yield of VANOL that was 21% ee enriched in the (*S*)-enantiomer. This represents a 78% conversion of the (*R*)-enantiomer to the (*S*)-enantiomer. This experiment suggests that it should be possible to selectively convert a racemic vaulted biaryl ligand selectively to one enantiomer or the other. Optimization of this process will likely involve the optimization of the nature of the diamine in the nonchiral copper complex, the catalyst loading of the copper complex, the reaction temperature and reaction time.

3. CONCLUSIONS

A new method for the resolution of vaulted biaryl ligands has been developed involving the use of cinchona alkaloids as resolving agents. The racemic ligand is reacted with $BH_3{\cdot}SMe_2$ and then with quinine or quinidine. After filtration of the precipitate that forms, the (*S*)-ligand can be liberated by hydrolysis of the borate complex from quinine in greater than 99% ee. Likewise, the (*R*)-ligand from the borate complex with quinidine can also be obtained in greater than 99% ee. This holds true for 16 different vaulted biaryl ligands of VANOL and VAPOL with the single exception of the 7,7′-di-1-adamantylVANOL ligand, which is described here for the first time. Resolution of this ligand gives the (*S*)-enantiomer in >99% ee from either the quinine or quinidine borate complex. This work describes the synthesis and resolution of nine new vaulted biaryl VANOL derivatives. Of the four new VANOL ligands with substituents in the 5- and 5′-positions, two were found to epimerize (methyl and trifluoromethyl), but the unsubstituted VANOL ligand did not. Finally, it was demonstrated that a dynamic thermodynamic resolution of VANOL is possible by utilizing this borate process coupled with a catalytic amount of a copper(II) complex.

4. EXPERIMENTAL SECTION

General Experimental. All reactions were carried out in flame-dried glassware under an atmosphere of nitrogen unless otherwise indicated. Unless otherwise specified, all solvents were strictly dried before use: dichloromethane was distilled over calcium hydride under nitrogen; tetrahydrofuran and diethyl ether were distilled from sodium and benzophenone, and toluene was distilled from sodium under nitrogen. Hexanes and ethyl acetate were ACS grade and used as purchased.

Melting points (mp) were recorded on a Thomas-Hoover capillary melting point apparatus and are uncorrected. IR spectra were recorded in KBr matrix (for solids) and on NaCl disc (for liquids) on a Nicolet IR/42 spectrometer. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Inova 300 MHz or Varian Unity Plus 500 MHz or Varian Inova 600 MHz spectrometer using $CDCl_3$ as solvent (unless otherwise noted). The residual peak of $CDCl_3$ or TMS was used as the internal standard for both ^{1}H NMR (δ = 7.24 ppm for $CDCl_3$ or δ = 0 ppm for TMS) and ^{13}C NMR (δ = 77.0 ppm). Chemical shifts were reported in parts per million (ppm). High resolution mass spectrometry was performed by the Department of Chemistry at the Michigan State University Mass Facility.

Analytical thin-layer chromatography (TLC) was performed on Silicycle silica gel plates with F-254 indicator. Visualization was by short wave (254 nm) and long wave (365 nm) ultraviolet light or by staining with potassium permanganate. Column chromatography was performed with silica gel 60 (230−450 mesh). HPLC analyses were performed using a Varian Prostar 210 Solvent Delivery Module with a Prostar 330 PDA Detector and a Prostar Workstation.

Optical rotations were obtained at a wavelength of 589 nm (sodium D line) using a 1.0 decimeter cell with a total volume of 1.0 mL. Specific rotations are reported in degrees per decimeter at 20 °C, and the concentrations are given in gram per 100 mL in ethyl acetate unless otherwise noted.

https://dx.doi.org/10.1021/acs.joc.0c00494
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Synthesis of 5,5′-R_2VANOL Ligands (Table 2). General procedure A1 for the CEC process with thionyl chloride, illustrated for the synthesis of 5-bromo-3-phenyl-1-naphthol **19a** from 2-(2-bromophenyl)acetic acid **15a**.

*5-Bromo-3-phenyl-1-naphthol **19a**.* An oven-dried 500 mL round-bottomed flask equipped with an egg-shaped stirring bar (30 × 15 mm) and a condenser is placed under a nitrogen atmosphere through a gas inlet. After cooling to 23 °C, 2-(2-bromophenyl)acetic acid **15a** (21.505 g, 100.51 mmol) is added followed by addition of thionyl chloride (15.0 mL, freshly distilled, 200 mmol, 2.00 equiv). The condenser is vented by an adaptor to a bubbler and then into a beaker filled with aqueous sodium hydroxide solution to trap acid gases. The mixture is heated in a 70 °C oil bath until the gas evolution ceases (1 h). The excess of thionyl chloride was removed by distillation under aspirator pressure (60 °C oil bath, ∼25 mmHg). Anhydrous toluene (40 mL) is added, and the mixture is distilled under aspirator pressure again. The process is repeated twice to ensure complete removal of all excess thionyl chloride. The crude mixture is then vacuum-dried at room temperature for 1 h to remove the excess toluene. The reaction flask containing the crude acid chloride is filled with nitrogen, and then phenylacetylene (15.0 mL, 130 mmol, 1.30 equiv) and isobutyric anhydride (33.0 mL, 200 mmol, 2.00 equiv) are added. The flask is fitted with a condenser flushed with nitrogen with a Teflon sleeve in the joint and Teflon tape wrapped around the joint to secure a tight seal. The reaction mixture was heated and stirred in a 190 °C oil bath for 48 h with a gentle nitrogen flow across the top of the condenser. The brown reaction mixture is cooled to about 60 °C (oil bath temperature), and an aqueous solution of potassium hydroxide (33.4 g, 0.600 mol, 6.00 equiv) in 120 mL of water is slowly added. After stirring in a 100 °C oil bath overnight (12 h), the orange solution is cooled to room temperature; diethyl ether (300 mL) is added, and the mixture is stirred for 30 min before the organic layer is isolated in a 2 L separatory funnel. The water layer is extracted twice with diethyl ether (300 mL × 2), and the combined organic layer is washed with brine (300 mL), dried over anhydrous magnesium sulfate, and filtered. The dark-colored organic solution is concentrated in vacuo using a rotary evaporator (40 °C, 15 mmHg), and the residue is dried under high vacuum (23 °C, 0.2 mmHg) overnight to give 40 g of the dark brown crude product. Recrystallization from dichloromethane/hexanes and column chromatography (silica gel, dichloromethane/hexanes: 1:3 to 1:1) gave the product **19a** as an off-white solid in 67% yield from **15a** (20.074 g, mp 133−134 °C, 67.362 mmol). Spectral data for **19a**: R_f = 0.48 (ethyl acetate/hexanes 1:4); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.12 (d, J = 1.5 Hz, 1H), 7.29 (dd, J = 8.4, 7.4 Hz, 1H), 7.35−7.44 (m, 1H), 7.41−7.53 (m, 2H), 7.63−7.75 (m, 2H), 7.80 (dd, J = 7.4, 1.1 Hz, 1H), 8.02 (dd, J = 1.5, 0.9 Hz, 1H), 8.18 (dt, J = 8.4, 1.0 Hz, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 109.1, 118.1, 121.6, 123.0, 124.8, 125.4, 127.5, 127.8, 128.9, 131.1, 133.42, 140.2, 140.6, 151.9. These spectral data match those previously reported for this compound.[4]

General procedure B for oxidative coupling of VANOL monomers, illustrated for the synthesis of 5,5′-Br_2VANOL **12a** from 5-bromo-3-phenyl-1-naphthol **19a**.

*5,5′-Br_2VANOL **12a**.* An oven-dried 250 mL three-necked round-bottomed flask equipped with an egg-shaped stirring bar (30 × 15 mm) is placed under a nitrogen atmosphere through a gas inlet. After cooling to 23 °C, naphthol **19a** (29.92 g, 100.0 mmol) is added by a funnel followed by the addition of 110 mL of light mineral oil through the same funnel, and then an oven-dried reflux condenser is attached. A needle is introduced into the flask via the second neck to about 5 cm above the surface of the naphthol solution and is used to provide a stream of house air which is maintained at a flow rate of 0.15−0.20 L/min. The third neck is sealed with a rubber septum. The stir bar in the oil bath was removed before the flask is introduced into the oil bath to warm it for about 15 min until the solid was melted. Airflow is allowed to flow into the flask while the molten **19a** is stirred as fast as possible. The airflow is switched to nitrogen after the reaction is kept at 165 °C for 36 h. The flask is removed from the oil bath and cooled to room temperature before hexanes (100 mL) are added to the flask. The mixture is stirred for 30 min and then cooled to −20 °C overnight (12 h) before the solid is collected by suction filtration. The crude product is dried on high vacuum and crystallized from dichloromethane. The dark-colored solution is cooled to room temperature and then to −20 °C overnight (12 h). The brown crystals are collected via suction filtration, washed with hexanes, and dried under vacuum to give **12a** (27.488 g, mp >260 °C, 46.280 mmol, 92%). Spectral data for **12a**: R_f = 0.40 (ethyl acetate/hexanes 1:4); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.78 (s, 2H), 6.61−6.69 (m, 4H), 6.97−7.04 (m, 4H), 7.11 (t, J = 7.3 Hz, 2H), 7.35−7.43 (m, 2H), 7.70 (s, 2H), 7.86 (d, J = 7.5 Hz, 2H), 8.33 (d, J = 8.3 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 113.3, 121.3, 122.7, 122.7, 124.1, 126.0, 127.1, 127.7, 128.9, 131.8, 133.2, 139.7, 141.9, 150.4. These spectral data match those previously reported for this compound.[4]

*5-Chloro-3-phenyl-1-naphthol **19b**.* 1-Naphthol **19b** was prepared from 2-(2-chlorophenyl)acetic acid **15b** (17.06 g, 100.4 mmol) using the general procedure A1. The crude product was purified by recrystallization from dichloromethane/hexanes and column chromatography (silica gel, dichloromethane/hexanes: 1:3 to 1:1) to give **19b** as a white crystal in 71% isolated yield from **15b** (18.013 g, mp 127−128 °C, 71.186 mmol). Spectral data for **19b**: R_f = 0.28 (ethyl acetate/hexanes 1:4); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.11 (d, J = 1.6 Hz, 1H), 7.29−7.44 (m, 2H), 7.42−7.56 (m, 2H), 7.60 (dd, J = 7.4, 1.1 Hz, 1H), 7.63−7.74 (m, 2H), 8.06 (dd, J = 1.5, 1.0 Hz, 1H), 8.13 (dt, J = 8.4, 1.0 Hz, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 109.2, 115.3, 120.8, 124.8, 124.9, 127.3, 127.4, 127.8, 128.9, 132.1, 132.3, 140.0, 140.6, 151.9. HRMS (ESI$^-$) m/z [M − H]$^-$ Calcd for $C_{16}H_{10}OCl$ 253.0420; Found 253.0430.

*5,5′-Cl_2VANOL **12b**.* VANOL derivative **12b** was prepared from 5-chloro-3-phenylnaphthalen-1-ol **19b** (12.74 g, 50.35 mmol) using the general procedure B with heating at 165 °C for 24 h. The crude product was purified by recrystallization from dichloromethane/hexanes and column chromatography (silica gel, dichloromethane/hexanes: 1:3 to 1:1) to give **12b** as an off-white solid in 75% isolated yield (9.500 g, mp 253−255 °C 18.81 mmol). Spectral data for **12b**: R_f = 0.40 (ethyl acetate/hexanes 1:4); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.87 (s, 2H), 6.63−6.74 (m, 4H), 6.96−7.07 (m, 4H), 7.13 (td, J = 7.3, 1.3 Hz, 2H), 7.47 (dd, J = 8.4, 7.5 Hz, 2H), 7.68 (dd, J = 7.5, 1.1 Hz, 2H), 7.76 (d, J = 1.0 Hz, 2H), 8.31 (dt, J = 8.4, 1.0 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 113.4, 118.6, 122.0, 124.1, 125.5, 127.0, 127.6, 127.9, 128.9, 131.9, 132.0, 139.7, 141.7, 150.5. HRMS (ESI$^-$) m/z [M − H]$^-$ Calcd for $C_{32}H_{19}O_2Cl_2$ 505.0762; Found 505.0805

*5-Methyl-3-phenyl-1-naphthol **19c**.* 1-naphthol **19c** was prepared from 2-(2-methylphenyl)acetic acid **15c** (15.02 g, 100.0 mmol) using the general procedure A1. The crude product was purified by recrystallization from dichloromethane/hexanes and column chromatography (silica gel, dichloromethane/hexanes: 1:3 to 1:1) to give **19c** as a white crystal in 52% isolated yield from **15c** (12.166 g, 52.420 mmol). Spectral data for **19c**: R_f = 0.48 (ethyl acetate/hexanes 1:4); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.71 (d, J = 0.9 Hz, 3H), 7.08 (d, J = 1.5 Hz, 1H), 7.33−7.40 (m, 3H), 7.44−7.51 (m, 2H), 7.59−7.71 (m, 2H), 7.71−7.89 (m, 1H), 8.01−8.13 (m, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 19.9, 108.3, 115.3, 119.6, 123.5, 125.0, 127.4, 127.4, 127.7, 128.8, 134.1, 134.5, 138.7, 141.4, 152.1. HRMS (ESI$^-$) [M − H]$^-$ m/z Calcd for $C_{17}H_{13}O$ 232.0888; Found 232.0890.

*5,5′-Me_2VANOL **12c**.* VANOL derivative **12c** was prepared from 5-methyl-3-phenyl-1-naphthol **19c** (11.720 g, 50.498 mmol) using the general procedure B with heating at 165 °C for 24 h. The crude product was purified by recrystallization from dichloromethane/hexanes and column chromatography (silica gel, dichloromethane/hexanes: 1:3 to 1:1) to give **12c** as an off-white solid in 72% isolated yield (8.4516 g, mp 248−251 °C, 18.168 mmol). Spectral data for **12c**: R_f = 0.53 (ethyl acetate/hexanes 1:4); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.64 (s, 6H), 5.82 (s, 2H), 6.67 (d, J = 7.4 Hz, 4H), 6.99 (t, J = 6.9 Hz, 4H), 7.05−7.13 (m, 2H), 7.41 (d, J = 6.5 Hz, 2H), 7.43−7.48 (m, 4H), 8.24 (d, J = 8.2 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 19.6, 112.5, 118.5, 121.0, 122.9, 125.3, 126.5, 127.5, 128.2, 129.0, 133.8, 134.3, 140.4, 140.6, 150.7. HRMS (ESI$^-$) m/z: [M − H]$^-$ Calcd for $C_{34}H_{25}O_2$ 465.1855; Found 465.1839

https://dx.doi.org/10.1021/acs.joc.0c00494
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5-Methoxy-3-phenyl-1-naphthol ***19d***. 1-Naphthol **19d** was prepared from 2-(2-methoxyphenyl)acetic acid **15d** (16.618 g, 100.07 mmol) using the general procedure A1. The crude product was purified by recrystallization from dichloromethane/hexanes and column chromatography (silica gel, dichloromethane/hexanes: 1:3 to 1:1) to give **19d** as a white crystal in 52% isolated yield from **15d** (13.042 g, mp 142−143 °C, 52.036 mmol). Spectral data for **19d**: R_f = 0.42 (ethyl acetate/hexanes 1:4); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.00 (s, 3H), 6.86 (dd, J = 7.7, 0.9 Hz, 1H), 7.12 (d, J = 1.6 Hz, 1H), 7.27−7.52 (m, 4H), 7.70 (ddt, J = 10.6, 7.8, 1.0 Hz, 3H), 8.07 (dd, J = 1.7, 0.9 Hz, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 55.6, 104.8, 109.0, 113.0, 113.5, 124.4, 125.4, 127.1, 127.3, 127.3, 128.7, 138.1, 141.1, 151.5, 155.7. HRMS (ESI$^-$) *m/z*: [M − H]$^-$ Calcd for $C_{17}H_{13}O_2$ 249.0916; Found 249.0937.

5,5′-OMe$_2$*VANOL* ***12d***. VANOL derivative **12d** was prepared from 5-methoxy-3-phenyl-1-naphthol **19d** (12.520 g, 50.263 mmol) using the general procedure B with heating at 165 °C for 24 h. The crude product was purified by recrystallization from dichloromethane/hexanes and column chromatography (silica gel, dichloromethane/hexanes: 1:3 to 1:1) to give **12d** as an off-white solid in 72% isolated yield (8.9962 g, mp >260 °C 19.340 mmol). Spectral data for **12d**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.97 (s, 6H), 5.78 (s, 2H), 6.67 (d, J = 7.5 Hz, 4H), 6.90 (d, J = 7.8 Hz, 2H), 6.93−7.00 (m, 4H), 7.02−7.11 (m, 2H), 7.42−7.50 (m, 2H), 7.74 (s, 2H), 7.91 (d, J = 8.4 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 55.5, 105.3, 113.4, 114.8, 116.2, 123.8, 125.7, 126.4, 126.7, 127.4, 128.9, 139.9, 140.5, 150.1, 155.3. HRMS (ESI$^-$) *m/z*: [M − H]$^-$ Calcd for $C_{34}H_{25}O_2$ 465.1655; Found 465.1649.

5-Trifluoromethyl-3-phenyl-1-naphthol ***19e***. 1-Naphthol **19e** was prepared from 2-(2-trifluoromethylphenyl)acetic acid **15e** (20.42 mL, 100.0 mmol) using the general procedure A1. The crude product was purified by recrystallization from dichloromethane/hexanes and column chromatography (silica gel, dichloromethane/hexanes: 1:3 to 1:1) to give **19e** as a white crystal in 66% isolated yield from **15e** (19.206 g, mp 122−123 °C, 66.904 mmol). Spectral data for **19e**: R_f = 0.48 (ethyl acetate/hexanes 1:4); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.46 (s, 1H), 7.14 (d, J = 1.4 Hz, 1H), 7.32−7.55 (m, 4H), 7.61−7.73 (m, 2H), 7.78−8.03 (m, 2H), 8.43 (d, J = 8.4 Hz, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 109.1, 115.2, 115.2, 123.5, 124.2, 125.8 (q, J = 5 Hz), 125.9, 126.5, 127.5, 127.9, 129.0, 130.5, 140.6, 140.8, 152. HRMS (ESI$^-$) *m/z*: [M − H]$^-$ Calcd for $C_{17}H_{10}F_3O$ 287.0684; Found 287.0682.

5,5′-(CF$_3$*)*$_2$*VANOL* ***12e***. VANOL derivative **12e** was prepared from 5-trifluoromethyl-3-phenyl-1-naphthol **19e** (14.41, 50.20 mmol) using the general procedure B with heating at 165 °C for 24 h. The crude product was purified by recrystallization from dichloromethane/hexanes and column chromatography (silica gel, dichloromethane/hexanes: 1:3 to 1:1) to give **12e** as an off-white solid in 65% isolated yield (9.382 g, mp >260 °C, 16.37 mmol). Spectral data for **12e**: R_f = 0.32 (dichloromethane/hexanes 1:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.84 (d, J = 18.0 Hz, 2H), 6.58−6.71 (m, 4H), 7.00 (td, J = 7.8, 2.8 Hz, 4H), 7.06−7.18 (m, 2H), 7.54−7.68 (m, 4H), 7.96 (d, J = 7.2 Hz, 2H), 8.58 (d, J = 8.4 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 113.1, 113.2, 118.5, 123.5, 123.6, 124.1, 125.6, 125.8, 126.1, 126.4, 126.4, 126.5, 126.5, 127.2, 127.4, 127.7, 128.8, 130.3, 139.5, 139.6, 142.3, 150.7, 150.7. ^{19}F NMR (470 MHz, $CDCl_3$) δ −59.76 (s). HRMS (ESI$^-$) *m/z*: [M − H]$^-$ Calcd for $C_{34}H_{19}F_6O_2$ 573.1289; Found 573.1265.

Synthesis of 3,3′-R_2*VANOL Ligands (Scheme 4).* General procedure A3 for the CEC process with 2-phenylacetyl chloride, illustrated for the synthesis the of 3-(4-ethylphenyl)-1-naphthol **21a** with 1-ethyl-4-ethynylbenzene.

3-(4-Ethylphenyl)-1-naphthol ***21a*** *(Scheme 4).* An oven-dried 500 mL round-bottomed flask equipped with an egg-shaped stirring bar (30 × 15 mm) and a condenser is placed under a nitrogen atmosphere through a gas inlet. After cooling to 23 °C, 2-phenylacetyl chloride (13.22 mL, 100.0 mmol, 1.000 equiv) is added followed by 1-ethyl-4-ethynylbenzene **20a** (18.2 mL, 130 mmol, 1.30 equiv) and isobutyric anhydride (33.0 mL, 200 mmol, 2.00 equiv). The flask is fitted with a condenser flushed with nitrogen with a Teflon sleeve in the joint and Teflon tape wrapped around the joint to secure a tight seal. The reaction mixture was heated and stirred in a 190 °C oil bath for 48 h with a gentle nitrogen flow across the top of the condenser. The brown reaction mixture is cooled to about 60 °C (oil bath temperature), and an aqueous solution of potassium hydroxide (33.4 g, 0.600 mol, 6.00 equiv) in 120 mL of water is slowly added. After stirring in a 100 °C oil bath overnight (12 h), the orange solution is cooled to room temperature; diethyl ether (300 mL) is added, and the mixture stirred for 30 min before the organic layer is isolated in a 2 L separatory funnel. The water layer is extracted twice with diethyl ether (300 mL× 2), and the combined organic layer is washed with brine (300 mL), dried over anhydrous magnesium sulfate and filtered. The dark-colored organic solution is concentrated in vacuo using a rotary evaporator (40 °C, 15 mmHg) and the residue is dried under high vacuum (23 °C, 0.2 mmHg) overnight to give 40 g of the dark brown crude product. Recrystallization from dichloromethane/hexanes and column chromatography (silica gel, dichloromethane/hexanes: 1:3 to 1:1) gave the product **21a** as an off-white solid (15.2948 g, mp 117−120 °C, 61.8942 mmol) in a yield of 62% from phenylacetyl chloride. Spectral data for **21a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.28 (t, J = 7.6, 3H), 2.70 (q, J = 7.6 Hz, 2H), 5.26 (s, 1H), 7.07 (d, J = 1.7 Hz, 1H), 7.26−7.35 (m, 2H), 7.48 (dddd, J = 18.0, 8.1, 6.8, 1.4 Hz, 2H), 7.56−7.68 (m, 3H), 7.79−7.89 (m, 1H), 8.15 (ddd, J = 8.0, 1.6, 0.8 Hz, 1H). ^{13}C{ ^{1}H} NMR (126 MHz, $CDCl_3$) δ 15.6, 28.5, 108.4, 118.5, 121.4, 123.4, 125.2, 126.8, 127.2, 128.0, 128.4, 135.0, 138.2, 138.8, 143.7, 151.6. HRMS (ESI$^-$) *m/z*: [M − H]$^-$ Calcd for $C_{18}H_{15}O$ 247.1123; Found 247.1138.

3,3′-pEtPh$_2$*VANOL* ***11a*** *(Scheme 4).* VANOL derivative **11a** was prepared from 3-(4-ethylphenyl)-1-naphthol **21a** (12.416 g, 50.244 mmol) using the general procedure B with heating at 165 °C for 36 h. The crude product was purified by recrystallization from dichloromethane/hexanes and column chromatography (silica gel, dichloromethane/hexanes: 1:3 to 1:1) to give **11a** as an off-white solid in 63% isolated yield (7.823 g, mp 178−180 °C, 15.86 mmol). Spectral data for **11a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.15 (td, J = 7.6, 0.9 Hz, 6H), 2.51 (q, J = 7.6 Hz, 4H), 5.79 (d, J = 1.1 Hz, 2H), 6.51−6.63 (m, 4H), 6.79 (d, J = 8.0 Hz, 4H), 7.34 (s, 2H), 7.47−7.61 (m, 4H), 7.73−7.84 (m, 2H), 8.34 (ddd, J = 7.4, 2.2, 0.9 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz $CDCl_3$) δ 15.6, 28.4, 112.8, 121.9, 122.8, 122.8, 125.4, 127.0, 127.4, 127.6, 128.7, 134.6, 137.5, 140.7, 142.6, 150.2. HRMS (ESI$^-$) *m/z*: [M − H]$^-$ Calcd for $C_{36}H_{29}O_2$ 493.2168; Found 493.2176.

3-(4-Methoxyphenyl)-1-naphthol ***21b*** *(Scheme 4).* 1-Naphthol **21b** was prepared from 4-ethynylanisole **20b** (17.2 mL, 130 mmol) using the general procedure A3. The crude product was purified by recrystallization from dichloromethane/hexanes and column chromatography (silica gel, dichloromethane/hexanes: 1:3 to 1:1) to give **21b** as an off-white crystal in 47% isolated yield from phenylacetal chloride (11.8537 g, mp 155−156 °C, 47.5877 mmol). Spectral data for **21b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.85 (s, 3H), 5.29 (s, 1H), 6.96−7.02 (m, 2H), 7.03−7.06 (m, 1H), 7.47 (dddd, J = 20.2, 8.1, 6.8, 1.4 Hz, 2H), 7.57−7.64 (m, 3H), 7.80−7.86 (m, 1H), 8.14 (ddd, J = 8.2, 1.5, 0.8 Hz, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 55.4, 108.2, 114.3, 118.0, 121.4, 123.2, 125.0, 126.8, 127.9, 128.3, 133.4, 135.0, 138.5, 151.6, 159.3. HRMS (ESI$^-$) *m/z*: [M − H]$^-$ Calcd for $C_{17}H_{13}O$ 249.0916; Found 249.0937. These spectral data match those previously reported for this compound.[16]

3,3′-pOMePh$_2$*VANOL* ***11b*** *(Scheme 4).* VANOL derivative **11b** was prepared from 5-methoxy-3-phenylnaphthalen-1-ol **21b** (11.264 g, 45.220 mmol, 1.00 equiv) using the general procedure B with heating at 165 °C for 36 h. The crude product was purified by recrystallization from dichloromethane/hexanes and column chromatography (silica gel, dichloromethane/hexanes: 1:3 to 1:1) to give **11b** as an off-white solid in 68% (76% brsm) isolated yield (7.6002 g, mp 243−244 °C, 15.287 mmol). Spectral data for **11b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.68 (s, 6H), 5.79 (s, 2H), 6.51 (d, J = 9.8 Hz, 4H), 6.61 (d, J = 8.3 Hz, 4H), 7.30 (s, 2H), 7.45−7.58 (m, 4H), 7.77 (d, J = 7.1 Hz, 2H), 8.32 (d, J = 7.8 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 55.1, 112.9, 112.9, 121.8, 122.7, 122.8, 125.4, 127.4, 127.6,

https://dx.doi.org/10.1021/acs.joc.0c00494
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129.9, 132.8, 134.6, 140.3, 150.2, 158.4. HRMS (ESI^-) *m/z*: $[M - H]^-$ Calcd for $C_{34}H_{25}O_4$ 497.1753; Found 497.1792.

*3-(4-Butylphenyl)-1-naphthol **21c***. 1-Naphthol **21c** was prepared from 1-butyl-4-ethynylbenzene **20c** (22.7 mL, 130 mmol, 1.30 equiv) using the general procedure A3. The crude product was purified by recrystallization from dichloromethane/hexanes and column chromatography (silica gel, dichloromethane/hexanes: 1:3 to 1:1) to give **21c** as a yellow crystal in 58% combined isolated yield (15.96 g, mp 110−111 °C, 57.70 mmol). Spectral data for **21c**: ^1H NMR (500 MHz, $CDCl_3$) δ 0.94 (t, J = 7.3 Hz, 3H), 1.39 (h, J = 7.4 Hz, 2H), 1.59−1.70 (m, 2H), 2.66 (t, J = 7.6 Hz, 2H), 5.24 (s, 1H), 7.07 (d, J = 1.6 Hz, 1H), 7.27 (d, J = 7.9 Hz, 2H), 7.43−7.54 (m, 2H), 7.58 (d, J = 8.1 Hz, 2H), 7.63 (s, 1H), 7.83 (d, J = 8.1 Hz, 1H), 8.15 (d, J = 8.3 Hz, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 14.0, 22.4, 33.7, 35.3, 108.4, 118.5, 121.4, 123.4, 125.2, 126.9, 127.1, 128.0, 128.9, 135.0, 138.2, 138.9, 142.4, 151.6. HRMS (ESI−) *m/z*: $[M - H]^-$ Calcd for $C_{20}H_{19}O$ 275.1436; Found 275.1458.

*3,3′-pBuPh$_2$VANOL **11c***. VANOL derivative **11c** was prepared from 3-(4-butylphenyl)-1-naphthol **21c** (13.82 g, 50.00 mmol, 1.30 equiv) using the general procedure B with heating at 165 °C for 36 h. The crude product was purified by recrystallization from dichloromethane/hexanes and column chromatography (silica gel, dichloromethane/hexanes: 1:3 to 1:1) to give **11c** as a yellow solid in 49% combined isolated yield (6.798 g, mp 161−163 °C, 12.30 mmol). Spectral data for **11c**: ^1H NMR (500 MHz, $CDCl_3$) δ 0.89 (t, J = 7.3 Hz, 6H), 1.21−1.35 (m, 4H), 1.42−1.58 (m, 5H), 2.46 (t, J = 7.7 Hz, 4H), 5.79 (s, 2H), 6.54 (d, J = 7.5 Hz, 4H), 6.75 (d, J = 8.0 Hz, 4H), 7.33 (s, 2H), 7.47−7.59 (m, 4H), 7.78 (d, J = 7.3 Hz, 2H), 8.33 (d, J = 7.4 Hz, 2H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 14.0, 22.3, 33.6, 35.1, 112.9, 121.9, 122.8, 122.8, 125.5, 127.4, 127.5, 127.6, 128.7, 134.6, 137.4, 140.7, 141.2, 150.2. HRMS (ESI−) *m/z*: $[M - H]^-$ Calcd for $C_{40}H_{37}O_2$ 549.2794; Found 549.2801.

*2-(4-Adamantylphenyl)acetic Acid **26e** (Scheme 5). 1-Phenyladamantane **23***. An oven-dried 250 mL round-bottomed flask equipped with an egg-shaped stirring bar (30 × 15 mm) is placed under a nitrogen atmosphere through a gas inlet. After cooling to 23 °C, bromobenzene **39** (7.90 mL, 75.0 mmol, 1.50 equiv) and anhydrous diethyl ether (75 mL) was added. The solution was cooled to 0 °C in an ice bath for 10 min. To the round-bottom flask magnesium (1.82 g, 75.0 mmol, 1.50 equiv) was added and activated with 1 drop of chlorotrimethylsilane under nitrogen. The reaction mixture was stirred at room temperature for 2 h. After completion of the reaction, the diethyl ether solution of Grignard reagent was transferred to another oven-dried 250 mL round-bottomed flask to remove the residual magnesium. diethyl ether was removed in vacuo to give a solid. A solution of 1-bromoadamantane **22** (9.832 g, 50.0 mmol, 1.00 equiv) in dichloromethane (40 mL) was added to the solidified Grignard reagent diluted with dichloromethane (60 mL) at room temperature under nitrogen, and then the mixture was refluxed for 12 h. After cooling, the reaction system was carefully poured into aqueous hydrogen chloride solution (100 mL, 2 M) at 0 °C, and the layers were separated. The aqueous layer was extracted with hexanes (100 mL × 3). The combined organic layer was washed with water and dried over anhydrous sodium sulfate. After filtration and evaporation, the residue was purified by column chromatography (silica gel, hexanes) to give **23** (9.615 g, 91%, 45.3 mmol, mp 76−78 °C) as a white solid. Eight different runs of this reaction were performed on 50 mmol scale to give yields in the range of 91−96%. Spectral data for **23**: R_f = 0.24 (hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 1.65−1.86 (m, 6H), 1.91 (d, J = 3.0 Hz, 6H), 2.01−2.13 (m, 3H), 7.12−7.20 (m, 1H), 7.25−7.40 (m, 4H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 29.0, 36.2, 36.8, 43.1, 124.8, 125.5, 128.1, 151.3. These spectral data match those previously reported for this compound.[14]

*4-Adamantylacetophenone **24***. To a flame-dried 100 mL round-bottom flask was added aluminum chloride (14.7 g, 110 mmol, 1.10 equiv) and carbon disulfide (30 mL). The solution was cooled to −78 °C for 10 min. To the stirred mixture at −78 °C was added a solution of 1-phenyladamantane **23** (21.23 g, 100 mmol, 1.00 equiv) and acetyl chloride (7.85 mL, 110 mmol, 1.10 equiv) in carbon disulfide (20 mL). The reaction mixture was warmed to 0 °C and maintained for 1 h, after which time the ice bath was removed and stirred at room temperature for 4 h. The mixture was poured into a mixture of ice (300 g) and 2 M aqueous sulfuric acid. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (50 mL × 3). The combined organic layer was washed with brine (100 mL), dried over anhydrous sodium sulfate. After filtration and evaporation, the residue was purified by flash column chromatography (silica gel, hexanes/ethyl acetate 10:1) to give **24** (22.698 g, 89%, 89.2 mmol, mp 97−100 °C) as a white solid. Three different runs of this reaction were performed on 87−100 mmol scale to give yields in the range of 81−91%. Spectral data for **24**: R_f = 0.52 (ethyl acetate/hexanes 1:10); ^1H NMR (500 MHz, $CDCl_3$) δ 1.58−1.71 (m, 6H), 1.78 (s, 6H), 1.97 (s, 3H), 2.42 (s, 3H), 7.30 (d, J = 7.5 Hz, 2H), 7.78 (d, J = 8.4 Hz, 2H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 26.1, 28.5, 31.3, 36.3, 42.5, 124.7, 128.0, 128.0, 134.3, 156.4, 197.1. These spectral data match those previously reported for this compound.[15]

*1-Morpholino-2-(4-adamantylphenyl)ethane-1-thione **25***. To a flame-dried 250 mL round-bottom flask was added 4-adamantylacetophenone **24** (22.332 g, 87.8 mmol), sulfur (7.04 g, 220 mmol, 2.50 equiv) and morpholine (29 mL, 330 mmol, 3.80 equiv). The mixture was heated to 145 °C for 12 h. After being cooled to room temperature, the mixture was refluxed with ethanol (50 mL) for 1 h. The mixture was cooled to −20 °C for 1 h then the precipitated solid was collected by suction filtration and wash by ethanol. This crude **25** (26.533 g, 85%, 74.488 mmol, mp 171−174 °C) appeared pure by ^1H NMR analysis and was used in the next step without further purification. Three different runs of this reaction were performed on 88−167 mmol scale to give a combined yield of 85% for the three runs. Spectral data for **25**: R_f = 0.19 (ethyl acetate/hexanes 1:4); ^1H NMR (500 MHz, $CDCl_3$) δ 1.78 (q, J = 10 Hz, 6H), 1.87 (d, J = 2.9 Hz, 6H), 2.07 (p, J = 3.2 Hz, 3H), 3.31−3.43 (m, 2H), 3.56−3.66 (m, 2H), 3.66−3.78 (m, 2H), 4.31 (s, 2H), 4.32−4.38 (m, 2H), 7.19−7.24 (m, 2H), 7.26−7.32 (m, 2H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 28.9, 36.0, 36.7, 43.1, 50.1, 50.2, 50.8, 66.1, 66.3, 125.4, 127.4, 132.6, 150.3, 200.3. HRMS (ESI-TOF) *m/z*: $[M - H]^-$ Calcd for $C_{18}H_{26}NO_4$ 356.2048; Found 356.2053.

*2-(4-Adamantylphenyl)acetic acid **26e***. To a flame-dried 500 mL round-bottom flask was added morpholinyl ethanethione **25** (37.981 g, 106.63 mmol), 1,4-dioxane (100 mL), concentrated hydrochloric acid (50 mL, 12 N), and acetic acid (25 mL). The resulting mixture was heated to reflux at 120 °C for 12 h. After being cooled to room temperature, the solvent was evaporated. The mixture was stirred with aqueous hydrogen chloride solution (50 mL, 1 N) and cooled to 0 °C for 1 h. The precipitated solid was collected by suction filtration and washed by cold aqueous hydrogen chloride solution (20 mL, 1 N) followed by exposure to high vacuum overnight. This crude product can be purified by recrystallization from ethyl acetate/hexanes (1:3) to afford **26e** (24.712 g, 86% combined yield from 3 crops, 91.814 mmol, mp 186−187 °C) as a yellow solid. Two different runs of this reaction were performed on 96−107 mmol scale to give a combined yield of 86% for the two runs. Spectral data for **26e**: R_f = 0.21 (dichloromethane); ^1H NMR (500 MHz, $CDCl_3$) δ 1.75 (q, J = 12.2 Hz, 6H), 1.88 (d, J = 2.9 Hz, 6H), 2.07 (s, 3H), 3.60 (s, 2H), 7.21 (d, J = 8.3 Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 28.9, 36.0, 36.7, 40.5, 43.1, 125.2, 129.0, 130.2, 150.5, 177.6. HRMS (ESI^-) *m/z*: $[M - H]^-$ Calcd for $C_{18}H_{21}O_2$ 269.1542; Found 269.1544.

*Synthesis of 7,7′-Disubstituted VANOL Ligands **13a**, **13b**, and **13e** (Scheme 6). 2-(4-(tert-Butyl)phenyl)acetic Acid **26a***. An oven-dried 2 L round-bottomed flask equipped with an egg-shaped stirring bar (50 × 20 mm) is placed under a nitrogen atmosphere through a gas inlet. After cooling to 23 °C, methyl 2-(4-(*tert*-butyl)phenyl)-acetate **27a** (100 g, 48.5 mmol, 1.00 equiv) is added followed by addition of methyl alcohol (500 mL), tetrahydrofuran (500 mL), and aqueous sodium hydroxide solution (160 mL, 6 M, 96.0 mmol, 2.00 equiv). The mixture is stirred at room temperature (23 °C) for 12 h. The reaction mixture is concentrated in vacuo using a rotary evaporator (40 °C, 15 mmHg) then cooled in the ice bath for 10 min. To the reaction mixture is added aqueous hydrogen chloride solution

https://dx.doi.org/10.1021/acs.joc.0c00494
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(10 × 10 mL, 6 N) in portions, and the white precipitate is then filtered and allowed to dry overnight. The white solid is put under high vacuum (23 °C, 0.2 mmHg) for 30 min to yield 93.23 g of the product **26a** as a white solid at >99% purity (48.5 mmol, mp 80−82 °C, 100% yield). Spectral data for **26a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.30 (s, 9H), 3.60 (s, 2H), 7.21 (d, J = 8.3 Hz, 2H), 7.34 (d, J = 8.3 Hz, 2H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 31.3, 34.5, 40.5, 125.6, 129.0, 130.2, 150.2, 178.1. This data match that previously reported for this compound.[4]

General procedure A2 for the CEC process with oxalyl chloride, illustrated for synthesis of 7-(*tert*-butyl)-3-phenylnaphthalen-1-ol **29a** from 2-(4-(*tert*-butyl)phenyl)acetic acid **26a**.

*7-(tert-Butyl)-3-phenyl-1-naphthol **29a**.* An oven-dried 1 L round-bottomed flask equipped with an egg-shaped stirring bar (30 × 15 mm) is placed under a nitrogen atmosphere through a gas inlet. After cooling to 23 °C, 2-(4-(*tert*-butyl)phenyl)acetic acid **26a** (46.3 g, 241 mmol, 1.00 equiv) is added followed by addition of anhydrous dichloromethane (240 mL) before cooling in the ice bath for 10 min. To the solution is added oxalyl chloride (50.0 mL, 600 mmol, 2.50 equiv) in one portion followed by addition of 10 drops of anhydrous *N*,*N*-dimethylformamide. The ice bath is removed. The mixture is stirred and allowed to warm to room temperature (23 °C). After 2 h, the reaction mixture is concentrated in vacuo using a rotary evaporator (40 °C, 15 mmHg) and then put under high vacuum (23 °C, 0.2 mmHg) for 30 min to completely remove excess oxalyl chloride.

The reaction flask containing the crude acid chloride is filled with nitrogen, and then phenylacetylene (34.0 mL, 313 mmol, 1.30 equiv) and isobutyric anhydride (80.0 mL, 482 mmol, 2.00 equiv) are added. The flask is fitted with a condenser flushed with nitrogen with a Teflon sleeve in the joint and Teflon tape wrapped around the joint to secure a tight seal. The reaction mixture is heated and stirred in a 190 °C oil bath for 48 h with a gentle nitrogen flow across the top of the condenser. The brown reaction mixture is cooled to about 60 °C (oil bath temperature), and an aqueous solution of potassium hydroxide (80.0 g, 1.43 mol, 6.00 equiv) in 320 mL of water is slowly added. After stirring in a 100 °C oil bath overnight (15 h), the orange solution is cooled to room temperature; diethyl ether (300 mL) is added, and the mixture is stirred for 30 min before the organic layer is isolated in a 2 L separatory funnel. The water layer is extracted twice with diethyl ether (300 mL × 2), and the combined organic layer is washed with brine (300 mL), dried over anhydrous magnesium sulfate, and filtered. The dark-colored organic solution is concentrated in vacuo using a rotary evaporator (40 °C, 15 mmHg), and the residue is dried under high vacuum (23 °C, 0.2 mmHg) overnight to give dark brown crude product (40 g). Recrystallization from dichloromethane/hexanes gave 26.46 g product **29a** (mp 135−136 °C) as solid crystals (95.7 mmol, 39.7%, first crop). Successive crystallization yields the product **29a** a combined yield of 59% (8.7%, 5.77 g, mp 137−138 °C, second crop; 10.1%, 6.72 g, mp 135−138 °C, third crop). Spectral data for **29a**: R_f = 0.34 (ethyl acetate/hexanes 1:4); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.43 (s, 9H), 5.36 (s, 1H), 7.06 (d, J = 1.6 Hz, 1H), 7.30−7.39 (m, 1H), 7.45 (dd, J = 8.5, 7.0 Hz, 2H), 7.57−7.70 (m, 4H), 7.80 (d, J = 8.7 Hz, 1H), 8.09 (dd, J = 1.8, 0.9 Hz, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 31.3, 35.1, 108.3, 116.2, 118.3, 123.2, 125.8, 127.2, 127.3, 127.8, 128.8, 133.2, 138.1, 141.0, 148.3, 151.7. These spectral data match those previously reported for this compound.[4]

*7,7′-Ditert-butyl-3,3′-diphenyl-[2,2′-binaphthalene]-1,1′-diol (7,7′-tBu$_2$VANOL) **13a**.* VANOL derivative **13a** was prepared from 7-(*tert*-butyl)-3-phenyl-1-naphthol **29a** (27.64 g, 100.0 mmol, 1.00 equiv) using the general procedure B with heating at 150 °C for 24 h. The crude product was purified by recrystallization from dichloromethane/hexanes and column chromatography (silica gel, dichloromethane/hexanes: 1:3 to 1:1) to give **13a** as an off-white solid in 71% isolated yield (19.62 g, mp 154−157 °C, 35.6 mmol). Spectral data for **13a**: R_f = 0.39 (ethyl acetate/hexanes 1:4); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.47 (s, 18H), 5.82 (s, 2H), 6.60 (dt, J = 7.0, 1.3 Hz, 4H), 6.95 (t, J = 7.7 Hz, 4H), 6.98−7.09 (m, 2H), 7.27 (s, 2H), 7.60−7.75 (m, 4H), 8.29 (d, J = 1.9 Hz, 2H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 31.3, 35.2, 112.7, 117.7, 121.6, 122.6, 126.4, 126.4, 127.4, 127.4, 128.9, 132.8, 140.0, 140.3, 148.6, 150.2. These spectral data match those previously reported for this compound.[4]

*7-Bromo-3-phenyl-1-naphthol **29b**.* 1-Naphthol **29b** was prepared from 2-(4-bromophenyl)acetic acid **26b** (53.76 g, 250.0 mmol, 1.000 equiv) using the general procedure A1. The crude product was purified by recrystallization from dichloromethane/hexanes and column chromatography (silica gel, dichloromethane/hexanes: 1:3 to 1:1) to give **29b** as an off-white solid in 59% isolated yield (44.352 g, mp 94−97 °C, 148 mmol). Spectral data for **29b**: R_f = 0.35 (dichloromethane). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.27 (s, 1H), 7.04 (d, J = 1.6 Hz, 1H), 7.35 (t, J = 7.4 Hz, 1H), 7.44 (dd, J = 8.4, 6.9 Hz, 2H), 7.51−7.58 (m, 2H), 7.59−7.64 (m, 2H), 7.68 (d, J = 8.7 Hz, 1H), 8.33 (d, J = 2.0 Hz, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 109.2, 118.6, 119.3, 124.3, 124.6, 127.2, 127.7, 128.9, 129.6, 130.3, 133.3, 139.3, 140.4, 150.8. These spectral data match those previously reported for this compound.[1]

*7,7′-Br$_2$VANOL **13b**.* VANOL derivative **13b** was prepared from 7-bromo-3-phenylnaphthalen-1-ol **29b** (44.88 g, 150.0 mmol, 1.000 equiv) by the general procedure with heating at 165 °C for 24 h. The crude product was purified by recrystallization from dichloromethane/hexanes and column chromatography (silica gel, dichloromethane/hexanes: 1:3 to 1:1) to give **13b** as a light brown solid in 60% isolated yield (26.879 g, mp 136−138 °C, 45.1 mmol). Spectral data for **13b**: R_f = 0.51 (dichloromethane). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.53−6.61 (m, 4H), 6.92 (t, J = 7.5 Hz, 4H), 7.03 (t, J = 7.4 Hz, 2H), 7.18 (s, 2H), 7.51−7.62 (m, 4H), 8.48−8.57 (m, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 115.3, 119.3, 121.4, 124.5, 125.3, 126.6, 127.3, 128.9, 129.2, 130.4, 132.7, 140.0, 141.4, 149.9. These spectral data match those previously reported for this compound.[4]

*7-Adamantyl-3-phenyl-1-naphthol **29e**.* 1-Naphthol **29e** was prepared from 2-(4-adamantylphenyl)acetic acid **26e** (27.037 g, 100.45 mmol) using the general procedure **A2**. The crude product was purified by recrystallization from dichloromethane/hexanes and column chromatography (silica gel, dichloromethane/hexanes: 1:3 to 1:1) to give **29e** as a white crystal in 54% isolated yield from **26e** (19.131 g, mp 201−203 °C, 54.166 mmol). A second run on 100 mmol scale gave a 52% yield of **29e**. Spectral data for **29e**: R_f = 0.35 (dichloromethane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.69−1.87 (m, 6H), 2.03 (d, J = 2.8 Hz, 6H), 2.14 (s, 3H), 5.31 (s, 1H), 7.06 (d, J = 1.5 Hz, 1H), 7.26−7.39 (m, 1H), 7.40−7.53 (m, 2H), 7.51−7.71 (m, 4H), 7.80 (d, J = 8.7 Hz, 1H), 8.03 (dd, J = 1.9, 0.9 Hz, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 29.0, 36.6, 36.8, 43.1, 108.2, 116.2, 118.4, 123.4, 125.2, 127.2, 127.3, 127.7, 128.8, 133.3, 138.1, 141.1, 148.5, 151.7. HRMS (ESI$^-$) *m/z*: $[M - H]^-$ Calcd for $C_{26}H_{25}O$ 353.1905; Found 353.1917.

*7,7′-Ad$_2$VANOL **13e** (Scheme 6).* VANOL derivative **13e** was prepared from 7-adamantyl-3-phenyl-1-naphthol **29e** (35.45 g, 100.4 mmol) using the general procedure B with heating at 195 °C for 24 h. The crude product was purified by recrystallization from dichloromethane/hexanes and column chromatography (silica gel, dichloromethane/hexanes: 1:3 to 1:1) to give **13e** as an off-white solid in 94% isolated yield (33.245 g, mp 360 °C (decomposed), 47.131 mmol). Spectral data for **13e**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.77−1.88 (m, 12H), 2.08 (d, J = 2.9 Hz, 12H), 2.09−2.25 (m, 6H), 5.83 (s, 2H), 6.52−6.70 (m, 4H), 6.94 (t, J = 7.7 Hz, 4H), 6.98−7.11 (m, 2H), 7.27 (s, 2H), 7.56−7.84 (m, 4H), 8.23 (d, J = 1.9 Hz, 2H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 29.0, 36.7, 36.8, 43.1, 112.6, 117.6, 121.6, 122.7, 125.8, 126.4, 127.4, 127.4, 128.9, 132.9, 140.0, 140.4, 148.8, 150.3. HRMS (ESI$^-$) *m/z*: $[M - H]^-$ Calcd for $C_{52}H_{49}O_2$ 705.3733: Found 705.3748.

*Synthesis of 7,7′-Dialkyl Substituted VANOL Ligands **13c** and **13d** via Kumada Coupling (Scheme 7). 7,7′-Br$_2$VANOL-MOM$_2$ **30**.* To a flame-dried 250 mL round-bottom flask were added sodium hydride (2.000 g, 60% in mineral oil, 50.0 mmol, 2.50 equiv) and anhydrous tetrahydrofuran (80 mL). The resulting mixture was cooled to 0 °C and a solution of 7,7′-Br$_2$VANOL **13b** (11.930 g, 20.00 mmol, 1.000 equiv) in anhydrous tetrahydrofuran (20 mL) was added. The mixture was stirred at 0 °C for 30 min and then allowed

https://dx.doi.org/10.1021/acs.joc.0c00494
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to warm to room temperature for 15 min. The mixture was recooled to 0 °C, and chloromethyl methyl ether (3.80 mL, 50.0 mmol, 2.50 equiv) was added. The mixture was warmed to room temperature and stirred for an additional 12 h. Saturated aqueous ammonium chloride solution (30 mL) was added to the mixture, and the organic solvent was removed on a rotary evaporator. The residue was extracted with dichloromethane (50 mL × 3). The combined organic layer was washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to dryness. Purification of the crude product by column chromatography on silica gel (dichloromethane/hexanes 1:2 to 3:4 to 1:1) gave **30** as a white solid (13.045 g, 19.1 mmol, mp 97−98 °C) in 95% yield. Spectral data for **30**: R_f = 0.22 (dichloromethane/hexanes 1:1). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.73 (s, 6H), 5.06−5.10 (m, 4H), 6.71 (dd, 4H, J = 8.5, 1.0 Hz), 6.89−6.93 (m, 4H), 7.03−7.09 (m, 2H), 7.47 (s, 2H), 7.57 (dd, 2H, J = 8.5, 2.0 Hz), 7.69 (d, 2H, J = 9.0 Hz), 8.32−8.34 (m, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz) δ 56.4, 99.5, 120.4, 125.1, 125.5, 126.3, 127.5, 127.5, 128.0, 129.0, 129.9, 130.0, 132.8, 140.4, 141.1, 151.5. These spectral data match those previously reported for this compound.[4]

General procedure C synthesis of 7,7′-dialkyl VANOL ligands by Kumada coupling and MOM deprotection, illustrated for synthesis of 7,7′-isoamyl$_2$VANOL **13d**.

*7,7′-Isoamyl$_2$VANOL-MOM$_2$ **31d**.* An oven-dried 100 mL round-bottomed flask equipped with an egg-shaped stirring bar (30 × 15 mm) is placed under a nitrogen atmosphere through a gas inlet. After cooling to 23 °C, 1-bromo-3-methylbutane **37** (3.84 mL, 32.0 mmol, 4.00 equiv) and diethyl ether (15 mL) were added. The solution was cooled to 0 °C in an ice bath for 10 min. To the round-bottom flask was added magnesium (800 mg, 32.9 mmol, 4.11 equiv) and activated with 1 drop of chlorotrimethylsilane under nitrogen. The reaction mixture was stirred at room temperature for 0.5 h and then was refluxed for 1 h until most of the magnesium disappeared. To a separate oven-dried 250 mL round-bottomed flask was added 7,7′-Br$_2$VANOL-MOM$_2$ **30** (5.476 g, 8.00 mmol, 1.00 equiv), [1,3-bis(diphenylphosphino)-propane]dichloronickel(II) (432 mg, 0.800 mmol, 0.100 equiv), and anhydrous tetrahydrofuran (40 mL) and then cooled to 0 °C for 10 min. To this mixture was added dropwise the resulting solution of Grignard reagent from the 100 mL round-bottomed flask at 0 °C. The reaction mixture was then warmed to room temperature and heated to reflux (45 °C) for 12 h. After cooling to room temperature, saturated aqueous ammonium chloride solution (20 mL) was added to the mixture. and the layers were separated. The aqueous layer was extracted with ethyl acetate (30 mL × 3). The combined organic layer was washed with water, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford crude **31** (4.5750 g) as a yellow solid. The crude product was used in the next step without further separation.

*7,7′-Isoamyl$_2$VANOL **13d**.* To a 500 mL round-bottomed flask, the purified mixture obtained above was dissolved in a mixture of tetrahydrofuran and methanol (160 mL, 1:1), and Amberlyst 15 (4.00 g) was added. The mixture was stirred at 65 °C for 15 h under nitrogen. After cooling to room temperature, the mixture was filtered through filter paper and concentrated to dryness. Purification of the crude product by column chromatography on silica gel (dichloromethane/hexanes 2:1) gave **13d** as a white solid (3.8975 g, mp 192−193 °C, 6.7511 mmol) in 84% yield over two steps. Spectral data for **13d**: R_f = 0.36 (dichloromethane/hexanes 1:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.01 (dd, J = 6.2, 1.9 Hz, 12H), 1.60−1.87 (m, 6H), 2.86 (dd, J = 9.1, 6.5 Hz, 4H), 5.82 (s, 2H), 6.54−6.70 (m, 4H), 6.97 (t, J = 7.7 Hz, 4H), 7.04−7.15 (m, 2H), 7.30 (s, 2H), 7.44 (dd, J = 8.4, 1.8 Hz, 2H), 7.72 (d, J = 8.3 Hz, 2H), 8.06−8.19 (m, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 22.6, 22.7, 27.9, 34.2, 40.9, 112.7, 121.0, 121.8, 122.9, 126.4, 127.4, 127.6, 128.9, 129.0, 133.0, 139.7, 140.3, 140.8, 149.9. HRMS (ESI$^-$) *m/z*: [M − H]$^-$ Calcd for $C_{42}H_{41}O_2$ 577.3107: Found 577.3130.

*7,7′-Cy$_2$VANOL **13c**.* VANOL derivative **13c** is obtained by following general procedure C with bromocyclohexane **38** (4.00 mL, 32.0 mmol, 4.00 equiv) using 5 mol % [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (293 mg, 0.400 mmol, 0.050 equiv) as catalyst instead of [1,3-bis(diphenylphosphino)-propane]dichloronickel(II). The crude reaction mixture of the bis-MOM derivative of VANOL ligand **13c** and its monodeprotected derivative are deprotected using the procedure described above for the deprotection step of **31d** above to give **13c** as a white solid (4.5032 g, mp 135−137 °C, 7.4640 mmol) in 93% yield over two steps from **30**. Spectral data for **13c**: R_f = 0.38 (dichloromethane/hexanes 1:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.83−1.13 (m, 4H), 1.14−1.38 (m, 4H), 1.58 (d, J = 13.2 Hz, 4H), 1.62−1.72 (m, 4H), 1.72−1.81 (m, 4H), 2.20 (tt, J = 11.8, 3.2 Hz, 2H), 5.19 (s, 2H), 7.46 (ddd, J = 8.2, 6.8, 1.3 Hz, 2H), 7.50 (s, 2H), 7.54 (ddd, J = 8.2, 6.8, 1.3 Hz, 2H), 7.83 (d, J = 8.2 Hz, 2H), 8.22 (d, J = 8.3 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 26.0, 26.8, 26.8, 33.7, 36.1, 41.4, 112.7, 117.9, 122.4, 122.7, 124.8, 127.1, 127.2, 135.0, 146.2, 149.8. HRMS (ESI$^-$) *m/z*: [M − H]$^-$ Calcd for $C_{44}H_{43}O_2$ 603.3263; Found 603.3262. These spectral data match those previously reported for this compound.[4]

Resolution of Vaulted Biaryl Ligands with Quinine (Table 4). General procedure D for chiral resolution of VANOL derivatives with quinine borates, illustrated for resolution of (±)-5,5′-Br$_2$VANOL *rac*-**12a**:

*(S)-5,5′-Br$_2$VANOL (S)-**12a**.* An oven-dried 100 mL round-bottomed flask equipped with an egg-shaped stirring bar (30 × 15 mm) is placed under a nitrogen atmosphere through a gas inlet. After cooling to 23 °C, (±)-5,5′-Br$_2$VANOL **12a** (1.192 g, 2.00 mmol, 1.00 equiv) is added followed by addition of anhydrous tetrahydrofuran (10 mL) and borane dimethyl sulfide complex (1.10 mL, 2 M solution in toluene, 2.20 mmol, 1.10 equiv). An oven-dried reflux condenser with an outlet connected to a bubbler is attached to the flask. The mixture is stirred and refluxed in an 80 °C oil bath for 30 min, and the evolution of gas ceases. After cooling to room temperature (23 °C), the clear solution is concentrated in vacuo using a rotary evaporator (40 °C, 15 mmHg), and the residue is dried under high vacuum (60 °C, 0.2 mmHg) for 30 min. After cooling to 23 °C, anhydrous tetrahydrofuran (9 mL) is added followed by addition of quinine (681 mg, 2.10 mmol, 1.05 equiv). The reflux condenser is reconnected, and the mixture is stirred and refluxed in an 80 °C oil bath overnight (12 h). The flask containing the reaction mixture is cooled to room temperature and then to −20 °C for 30 min before the solid is collected by suction filtration and washed with ice-cold anhydrous tetrahydrofuran (9 mL).

The solid is transferred to a 100 mL round-bottomed flask and ethyl acetate (10 mL) is added followed by addition of aqueous hydrogen chloride solution (10 mL, 2 M) and an egg-shaped stirring bar (30 × 15 mm). The mixture was stirred for 30 min at room temperature before the organic layer is isolated in a 60 mL separatory funnel. The water layer is extracted twice with ethyl acetate (15 mL × 2), and the combined organic layer is washed with brine (10 mL), dried over anhydrous magnesium sulfate and filtered. The water layer containing chloride salt of protonated quinine is transferred to a clean container for recovery. The organic solution is concentrated in vacuo using a rotary evaporator (40 °C, 15 mmHg). The residue is dissolved in a minimum amount of dichloromethane and loaded onto a silica gel column wet loaded with hexanes. The column is eluted with a mixture of dichloromethane and hexanes (1:2) to afford (*S*)-5,5′-Br$_2$VANOL (*S*)-**12a** as a white solid (0.549 g, 0.921 mmol, 46%). The optical purity of (*S*)-**12a** is determined to be >99% ee by HPLC analysis. (Pirkle D-phenylglycine column, 98:2 hexane/iPrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: R_t = 24.99 min for (*R*)-**12a** (minor) and R_t = 27.43 min for (*S*)-**12a** (major). $[\alpha]^{20}_D$ = −148.7 (*c* 1.0, dichloromethane) on >99% ee (*S*)-**12a** (HPLC).

*(R)-5,5′-Br$_2$VANOL (R)-**12a**.* The mother liquor is transferred to a 100 mL round-bottomed flask and concentrated in vacuo using a rotary evaporator (40 °C, 15 mmHg). Dichloromethane (15 mL) is added followed by addition of aqueous hydrogen chloride solution (15 mL, 2 M) and an egg-shaped stirring bar (30 × 15 mm). The mixture was stirred for 30 min at room temperature before the organic layer is separated in a 60 mL separatory funnel. The water layer is extracted twice with dichloromethane (15 mL × 2), and the combined organic layer is washed with brine (10 mL), dried over anhydrous magnesium sulfate and filtered. The water layer containing

https://dx.doi.org/10.1021/acs.joc.0c00494
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chloride salt of protonated quinine is transferred to a clean container for recovery. The organic solution is concentrated in vacuo using a rotary evaporator (40 °C, 15 mmHg). The residue was dissolved in a minimum amount of dichloromethane and loaded onto a silica gel column wet loaded with hexanes. The column is eluted with a mixture of dichloromethane and hexanes (1:2) to afford (*R*)-5,5′-Br_2VANOL (*R*)-**12a** as a white solid (824.7 mg, 1.38 mmol, 69%). The optical purity of (*R*)-**12a** is determined to be 72% ee by HPLC analysis.

*(S)-5,5′-Cl$_2$VANOL (S)-**12b**.* VANOL derivative (±)-**12b** (1.015 g, 2.00 mmol, 1.00 equiv) was resolved using the general procedure D with 9 mL of refluxing anhydrous tetrahydrofuran to afford (*S*)-5,5′-Cl_2VANOL (*S*)-**12b** as a white solid (451.8 mg, 0.890 mmol, 45%). The optical purity of (*S*)-**12b** was determined to be >99% ee by HPLC analysis (Pirkle D-phenylglycine column, 98:2 hexane/iPrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: R_t = 21.73 min for (*R*)-**12b** (minor) and R_t = 24.79 min for (*S*)-**12b** (major). $[\alpha]^{20}_D$ ND.

*(R)-5,5′-Cl$_2$VANOL (R)-**12b**.* VANOL derivative (*R*)-**12b** is obtained by following general procedure D. Its optical purity was determined to be 76% ee by HPLC analysis.

*(S)-5,5′-Me$_2$VANOL (S)-**12c**.* VANOL derivative (±)-**12c** (933.2 mg, 2.00 mmol, 1.00 equiv) was resolved using the general procedure D with 9 mL of refluxing anhydrous tetrahydrofuran to afford (*S*)-5,5′-Me_2VANOL (*S*)-**12c** as a white solid (411.6 mg, 0.882 mmol, 44%). The optical purity of (*S*)-**12c** was determined to be >99% ee by HPLC analysis. (Pirkle D-phenylglycine column, 98:2 hexane/iPrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: R_t = 17.28 min for (*R*)-**12c** (minor) and R_t = 20.72 min for (*S*)-**12c** (major).

*(R)-5,5′-Me$_2$VANOL (R)-**12c**.* VANOL derivative (*R*)-**12c** is obtained by following general procedure D. Its optical purity is determined to be 75% ee by HPLC analysis.

*(S)-5,5′-OMe$_2$VANOL (S)-**12d**.* VANOL derivative (±)-**12d** (997.2 mg, 2.00 mmol, 1.00 equiv) was resolved using the general procedure D refluxing with 8 mL of anhydrous tetrahydrofuran and 4 mL of hexanes to afford (*S*)-5,5′-OMe_2VANOL (*S*)-**12d** as a white solid (469.0 mg, 0.941 mmol, 47%). The optical purity of (*S*)-**12d** is determined to be >99% ee by HPLC analysis (Pirkle D-phenylglycine column, 98:2 hexane/iPrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: R_t = 32.05 min for (*R*)-**12d** (minor) and R_t = 36.45 min for (*S*)-**12d** (major). $[\alpha]^{20}_D$ = −178.6 (*c* 1.0, dichloromethane) on >99% ee (*S*)-**12d** (HPLC).

*(R)-5,5′-OMe$_2$VANOL (R)-**12d**.* VANOL derivative (*R*)-**12d** is obtained by following general procedure D. Its optical purity is determined to be 80% ee by HPLC analysis.

*(S)-5,5′-(CF$_3$)$_2$VANOL (S)-**12e**.* VANOL derivative (±)-**12e** (1.149 g, 2.00 mmol, 1.00 equiv) was resolved using the general procedure D refluxing with 8 mL of anhydrous tetrahydrofuran and 4 mL of hexanes to afford (*S*)-5,5′-$(CF_3)_2$VANOL (*S*)-**12e** as a white solid (0.4492 g, 0.783 mmol, 39%). The optical purity of (*S*)-**12e** is determined to be >99% ee by HPLC analysis (Pirkle D-phenylglycine column, 98:2 hexane/iPrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: R_t = 11.65 min for (*R*)-**12e** (minor) and R_t = 12.93 min for (*S*)-**12e** (major). $[\alpha]^{20}_D$ ND

*(R)-5,5′-(CF$_3$)$_2$VANOL (R)-**12e**.* VANOL derivative (*R*)-**12e** is obtained by following general procedure D. Its optical purity is determined to be 12% ee by HPLC analysis.

*(S)-3,3′-pEtPh$_2$VANOL (S)-**11a**.* VANOL derivative (±)-**11a** (989.3 mg, 2.00 mmol, 1.00 equiv) was resolved using the general procedure D refluxing with 6 mL of anhydrous tetrahydrofuran and 6 mL of hexanes to afford (*S*)-3,3′-$pEtPh_2$VANOL (*S*)-**11a** as a white solid (0.358 g, 0.724 mmol, 36%). The optical purity of (*S*)-**11a** was determined to be >99% ee by HPLC analysis (Pirkle D-phenylglycine column, 98:2 hexane/iPrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: R_t = 14.83 min for (*R*)-**11a** (minor) and R_t = 16.42 min for (*S*)-**11a** (major).

*(R)-3,3′-pEtPh$_2$VANOL (R)-**11a**.* VANOL derivative (*R*)-**11a** is obtained by following general procedure D. Its optical purity is determined to be 60% ee by HPLC analysis.

*(S)-3,3′-pOMePh$_2$VANOL (S)-**11b**.* VANOL derivative (±)-**11b** (997.2 mg, 2.00 mmol, 1.00 equiv) was resolved using the general procedure D refluxing with 6 mL of anhydrous tetrahydrofuran and 6 mL of hexanes to afford (*S*)-3,3′-$pOMePh_2$VANOL (*S*)-**11b** as a white solid (0.342 g, 0.686 mmol, 34%). The optical purity of (*S*)-**11b** was determined to be >99% ee by HPLC analysis (Pirkle D-phenylglycine column, 98:2 hexane/iPrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: R_t = 6.31 min for (*R*)-**11b** (minor) and R_t = 7.02 min for (*S*)-**11b** (major). $[\alpha]^{20}_D$ ND.

*(R)-3,3′-pOMePh$_2$VANOL (R)-**11b**.* VANOL derivative (*R*)-**11b** is obtained by following general procedure D. Its optical purity is determined to be 59% ee by HPLC analysis.

*(S)-7,7′-Br$_2$VANOL (S)-**13b**.* VANOL derivative (±)-**13b** (1.192 g, 2.00 mmol, 1.00 equiv) was attempted to be resolved using the general procedure D with 6 mL of refluxing anhydrous tetrahydrofuran but failed. The use of 8 mL of refluxing anhydrous toluene worked and afforded (*S*)-7,7′-Br_2VANOL (*S*)-**13b** as a white solid (0.381 g, 0.639 mmol, 32%). The optical purity of (*S*)-**13b** was determined to be >99% ee by HPLC analysis (Pirkle D-phenylglycine column, 98:2 hexane/iPrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: R_t = 33.57 min for (*R*)-**13b** (Minor) and R_t = 41.64 min for (*S*)-**13b** (Major).

*(R)-7,7′-Br$_2$VANOL (R)-**S-13b**.* VANOL derivative (*R*)-**13b** is obtained by following general procedure D. Its optical purity is determined to be 54% ee by HPLC analysis.

*(S)-7,7′-Cy$_2$VANOL (S)-**13c**.* VANOL derivative (±)-**13c** (1.206 g, 2.00 mmol, 1.00 equiv) was resolved using the general procedure D with 8 mL of refluxing anhydrous tetrahydrofuran to afford (*S*)-7,7′-Cy_2VANOL (*S*)-**13c** as a white solid (0.313 g, 0.519 mmol, 26%). The optical purity of (*S*)-**13c** was determined to be >99% ee by HPLC analysis (CHIRALCEL OD-H column, 95:5 hexanes/2-propanol at 210 nm, flow-rate: 1 mL/min). Retention times: R_t = 2.82 min for (*S*)-**13c** (major) and R_t = 4.65 min for (*R*)-**13c** (minor). $[\alpha]^{20}_D$ = −206.1 (*c* 1.0, dichloromethane) on >99% ee (*S*)-**13c** (HPLC).

*(R)-7,7′-Cy$_2$VANOL (R)-**13c**.* VANOL derivative (*R*)-**13c** is obtained by following general procedure D. Its optical purity is determined to be 20% ee by HPLC analysis.

*(S)-7,7′-isoamyl$_2$VANOL (S)-**13d**.* VANOL derivative (±)-**13d** (1.158 g, 2.00 mmol, 1.00 equiv) was resolved using the general procedure D refluxing with 6 mL of anhydrous tetrahydrofuran and 6 mL of hexanes to afford (*S*)-7,7′-isoamyl$_2$VANOL (*S*)-**13d** as a white solid (0.2681 g, 0.463 mmol, 23%). The optical purity of (*S*)-**13d** was determined to be >99% ee by HPLC analysis (Pirkle D-phenylglycine column, 98:2 hexane/iPrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: R_t = 6.75 min for (*R*)-**13d** (minor) and R_t = 7.25 min for (*S*)-**13d** (major). $[\alpha]^{20}_D$ = −235.9 (*c* 1.0, dichloromethane) on >99% ee (*S*)-**13d** (HPLC).

*(R)-7,7′-isoamyl$_2$VANOL (R)-**13d**.* VANOL derivative (*R*)-**13d** is obtained by following general procedure D. Its optical purity is determined to be 19% ee by HPLC analysis.

*(S)-7,7′-Ad$_2$VANOL (S)-**13e**.* VANOL derivative (±)-**13e** (1.414 g, 2.00 mmol, 1.00 equiv) was resolved using the general procedure D with 8 mL of refluxing anhydrous tetrahydrofuran to afford (*S*)-7,7′-Ad_2VANOL (*S*)-**13e** as a white solid (0.577 g, 0.816 mmol, 41%). The optical purity of (*S*)-**13e** was determined to be 99% ee by HPLC analysis. (CHIRALCEL OD-H column, 97:3 hexanes/2-propanol at 210 nm, flow-rate: 1 mL/min). Retention times: R_t = 4.47 min for (*R*)-**13e** (minor) and R_t = 5.48 min for (*S*)-**13e** (major). $[\alpha]^{20}_D$ = −160.6 (*c* 1.0, dichloromethane) on 99% ee (*S*)-**13e** (HPLC).

*(R)-7,7′-Ad$_2$VANOL (R)-**13e**.* VANOL derivative (*R*)-**13e** is obtained by following general procedure D. Its optical purity was determined to be 67% ee by HPLC analysis.

*(S)-VANOL (S)-**1**.* VANOL (±)-**1** (877.0 mg, 2.00 mmol, 1.00 equiv) was resolved using the general procedure D with 6 mL of refluxing anhydrous tetrahydrofuran to afford (*S*)-VANOL (*S*)-**1** as a white solid (0.4071 g, 0.928 mmol, 46%). The optical purity of (*S*)-**1** is determined to be >99% ee by HPLC analysis (Pirkle D-phenylglycine column, 98:2 hexane/iPrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: R_t = 16.93 min for (*R*)-**1** (minor) and R_t = 19.70 min for (*S*)-**1** (major). $[\alpha]^{20}_D$ = −310 (*c* 1.0, dichloromethane) on >99% ee (*S*)-**1** (HPLC).

https://dx.doi.org/10.1021/acs.joc.0c00494
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*(R)-VANOL (R)-**1***. VANOL (*R*)-**1** is obtained by following general procedure D. Its optical purity is determined to be 69% ee by HPLC analysis.

*(S)-VAPOL (S)-**2***. VAPOL (±)-**2** (1.077 g, 2.00 mmol, 1.00 equiv) was resolved using the general procedure D with 6 mL of refluxing anhydrous tetrahydrofuran to afford (*S*)-VAPOL (*S*)-**2** as a white solid (476 mg, 0.884 mmol, 44%). The optical purity of (*S*)-**2** is determined to be >99% ee by HPLC analysis. (Pirkle D-phenylglycine column, 75:25 hexane/iPrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: R_t = 14.69 min for (*R*)-**2** (minor) and R_t = 21.96 min for (*S*)-**2** (major). $[\alpha]^{20}_D$ ND.

*(R)-VAPOL (R)-**2***. VAPOL derivative (*R*)-**2** is obtained by following general procedure D. Its optical purity is determined to be 68% ee by HPLC analysis.

*(S)-isoVAPOL (S)-**10***. *iso*VAPOL (±)-**10** (1.077 g, 2.00 mmol, 1.00 equiv) was resolved using the general procedure D with 6 mL of refluxing anhydrous tetrahydrofuran to afford (*S*)-*iso*VAPOL (*S*)-**10** as a white solid (358.7 mg, 0.666 mmol, 33%). The optical purity of (*S*)-**10** was determined to be >99% ee by HPLC analysis (Pirkle D-phenylglycine column, 75:25 hexane/iPrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: R_t = 17.69 min for (*R*)-**10** (minor) and R_t = 21.68 min for (*S*)-**10** (major). $[\alpha]^{20}_D$ ND.

*(R)-isoVAPOL (R)-**10***. isoVANOL derivative (*R*)-**10** was obtained by following general procedure D. Its optical purity is determined to be 45% ee by HPLC analysis.

*(S)-BINOL (S)-**7***. BINOL (±)-7 (572.7 g, 2.00 mmol, 1.00 equiv) was resolved using the general procedure D with 5 mL of refluxing anhydrous tetrahydrofuran to afford (*S*)-BINOL (*S*)-7 as a white solid (264.0 mg, 0.461 mmol, 46%). The optical purity of (*S*)-7 was determined to be 91% ee by HPLC analysis (Pirkle D-phenylglycine column, 75:25 hexane/iPrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: R_t = 3.70 min for (*R*)-7 (minor) and R_t = 3.12 min for (*S*)-7 (major). $[\alpha]^{20}_D$ ND.

*(R)-BINOL (R)-**7***. VANOL derivative (*R*)-7 was obtained by following general procedure D. Its optical purity is determined to be 85% ee by HPLC analysis.

*(S)-6,6′-Br$_2$BINOL (S)-**14***. No precipitate formed when BINOL derivative (±)-**14** (888.2 mg, 2.00 mmol, 1.00 equiv) was attempted to be resolved using the general procedure D refluxing with 6 mL of anhydrous tetrahydrofuran and 12 mL of hexanes.

Resolution of Vaulted Biaryl Ligands with Quinidine (Table 5). General procedure E for chiral resolution of VANOL derivatives with quinidine borates, illustrated for resolution of (±)-5,5′-Br$_2$VANOL *rac*-**12a**:

*(R)-5,5′-Br$_2$VANOL (R)-**12a***. An oven-dried 100 mL round-bottomed flask equipped with an egg-shaped stirring bar (30 × 15 mm) is placed under a nitrogen atmosphere through a gas inlet. After cooling to 23 °C, (±)-5,5-Br$_2$VANOL *rac*-**12a** (1.192 g, 2.00 mmol, 1.00 equiv) is added followed by addition of anhydrous tetrahydrofuran (10 mL) and borane dimethyl sulfide complex (1.10 mL, 2 M solution in toluene, 2.20 mmol, 1.10 equiv). An oven-dried reflux condenser with an outlet connected to a bubbler is attached to the flask. The mixture is stirred and refluxed in an 80 °C oil bath for 30 min, and the evolution of gas ceases. After cooling to room temperature (23 °C), the clear solution is concentrated in vacuo using a rotary evaporator (40 °C, 15 mmHg) and the residue is dried under high vacuum (60 °C, 0.2 mmHg) for 30 min. After cooling to 23 °C, anhydrous tetrahydrofuran (8 mL) is added followed by addition of quinidine (681.3 mg, 2.10 mmol, 1.05 equiv). The reflux condenser is reconnected, and the mixture is stirred and refluxed in an 80 °C oil bath overnight (12 h). The flask containing reaction mixture is cooled to room temperature and then to −20 °C for 30 min before the solid is collected by suction filtration and washed with ice-cold anhydrous tetrahydrofuran (8 mL).

The solid is transferred to a 100 mL round-bottomed flask, and ethyl acetate (10 mL) is added, followed by addition of aqueous hydrogen chloride solution (10 mL, 2 M) and an egg-shaped stirring bar (30 × 15 mm). The mixture was stirred for 30 min at room temperature before the organic layer is isolated in a 60 mL separatory funnel. The water layer is extracted twice with ethyl acetate (15 mL × 2), and the combined organic layer is washed with brine (10 mL), dried over anhydrous magnesium sulfate, and filtered. The water layer containing chloride salt of protonated quinidine is transferred to a clean container for recovery. The organic solution is concentrated in vacuo using a rotary evaporator (40 °C, 15 mmHg). The residue is dissolved in a minimum amount of dichloromethane and loaded onto a silica gel column wet loaded with hexanes. The column is eluted with a mixture of dichloromethane and hexanes (1:2) to afford (*R*)-5,5′-Br$_2$VANOL (*R*)-**12a** as a white solid (386.4 mg, 0.648 mmol, 32%). The optical purity of (*R*)-**12a** was determined to be >99% ee by HPLC analysis (Pirkle D-phenylglycine column, 98:2 hexane/iPrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: R_t = 24.99 min for (*R*)-**12a** (major) and R_t = 27.43 min for (*S*)-**12a** (minor). $[\alpha]^{20}_D$ = −148.7 (*c* 1.0, dichloromethane) on >99% ee (*S*)-**12a** (HPLC).

*(S)-5,5′-Br$_2$VANOL (S)-**12a***. The mother liquor is transferred to a 100 mL round-bottomed flask and concentrated in vacuo using a rotary evaporator (40 °C, 15 mmHg). dichloromethane (15 mL) is added followed by addition of aqueous hydrogen chloride solution (15 mL, 2 M) and an egg-shaped stirring bar (30 × 15 mm). The mixture was stirred for 30 min at room temperature before the organic layer is isolated in a 60 mL separatory funnel. The water layer is extracted twice with dichloromethane (15 mL × 2), and the combined organic layer is washed with brine (10 mL), dried over anhydrous magnesium sulfate and filtered. The water layer containing chloride salt of protonated quinidine was transferred to a clean container for recovery. The organic solution was concentrated in vacuo using a rotary evaporator (40 °C, 15 mmHg). The residue was dissolved in a minimum amount of dichloromethane and loaded onto a silica gel column wet loaded with hexanes. The column was eluted with a mixture of dichloromethane and hexanes (1:2) to afford (*S*)-5,5′-Br$_2$VANOL (*S*)-**12a** as a white solid (775.2 mg, 1.30 mmol, 65%). The optical purity of (*S*)-**12a** was determined to be 84% ee by HPLC analysis.

*(R)-5,5′-Cl$_2$VANOL (R)-**12b***. VANOL derivative (±)-**12b** (1.015 g, 2.00 mmol, 1.00 equiv) was resolved using the general procedure E with 8 mL of refluxing anhydrous tetrahydrofuran to afford (*R*)-5,5′-Cl$_2$VANOL (*R*)-**12b** as a white solid (416.2 mg, 0.820 mmol, 41%). The optical purity of (*R*)-**12b** was determined to be >99% ee by HPLC analysis (Pirkle D-phenylglycine column, 98:2 hexane/iPrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: R_t = 21.73 min for (*R*)-**12b** (major) and R_t = 24.79 min for (*S*)-**12b** (minor). $[\alpha]^{20}_D$ = +178.3 (*c* 1.0, dichloromethane) on >99% ee (*R*)-**12b** (HPLC).

*(S)-5,5′-Cl$_2$VANOL (S)-**12b***. VANOL derivative (*S*)-**12b** is obtained by following general procedure E. Its optical purity was determined to be 84% ee by HPLC analysis.

*(R)-5,5′-Me$_2$VANOL (R)-**12c***. VANOL derivative (±)-**12c** (933.2 mg, 2.00 mmol, 1.00 equiv) was resolved using the general procedure E refluxing with 8 mL of anhydrous tetrahydrofuran and 4 mL of hexanes to afford (*R*)-5,5′-Me$_2$VANOL (*R*)-**12c** as a white solid (364.4 mg, 0.781 mmol, 39%). The optical purity of (*R*)-**12c** was determined to be >99% ee by HPLC analysis (Pirkle D-phenylglycine column, 98:2 hexane/iPrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: R_t = 17.28 min for (*R*)-**12c** (major) and R_t = 20.72 min for (*S*)-**12c** (minor). $[\alpha]^{20}_D$ = +105.2 (*c* 1.0, dichloromethane) on >99% ee (*R*)-**12c** (HPLC).

*(S)-5,5′-Me$_2$VANOL (S)-**12c***. VANOL derivative (*S*)-**12c** is obtained by following general procedure E. Its optical purity was determined to be 76% ee by HPLC analysis.

*(R)-5,5′-OMe$_2$VANOL (R)-**12d***. VANOL derivative (±)-**12d** (997.2 mg, 2.00 mmol, 1.00 equiv) was resolved using the general procedure E refluxing with 8 mL of anhydrous tetrahydrofuran and 4 mL of hexanes to afford (*R*)-5,5′-OMe$_2$VANOL (*R*)-**12d** as a white solid (462.7 mg, 0.928 mmol, 46%). The optical purity of (*R*)-**12d** was determined to be >99% ee by HPLC analysis (Pirkle D-phenylglycine column, 98:2 hexane/iPrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: R_t = 32.05 min for (*R*)-**12d** (major) and R_t = 36.45 min for (*S*)-**12d** (minor).

https://dx.doi.org/10.1021/acs.joc.0c00494
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*(S)-5,5′-OMe$_2$VANOL (S)-**12d**.* VANOL derivative (*S*)-**12d** is obtained by following general procedure E. Its optical purity is determined to be 81% ee by HPLC analysis.

*(R)-5,5′-(CF$_3$)$_2$VANOL (R)-**12e**.* VANOL derivative (±)-**12e** (1.149 g, 2.00 mmol, 1.00 equiv) was resolved using the general procedure D refluxing with 8 mL of anhydrous tetrahydrofuran and 4 mL of hexanes to afford (*R*)-5,5′-(CF$_3$)$_2$VANOL (*R*)-**12e** as a white solid (0.1517 g, 0.264 mmol, 13%). The optical purity of (*R*)-**12e** was determined to be >99% ee by HPLC analysis (Pirkle D-phenylglycine column, 98:2 hexane/iPrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: R_t = 11.65 min for (*R*)-**12e** (major) and R_t = 12.93 min for (*S*)-**12e** (minor). $[\alpha]^{20}_D$ = +163.4 (*c* 1.0, dichloromethane) on >99% ee (*R*)-**12e** (HPLC).

*(S)-5,5′-(CF$_3$)$_2$VANOL (S)-**12e**.* VANOL derivative (*S*)-**12e** is obtained by following general procedure E. Its optical purity was determined to be 16% ee by HPLC analysis.

*(R)-3,3′-pOMePh$_2$VANOL (R)-**11b**.* VANOL derivative (*R*)-**11b** (2.079 g, 4.17 mmol, 79% ee) had its optically purity enhanced using the general procedure E refluxing with 13 mL of anhydrous tetrahydrofuran and 13 mL of hexanes to afford (*R*)-3,3′-*p*OMePh$_2$VANOL (*S*)-**11b** as a white solid (1.585 g, 3.178 mmol, 76%). The optical purity of (*S*)-**S-3n** was determined to be >99% ee by HPLC analysis (Pirkle D-phenylglycine column, 98:2 hexane/iPrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: R_t = 6.31 min for (*R*)-**11b** (major) and R_t = 7.02 min for (*S*)-**11b** (minor). $[\alpha]^{20}_D$ = +271.3 (*c* 1.0, dichloromethane) on >99% ee (*R*)-**11b** (HPLC).

*(S)-3,3′-pOMePh$_2$VANOL (S)-**11b**.* VANOL derivative (*S*)-**11b** is obtained by following general procedure E. Its optical purity was determined to be 89% ee by HPLC analysis.

*(R)-7,7′-Br$_2$VANOL (R)-**13b**.* VANOL derivative (±)-**13b** (1.192 g, 2.00 mmol, 1.00 equiv) was attempted to be resolved using the general procedure D with 6 mL of refluxing anhydrous tetrahydrofuran but failed. The use of 8 mL of refluxing anhydrous toluene worked and afforded (*R*)-7,7′-Br$_2$VANOL (*R*)-**13b** as a white solid (0.420 g, 0.704 mmol, 35%). The optical purity of (*R*)-**13b** was determined to be >99% ee by HPLC analysis (Pirkle D-phenylglycine column, 98:2 hexane/iPrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: R_t = 33.57 min for (*R*)-**13b** (major) and R_t = 41.64 min for (*S*)-**13b** (minor).

*(S)-7,7′-Br$_2$VANOL (S)-**13b**.* VANOL derivative (*S*)-**13b** is obtained by following general procedure E. Its optical purity is determined to be 57% ee by HPLC analysis.

*(S)-7,7′-Ad$_2$VANOL (S)-**13e**.* VANOL derivative (±)-**13e** (1.414 g, 2.00 mmol, 1.00 equiv) was resolved using the general procedure E with 8 mL of refluxing anhydrous tetrahydrofuran to afford (*S*)-7,7′-Ad$_2$VANOL (*S*)-**13e** as a white solid (0.493 g, 0.698 mmol, 35%). The optical purity of (*S*)-**13e** was determined to be 99% ee by HPLC analysis (CHIRALCEL OD-H column, 97:3 hexanes/2-propanol at 210 nm, flow-rate: 1 mL/min). Retention times: R_t = 4.48 min for (*R*)-**13e** (minor) and R_t = 5.48 min for (*S*)-**13e** (major). $[\alpha]^{20}_D$ = −160.6 (*c* 1.0, dichloromethane) on 99% ee (*S*)-**13e** (HPLC).

*(R)-7,7′-Ad$_2$VANOL (R)-**13e**.* VANOL derivative (*R*)-**13e** is obtained by following general procedure E. Its optical purity is determined to be 59% ee by HPLC analysis.

*(R)-VANOL (R)-**1**.* VANOL (±)-**1** (877.0 mg, 2.00 mmol, 1.00 equiv) was resolved using the general procedure E refluxing with 8 mL of anhydrous tetrahydrofuran and 8 mL of hexanes to afford (*R*)-VANOL (*R*)-**1** as a white solid (0.265 g, 0.602 mmol, 31%). The optical purity of (*R*)-**1** was determined to be 66% ee by HPLC analysis (Pirkle D-phenylglycine column, 98:2 hexane/iPrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: R_t = 16.93 min for (*R*)-**1** (major) and R_t = 19.70 min for (*S*)-**1** (minor).

*(S)-VANOL (S)-**1**.* VANOL(*S*)-**1** is obtained by following general procedure E. Its optical purity was determined to be 23% ee by HPLC analysis.

*(R)-VAPOL (R)-**2**.* VAPOL (±)-**2** (1.077 g, 2.00 mmol, 1.00 equiv) was resolved using the general procedure E with 6 mL of refluxing anhydrous tetrahydrofuran to afford (*R*)-VAPOL (*R*)-**2** as a white solid (301.7 mg, 0.560 mmol, 28%). The optical purity of (*R*)-**2** was determined to be >99% ee by HPLC analysis (Pirkle D-phenylglycine column, 75:25 hexane/iPrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: R_t = 14.69 min for (*R*)-**2** (major) and R_t = 21.96 min for (*S*)-**2** (minor). $[\alpha]^{20}_D$ ND.

*(S)-VAPOL (S)-**2**.* VAPOL derivative (*S*)-**2** is obtained by following general procedure E. Its optical purity was determined to be 31% ee by HPLC analysis.

*(R)-isoVAPOL (R)-**10**. iso*VAPOL (±)-**10** (1.077 g, 2.00 mmol, 1.00 equiv) was resolved using the general procedure E refluxing with 7 mL of anhydrous tetrahydrofuran and 3 mL of hexanes to afford (*R*)-*iso*VAPOL (*R*)-**10** as a white solid (284.4 mg, 0.528 mmol, 26%). The optical purity of (*R*)-**10** was determined to be >99% ee by HPLC analysis (Pirkle D-phenylglycine column, 75:25 hexane/iPrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: R_t = 17.69 min for (*R*)-**10** (major) and R_t = 21.68 min for (*S*)-**10** (minor). $[\alpha]^{20}_D$ ND.

*(S)-isoVAPOL (S)-**10**.* VANOL derivative (*S*)-**10** was obtained by following general procedure E. Its optical purity is determined to be 35% ee by HPLC analysis.

*(R)-BINOL (R)-**7**.* BINOL (±)-7 (572.7 g, 2.00 mmol, 1.00 equiv) was resolved using the general procedure E with 5 mL of refluxing anhydrous tetrahydrofuran to afford (*R*)-BINOL (*R*)-7 as a white solid (225.1 mg, 0.786 mmol, 39%). The optical purity of (*S*)-7 was determined to be 94% ee by HPLC analysis (Pirkle D-phenylglycine column, 75:25 hexane/iPrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: R_t = 3.70 min for (*R*)-7 (major) and R_t = 3.12 min for (*S*)-7 (minor). $[\alpha]^{20}_D$ = −6.0 (*c* 1.0, dichloromethane) on 94% ee (*R*)-7 (HPLC).

*(S)-BINOL (S)-**7**.* BINOL (*S*)-7 was obtained by following general procedure E. Its optical purity was determined to be 57% ee by HPLC analysis.

*(R)-6,6′-Br$_2$BINOL (R)-**14**.* BINOL (±)-**14** (888.2 mg, 2.00 mmol, 1.00 equiv) was resolved using the general procedure E refluxing with 6 mL of anhydrous tetrahydrofuran and 3 mL of hexanes to afford (*R*)-BINOL (*R*)-**14** as a white solid (427.3 mg, 0.962 mmol, 48%). The optical purity of (*R*)-**14** was determined to be >99% ee by HPLC analysis. (Pirkle D-phenylglycine column, 75:25 hexane/iPrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: R_t = 2.83 min for (*R*)-**14** (major) and R_t = 3.31 min for (*S*)-**14** (minor). $[\alpha]^{20}_D$ = +129.6 (*c* 1.0, dichloromethane) on >99% ee (*R*)-**14** (HPLC).

(S)-6,6-Br$_2$BINOL (S)-14. BINOL derivative (*S*)-**14** was obtained by following general procedure E. Its optical purity was determined to be 88% ee by HPLC analysis.

*Large Scale Resolution of tBu$_2$VANOL **13a** with Quinine, Enantioenrichment of (R)-**13a** and Recovery of Quinine (Scheme 8). (S)-tBu$_2$VANOL (S)-**13a** and (R)-tBu$_2$VANOL (R)-**13a**.* An oven-dried 250 mL round-bottomed flask equipped with an egg-shaped stirring bar (30 × 15 mm) is placed under a nitrogen atmosphere through a gas inlet. After cooling to 23 °C, (±)-*t*Bu$_2$VANOL *rac*-**13a** (8.81 g, 16.0 mmol, 1.00 equiv) is added followed by addition of anhydrous tetrahydrofuran (65 mL) and borane dimethyl sulfide complex (8.16 mL, 2 M solution in toluene, 16.32 mmol, 1.02 equiv). An oven-dried reflux condenser with an outlet connected to a bubbler is attached to the flask. The mixture is stirred and refluxed in an 80 °C oil bath for 30 min, and the evolution of gas ceases. After cooling to room temperature (23 °C), the clear solution is concentrated in vacuo using a rotary evaporator (40 °C, 15 mmHg), and the residue is dried under high vacuum (60 °C, 0.2 mmHg) for 30 min. After cooling to 23 °C, anhydrous tetrahydrofuran (65 mL) is added followed by addition of quinine (5.294 g, 16.32 mmol, 1.02 equiv). The reflux condenser is reconnected, and the mixture is stirred and refluxed in an 80 °C oil bath overnight (12 h). A white precipitate begins to crash out after 10 min of refluxing. The flask containing reaction mixture is cooled to room temperature and then to −20 °C for 30 min before the solid is collected by suction filtration, washed with ice-cold anhydrous tetrahydrofuran (60 mL).

The solid is transferred to a 100 mL round-bottomed flask, and dichloromethane (15 mL) is added followed by addition of aqueous hydrogen chloride solution (15 mL, 2 M) and an egg-shaped stirring bar (30 × 15 mm). The mixture was stirred for 30 min at room temperature before the organic layer is isolated in a 60 mL separatory

https://dx.doi.org/10.1021/acs.joc.0c00494
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funnel. The water layer is extracted twice with dichloromethane (15 mL × 2), and the combined organic layer is washed with brine (10 mL), dried over anhydrous magnesium sulfate, and filtered. The water layer containing chloride salt of protonated quinine is transferred to a clean container for recovery. The organic solution is concentrated in vacuo using a rotary evaporator (40 °C, 15 mmHg). The residue was dissolved in a minimum amount of dichloromethane and loaded onto a silica gel column wet loaded with hexanes. The column was eluted with a mixture of dichloromethane and hexanes (1:2) to afford (*S*)-tBu$_2$VANOL (*S*)-**13a** as a white solid (3.375 g, 6.13 mmol, 38%, >99% ee).

The mother liquor is transferred to a 100 mL round-bottomed flask and concentrated in vacuo using a rotary evaporator (40 °C, 15 mmHg). Dichloromethane (15 mL) is added followed by addition of aqueous hydrogen chloride solution (15 mL, 2 M) and an egg-shaped stirring bar (30 × 15 mm). The mixture was stirred for 30 min at room temperature before the organic layer is isolated in a 60 mL separatory funnel. The water layer is extracted twice with dichloromethane (15 mL × 2), and the combined organic layer is washed with brine (10 mL), dried over anhydrous magnesium sulfate and filtered. The water layer containing chloride salt of protonated quinine is transferred to a clean container for recovery. The organic solution is concentrated in vacuo using a rotary evaporator (40 °C, 15 mmHg). The residue was dissolved in a minimum amount of dichloromethane and loaded onto a silica gel column wet loaded with hexanes. The column was eluted with a mixture of dichloromethane and hexanes (1:2) to afford crude (*R*)-tBu$_2$VANOL (*R*)-**13a** as a white solid (3.589 g, mmol, 41%, 87% ee). The crude (*R*)-**13a** is transferred to a 500 mL round-bottomed flask and hexanes (250 mL) is added. The mixture was stirred for 60 min at room temperature before the precipitate (tBu$_2$VANOL racemate) is filtered by suction filtration. The mother liquor is transferred to a 250 mL round-bottomed flask and concentrated in vacuo using a rotary evaporator (40 °C, 15 mmHg) and dried under vacuum (23 °C, 0.2 mmHg) for 1 h to afford (*R*)-tBu$_2$VANOL (*R*)-**13a** as a white solid (3.312 g, 6.01 mmol, 38%, > 99% ee). This same resolution was repeated five times, and the range of yields and optical purities are indicated in Scheme 8.

Recovery of Quinine. The combined water phase from the extraction after the hydrolysis of both the precipitate and the mother liquor was transferred to a 500 mL Erlenmeyer flask. After cooling to 0 °C for 10 min, aqueous sodium hydroxide solution (1 M) was added until pH > 8.0. The suspension was extract with dichloromethane (50 mL × 3), and the combined organic layer is washed with brine (50 mL), dried over anhydrous sodium sulfate and filtered. The organic solution is concentrated in vacuo using a rotary evaporator (40 °C, 15 mmHg) to give the crude quinine (5.356 g, 101%). Purification by crystallization from toluene gave the recovered quinine (4.7117 g, 14.5 mmol) in 89% yield (>95% pure based on ^{1}H NMR).

Crystallization-Induced Thermodynamic Resolution of VANOL. (S)-VANOL (S)-1. An oven-dried 100 mL round-bottomed flask equipped with an egg-shaped stirring bar (30 × 15 mm) is placed under a nitrogen atmosphere through a gas inlet. After cooling to 23 °C, (*R*)-VANOL (438 mg, 1.00 mmol, 1.00 equiv, >99% ee) is added followed by addition of anhydrous tetrahydrofuran (5 mL) and borane dimethyl sulfide complex (0.55 mL, 2 M solution in toluene, 1.10 mmol, 1.10 equiv). An oven-dried reflux condenser with an outlet connected to a bubbler is attached to the flask. The mixture was stirred and refluxed in an 80 °C oil bath until the evolution of gas ceases (30 min). After cooling to room temperature (23 °C), the clear solution was concentrated in vacuo using a rotary evaporator (40 °C, 15 mmHg), and the residue was dried under high vacuum (60 °C, 0.2 mmHg) for 30 min. After cooling to 23 °C, anhydrous tetrahydrofuran (5 mL) was added, followed by addition of quinine (681.3 mg, 2.10 mmol, 1.05 equiv) and di-μ-hydroxo-bis[(*N*,*N*,*N*′,*N*′-tetramethylethylenediamine)copper(II)] chloride **36** (11.6 mg, 0.050 mmol, 0.050 equiv). The reflux condenser was reconnected, and the mixture was stirred and refluxed in an 80 °C oil bath for 2 h. The flask containing the reaction mixture was cooled to room temperature then to −20 °C for 30 min before the solid is collected by suction filtration and washed with ice-cold anhydrous tetrahydrofuran (5 mL).

The solid is transferred to a 100 mL round-bottomed flask and ethyl acetate (10 mL) was added followed by addition of aqueous hydrogen chloride solution (5 mL, 2 M) and an egg-shaped stirring bar (30 × 15 mm). The mixture was stirred for 30 min at room temperature before the organic layer is separated in a 60 mL separatory funnel. The water layer is extracted twice with ethyl acetate (15 mL × 2), and the combined organic layer is washed with brine (10 mL), dried over anhydrous magnesium sulfate, and filtered. The water layer containing chloride salt of protonated quinine is transferred to a clean container for recovery. The organic solution is concentrated in vacuo using a rotary evaporator (40 °C, 15 mmHg). The residue was dissolved in a minimum amount of dichloromethane and loaded onto a silica gel column wet loaded with hexanes. The column was eluted with a mixture of dichloromethane and hexanes (1:2) to afford (*S*)-VANOL (*S*)-**1** as a white solid (246.0 mg, 0.561 mmol, 56%). The optical purity of (*S*)-**1** was determined to be >99% ee by HPLC analysis. (Pirkle D-phenylglycine column, 98:2 hexane/iPrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: R_t = 16.93 min for (*R*)-**1** (minor) and R_t = 19.70 min for (*S*)-**1** (major).

The mother liquor was transferred to a 100 mL round-bottomed flask and concentrated in vacuo using a rotary evaporator (40 °C, 15 mmHg). Dichloromethane (15 mL) was added followed by addition of aqueous hydrogen chloride solution (15 mL, 2 M) and an egg-shaped stirring bar (30 × 15 mm). The mixture was stirred for 30 min at room temperature before the organic layer was isolated in a 60 mL separatory funnel. The water layer was extracted twice with dichloromethane (15 mL × 2), and the combined organic layer was washed with brine (10 mL), dried over anhydrous magnesium sulfate, and filtered. The organic solution was concentrated in vacuo using a rotary evaporator (40 °C, 15 mmHg). The residue was dissolved in a minimum amount of dichloromethane and loaded onto a silica gel column wet loaded with hexanes. The column was eluted with a mixture of dichloromethane and hexanes (1:2) to afford (*S*)-VANOL (*S*)-**1** as a white solid (159.4 mg, 0.364 mmol, 36%). The optical purity of (*S*)-**1** was determined to be 21% ee by HPLC analysis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c00494.

Spectroscopic data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

https://dx.doi.org/10.1021/acs.joc.0c00494
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■ ACKNOWLEDGMENTS

This work was supported by the National Institute of General Medical Sciences (GM 094478).

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