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Catalytic Asymmetric Aziridination of Benzhydryl Imines and Diazoacetate Esters with BOROX Catalysts from 3,3′-Disubstituted VANOL Ligands

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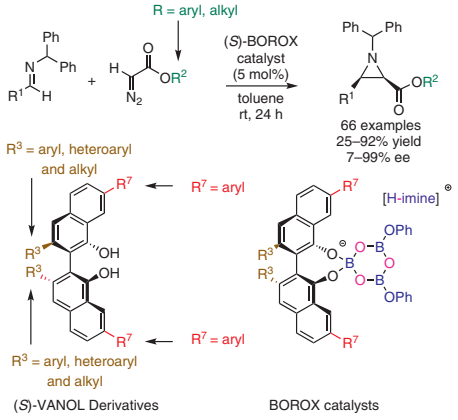

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Abstract This work details the synthesis of 22 new chiral VANOL ligands that differ by the nature of the substituent in the 3- and 3′-positions of the ligand. These ligands were incorporated into boroxinate catalysts that were used to screen the catalytic asymmetric aziridination of benzhydryl imines with ethyl diazoacetate. Each catalyst was screened in the reaction of imines generated from benzaldehyde and cyclohexanecarboxaldehyde and some with 4-nitro- and 4-methoxybenzaldehyde. In addition, the first report of the effect of the ester substituent of the diazoacetate ester on the asymmetric induction in these aziridination reactions is presented. The first X-ray structure of a boroxinate catalyst generated from a VANOL-derived ligand is also reported.

Keywords VANOL, asymmetric catalysis, aziridines, BOROX catalysts, imines

The catalytic asymmetric aziridination of imines with ethyl diazoacetate mediated by BOROX catalysts can give very high asymmetric inductions, yields and diastereoselectivities in the formation of *cis*-3-substituted aziridine-2-carboxylates.[1] The BOROX catalysts can be generated from the vaulted biaryl ligands VANOL and VAPOL directly by treatment with three equivalents of triphenylborate and three equivalents of water and one equivalent of a base, which, in the case of the aziridination reaction, is an imine,[2] or an amine[3] in a three-component reaction with an aldehyde. Alternatively, a pre-catalyst can be generated from the ligand and $B(OPh)_3$ and water as indicated in Scheme 1.[1e,g] In this case, the BOROX catalyst is generated when the imine is added to the pre-catalyst. The core structure of the BOROX catalyst is a boroxinate ring with two three-coordinate boron atoms and one four-coordinate boron.[2] The anionic charge on the boroxinate is countered with a protonated imine.[2] The catalyst functions by serving as a chiral anionic platform for the binding of both the protonated imine and the diazo compound by hydrogen bonds.[4]

The level of the enantio- and stereoselectivities is a function of the nature of the non-activating group on the imine nitrogen and on the nature of the ligand used to prepare the BOROX catalyst.[1d] In addition to the VANOL and VAPOL catalysts, we have prepared substituted VANOL ligands with substituents in all five open positions on the naphthalene core of VANOL, as indicated in structure **4** in Figure 1.[5] We have explored the effect of various substituents in positions 4–8 of VANOL on the aziridination reaction, but not variations in the 3-positions. It was found that substituents in the 7- and 7′-positions were the most beneficial to the asymmetric inductions in the aziridination reaction. We then prepared 31 different 7,7′-substituted VANOL ligands of the type **5** and found that a *t*-butyl group was the optimal substituent for the aziridination reaction.[5]

Catalysts generated from VANOL and VAPOL will catalyze the aziridination of the benzhydryl imine of benzaldehyde to give the aziridine **12a** in 93 and 94% ee; however, the reaction with the benzhydryl imine of cyclohexanecarboxaldehyde only gives the aziridine **12b** in 81 and 82% ee (Table 1, entries 1 and 2).[1e] Improved enantioselectivities were found for the imine of cyclohexanecarboxaldehyde if the N-protecting group was changed to MEDAM, which gave the aziridine **13b** in 91% ee for both the VANOL and VAPOL BOROX catalysts (entries 6 and 7).[1d] At the same time, the use of the MEDAM group increased the asymmetric induction with the imine of benzaldehyde to 97 and

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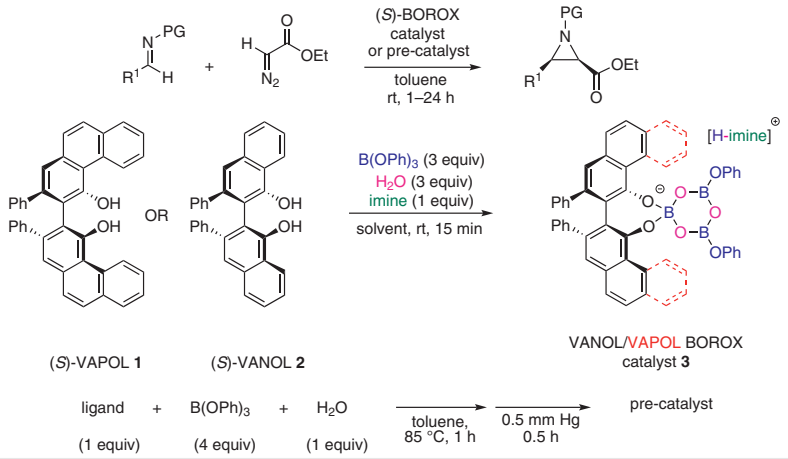


Scheme 1 Catalytic asymmetric aziridination of imines with BOROX catalysts

>99% ee. The introduction of substituents in the 7- and 7′-positions of the VANOL ligand also lead to enhanced asymmetric inductions, with the di-*t*-butyl derivative **5a** giving 98% ee for imine **8a** and 94% ee for imine **8b** (entry 3).[5]

The benzhydryl imines **8** are more attractive as substrates for the aziridination reaction because benzhydryl amine is commercially available whereas the amines for the preparation of the MEDAM and BUDAM imines are not. The subject of the present work was to explore ways to improve the yields and asymmetric inductions in the aziridination of benzhydryl imines with diazoacetates. This was done by exploring the effect of different diazoacetate esters **11** and by preparing and evaluating a series of disubstituted VANOL ligands of the type **6** and **7** where the substituent in the 3- and 3′-positions were varied with different aryl and alkyl substituents (Figure 1).

A screen of the effectiveness of different diazoacetate esters in the aziridination of the benzhydryl imine of benzaldehyde **8a** was performed and the results are summarized in Table 2. All of the diazo compounds presented in Table 2 were prepared from the tosylhydrazone of glyoxylic acid; details are given in the Supporting Information. It was of interest to observe that both the commercial and the freshly prepared ethyl diazoacetate gave essentially identical results for the formation of the aziridine **12** (entries 2 and 3). Surprisingly, there was not a great difference in either the yield or asymmetric induction of these reactions for the methyl, ethyl, isopropyl, *tert*-butyl or phenyl esters, with all giving 84–89% yield and 91–93% ee in carbon tetrachloride as solvent. Clearly, given the ease of access to ethyl diazoacetate from commercial sources, this was the diazo compound of choice for the BOROX catalyst aziridination reaction. The best solvent for the reaction with ethyl diazoacetate was carbon tetrachloride by a thin margin; however,

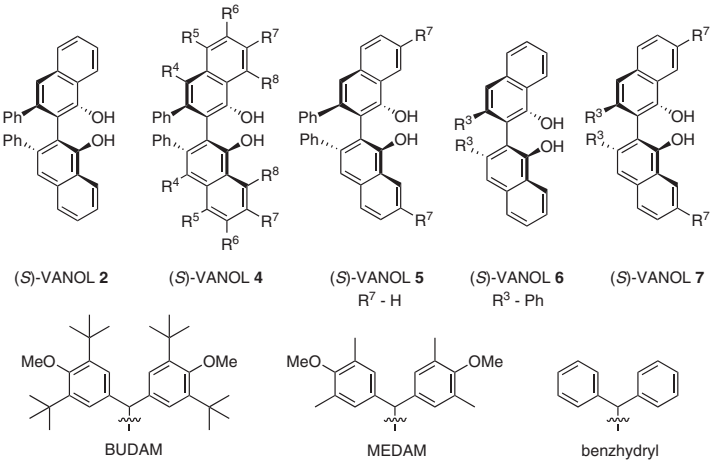
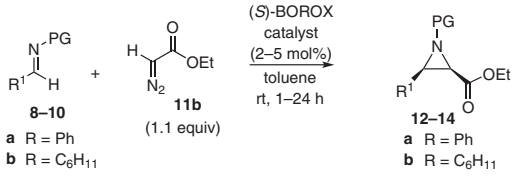


Figure 1 VANOL ligands and imine protecting groups

Table 1 Effects of Ligand and Imine Protecting Group on the Aziridination Reaction

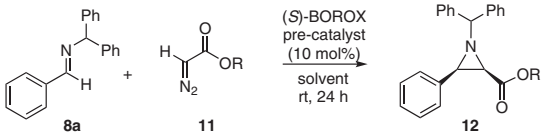


Entry	PG	Imine	Ligand	Aziridine	**a** R^1 = Ph		**b** R^1 = C_6H_{11}		Ref.
					Yield (%)	ee (%)	Yield (%)	ee (%)	
1	benzhydryl	**8**	VAPOL **1**	**12**	82	94	73	81	1e
2	benzhydryl	**8**	VANOL **2**	**12**	87	93	79	82	1e
3	benzhydryl	**8**	7,7′-*t*-Bu_2VANOL **5a**	**12**	82	98	88	94	5
4	benzhydryl	**8**	7,7′-Br_2VANOL **5b**	**12**	89	89	78	85	5
5	benzhydryl	**8**	7,7′-(4-*t*-$BuC_6H_4)_2$VANOL **5c**	**12**	85	97	83	93	5
6	MEDAM	**9**	VAPOL **1**	**13**	98	>99	98	91	1d
7	MEDAM	**9**	VANOL **2**	**13**	94	97	95	91	1d
8	BUDAM	**10**	VAPOL **1**	**14**	98	99	89	89	1f
9	BUDAM	**10**	VANOL **2**	**14**	97	98	87	84	1f

for reasons of cost and safety, toluene was identified as the solvent of choice. VAPOL gives a slightly better result than VANOL in methylene chloride (entries 4 vs 5) and VAPOL gives a slightly better induction in toluene than methylene chloride (entry 4 vs 6).

The preparation of the 3,3-disubstituted VANOL derivatives **6** follows from the procedure that we developed for the synthesis of VANOL and is outlined in Table 3.[6] The key step is the reaction of phenylacetyl chloride **19** with aryl acetylene **20** in the presence of isobutyric anhydride **21**. The reaction proceeds via a cycloaddition/electrocyclization cascade (CAEC) that results in the formation of the 3-aryl substituted naphthol **22**. This reaction proceeds via the intermediacy of phenyl ketene, which undergoes a [2+2] cycloaddition with the alkyne to give a cyclobutenone that subsequently undergoes a 4e⁻ electrocyclic ring-opening to give a vinyl ketene that then undergoes an 6e⁻ electrocyclization to the phenyl group to give naphthol **22** after tautomerization. The purpose of the anhydride **21** is to trap the naphthol **22** so that it does not react with phenyl ketene, a process that dramatically reduces the yield. A hydrolysis step is then necessary to liberate the naphthol **22** from its ester with isobutyric acid. Moderate to good yields were obtained with aryl acetylenes that bear electron-rich substituents including alkoxy groups as well as electron-poor substituents in the form of halogens. Higher yields were observed in the phenol coupling step in the preparation of **7**, which was carried out in air at 160 °C to give the racemic ligands **6**. Each of the optically pure ligands were obtained in >99% ee by deracemization with a copper complex of (–)-sparteine to give the (*S*)-enantiomer.[7] We have previously

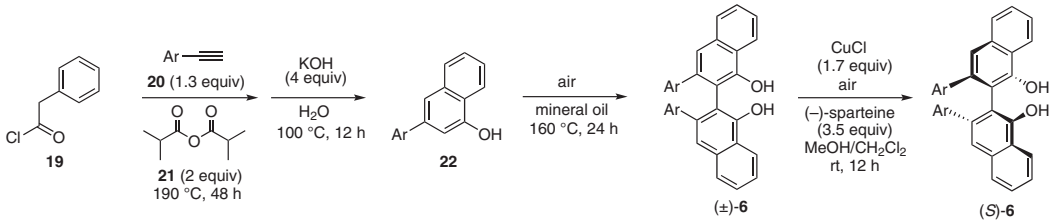
Table 2 Effects of the Diazoacetate Esters on the Azridination of Imine **8a**[a]



Entry	R	Diazo	Ligand	Solvent	Aziridine	Yield (%)[b]	ee (%)[c]
1	Me	**11a**	(*S*)-VAPOL	CCl_4	**15**	89	91
2	Et	**11b**	(*S*)-VAPOL	CCl_4	**12**	84	93
3[d]	Et	**11b**	(*S*)-VAPOL	CCl_4	**12**	85	93
4[d]	Et	**11b**	(*S*)-VAPOL	CH_2Cl_2	**12**	83	89
5[d]	Et	**11b**	(*S*)-VANOL	CH_2Cl_2	**12**	81	88
6[d]	Et	**11b**	(*S*)-VAPOL	toluene	**12**	83	91
7	*i*-Pr	**11c**	(*S*)-VAPOL	CCl_4	**16**	84	92
8	*t*-Bu	**11d**	(*S*)-VAPOL	CCl_4	**17**	89	92
9	Ph	**11e**	(*S*)-VAPOL	CCl_4	**18**	85	91

[a] Unless otherwise specified, all reactions were carried out at 0.5 M in imine with catalyst (10 mol%) and **11** (1.1 equiv). The pre-catalyst was made as indicated in Scheme 1 except that 3 equiv of $B(OPh)_3$ was used and H_2O was not included.
[b] Yield of pure *cis*-aziridine isolated by silica gel chromatography.
[c] Determined by HPLC on pure *cis*-aziridine.
[d] Diazo compound purchased from Aldrich Chemical Co.

Table 3 Preparation of 3,3-Disubstituted VANOL Ligands **6**



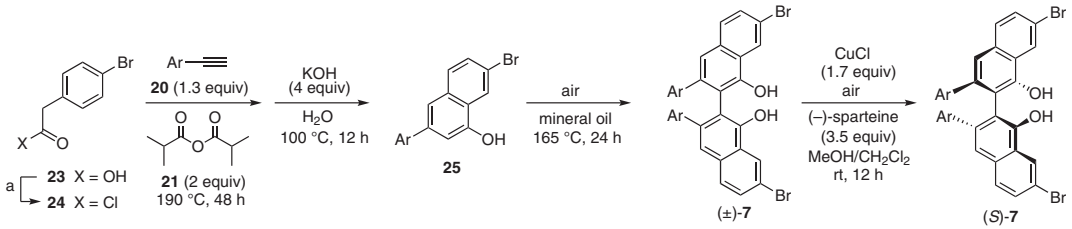
Entry	Series	Ar	Yield (%)			ee (%) of (*S*)-**6**
			22	(±)-**6**	(*S*)-**6**	
1	**a**	4-FC_6H_4	53	79	64	>99
2	**b**	4-BrC_6H_4	45	59	74	>99
3	**c**	4-PhC_6H_4	61	40	91	>99
4	**d**	3,5-$Me_2C_6H_3$	66	76	32	>99
5	**e**	4-$MeOC_6H_4$	41	62	17	>99
6	**f**	4-$EtOC_6H_4$	61	60	55	>99
7	**g**	3,5-Me_2-4-$MeOC_6H_2$	56	53	47	>99
8	**h**	2-thienyl	37	45	73	>99[a]
9	**i**	3-thienyl	57	59	40	>99[a]

[a] Reaction carried out with (+)-sparteine to give (*R*)-**6**.

established that the (*R*)-enantiomer of 7,7-disubstituted VANOL ligands can be prepared in good yield and in >99% ee by deracemization with (+)-sparteine and it would be expected that (+)-sparteine would be equally effective for 3,3-diaryl ligands of type **6**.[5]

Given that the 7,7′-disubstituted VANOL ligands were found to be clearly superior to VANOL as ligands in the aziridination reaction, we prepared a number of VANOL ligands with substituents in the 7,7′-positions and substituted phenyl substituents in the 3- and 3′-positions. It was envisioned that the most expedient method for the synthesis

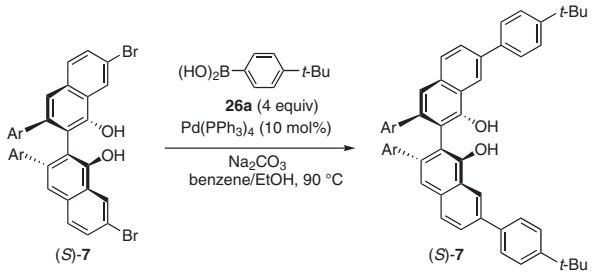
Table 4 Preparation of 3,3-Disubstituted VANOL Ligands **7**



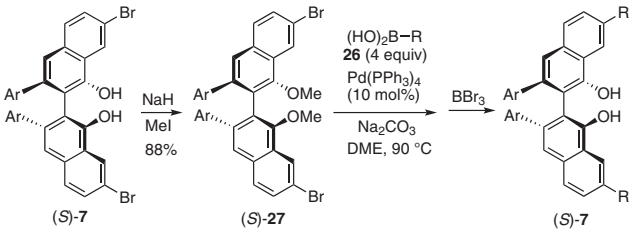
Entry	Series	Ar	Yield (%)			ee (%) of (*S*)-**7**
			25[b]	(±)-**7**	(*S*)-**7**	
1	**a**	4-FC_6H_4	37	70	87	>99
2	**d**	3,5-$Me_2C_6H_3$	61	65	75	>99
3	**e**	4-$MeOC_6H_4$	30	42[c]	69	>99
4	**g**	3,5-Me_2-4-$MeOC_6H_2$	50	40	74	>99
5	**j**	4-*n*-BuC_6H_4	68	62	80	>99
6	**k**	3,4,5-$(MeO)_3C_6H_2$	47	–[d]		

[a] $SOCl_2$, 90 °C, 1 h.
[b] Yield from **23**.
[c] Reaction at 175 °C.
[d] Not determined.

Table 5 Preparation of 3,3′- and 7,7′-Substituted VANOL Ligands 7



Entry	Starting material	Ar	Product	Yield (%)
1	**5b**	C_6H_5	**7o**	41
2	**7j**	4-*n*-BuC_6H_4	**7p**	50
3	**7d**	3,5-$Me_2C_6H_4$	**7q**	48
4	**7g**	3,5-Me_2-4-MeOC_6H_5	**7r**	26

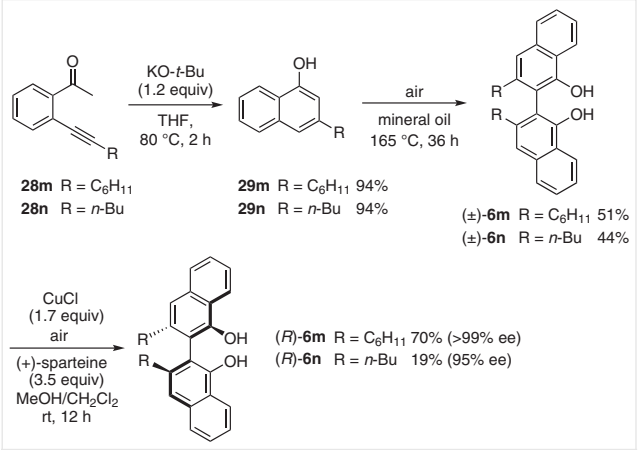


Entry	Starting material	Ar	R	Boronic acid	Product	Yield (%) from (*S*)-**27**
1	**7j**	4-*n*-BuC_6H_5	C_6H_5	**26b**	**7n**	74
2	**7j**	4-*n*-BuC_6H_5	9-anthracenyl	**26c**	**7s**	53

of these ligands would be to adopt the convergent synthesis illustrated in Table 4. Each of the aryl substituents would be first introduced with the CAEC cascade on various aryl acetylenes along with a bromo substituent in the 7,7′-positions. The bromo-substituent could then be used to introduce additional groups. Comparing the same syntheses of ligands of the type **6** (Table 3) with those of the same ligands that have the 7,7′-dibromo substituents (Table 4, entries 1–4) it can be seen that slightly lower yields are observed for the CAEC cascade step as well as for the phenol coupling step. However, the efficiency of the deracemization step is much greater, giving yields that are approximately double for the bromo series.

The preparation of the VANOL ligands **7n–s** are outlined in Table 5 and began with the corresponding optically pure 7,7′-dibromo-substituted VANOLs. The aryl groups at the 7- and 7′-positions were all introduced by the Suzuki coupling reaction with aryl boronic acids. Two strategies were employed; one without the protection of the phenol units (ligands **7o–r**) and one with protection of the phenol units (ligands **7n** and **7s**). It is our general observation that although two additional steps were required when the phenols were protected, the overall yields were higher.

The preparation of the VANOL derivatives **6m** and **6n** with alkyl groups in the 3- and 3′-positions is outlined in Scheme 2. The preparation of VANOL derivatives with methyl and *n*-decyl groups in the 3- and 3′-positions have been reported by the CAEC method.[8] We have examined an alternative method for the preparation of this class of



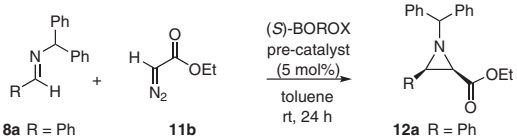
Scheme 2 Preparation of 3,3-disubstituted VANOL ligands **6m** and **6n**

VANOL ligands that begins with *o*-alkynyl acetophenones. This method relies on the base-induced cyclization of *o*-alkynyl acetophenones to give 3-substituted naphthols, as developed by Makra and co-workers.[9] Treatment of alkynyl acetophenone **28m** with potassium *t*-butoxide at 80 °C in THF gave 3-cyclohexyl-1-naphthol **29m** in 94% yield. Phenol coupling of **29m** in air at 165 °C gave the racemic 3,3′-dicyclohexyl VANOL **6m** in 51% yield. In a likewise manner, the racemic 3,3′-di-*n*-butyl VANOL **6n** was obtained in 94% and 44% yields, respectively, for the two steps. Deracemization with sparteine gave 3,3′-dicyclohexyl VANOL (*S*)-**6m** in 70% yield with >99% ee. Deracemization of (±)-**6m** gave 3,3′-di-*n*-butyl VANOL (*S*)-**6n** in ≥99% ee but the yield was only 19%. The reason for this low yield is not yet clear.

The effects of variations of the substituents in the 3- and 3′-positions of the VANOL ligands (R^3 in **6**, Figure 1) on the aziridination of imines **8a** and **8b** were surveyed and the results are presented in Table 6. The benzhydryl imine of benzaldehyde **8a** and of cyclohexanecarboxaldehyde **8b** were chosen as representative of aryl and aliphatic aldehydes. As controls, phenyl imine **8a** gave the aziridine **12a** with 92% ee with the BOROX catalyst generated from the VANOL ligand **2**, and the cyclohexyl substituted imine **8b** gave aziridine **12b** in 81% ee also with the unsubstituted VANOL catalyst (Table 6, entry 1). Most of the substituted VANOL ligands led to 2–4% higher asymmetric inductions with the phenyl imine **8a**, with the exception of the *para*-cyano ligand **6l** and the thiophene substituted ligands **6h** and **6i**. The best asymmetric induction of 96% ee with the phenyl imine **8a** was observed with a catalyst generated from ligand **6g** that has 3,5-dimethyl-4-methoxyphenyl substituents on the 3- and 3′-positions (entry 8). A precipitous drop in induction was noted for the ligands **6m** and **6n**, which have alkyl groups in the 3- and 3′-positions. At this point we have not investigated the source of this dramatic difference between aryl and alkyl groups in the 3- and 3′-positions. In the case of the cyclohexyl substituted imine **8b** there was a significant increase in the asymmetric induction of 6–7% observed with ligands that had methyl groups in the 3- and 5-positions of the aryl groups in the 3- and 3′-positions (entries 6 and 8). While the source of the effect of these methyl groups is not clear, it may be due to C–H π interactions between the ligand and the protonated imine substrate, as hinted by the X-ray structure of the BOROX catalyst generated from ligand **6g** binding with the protonated imine **30a** (Scheme 3 and Figure 2).

The results presented in Table 6 reveal the effect of the substituents at the 3- and 3′-positions of VANOL on the aziridination of the benzhydryl imine derived from benzaldehyde and, in Table 7, the synergistic effects of these ligands and the electronic nature of the imines are examined in the aziridination reaction. Two imines were chosen that

Table 6 Aziridinations with BOROX Catalysts Prepared from Ligand **6**[a]



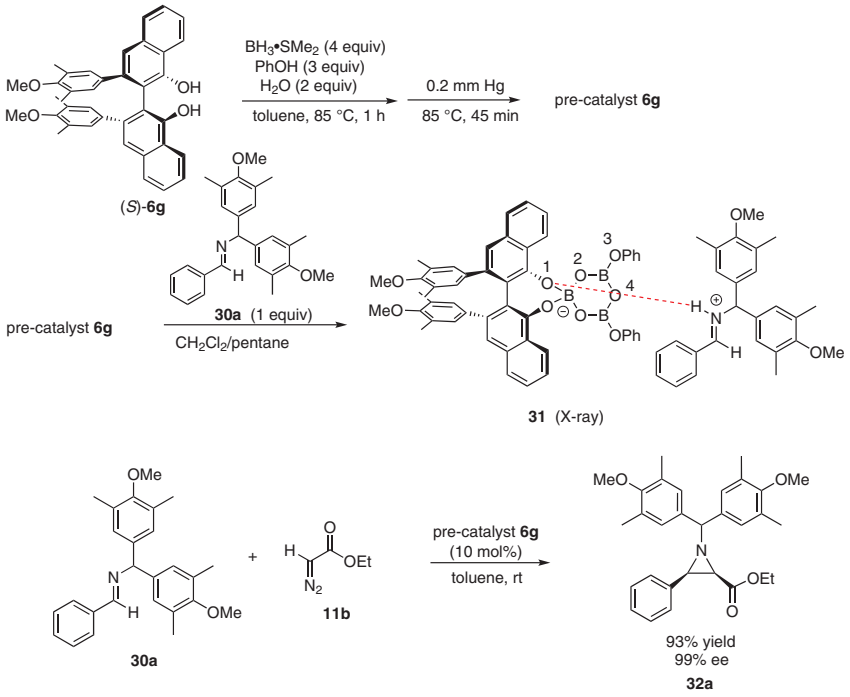
8a R = Ph
8b R = C_6H_{11}

11b (1.1 equiv)

12a R = Ph
12b R = C_6H_{11}

Entry	R^3 in **6**	Ligand	**12a** R^1 = Ph		**12b** R^1 = C_6H_{11}	
			Yield (%)[b]	ee (%)[c]	Yield (%)[b]	ee (%)[c]
1	C_6H_5	**2**	84	92	77	81
2	4-NCC_6H_4	**6l**	86	89		
3	4-FC_6H_4	**6a**	82	94	84	78
4	4-BrC_6H_4	**6b**	82	94	80	82
5	4-PhC_6H_4	**6c**	82	95	82	82
6	3,5-$Me_2C_6H_4$	**6d**	87	95	84	88
7	4-$MeOC_6H_4$	**6e**	81	95	80	80
8	3,5-Me_2-4-$MeOC_6H_3$	**6g**	85	96	79	87
9	2-thienyl	**6h**	92	89	83	77
10	3-thienyl	**6i**	91	89	83	79
11	cyclohexyl	**6m**	69	–11		
12	*n*-Bu	**6n**	71	7		

[a] Unless otherwise specified, all reactions were run at 0.5 M in imine in toluene on a 0.5 mmol scale with **11b** (1.2 equiv) at 25 °C for 24 h and went to 100% completion with 5 mol% catalyst. The pre-catalyst was prepared as indicated in Scheme 1.
[b] Yield of *cis*-aziridine isolated by silica gel chromatography.
[c] Determined by HPLC on pure *cis*-aziridine.



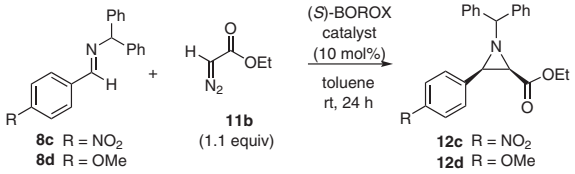
Scheme 3

had substantially different electronic characteristics, the electron-rich imine **8d** derived from *para*-methoxybenzaldehyde and the electron-poor imine **8c** derived from *para*-nitrobenzaldehyde. It was observed that the *para*-nitro substituted imine **8c** did not show any significantly different outcome in the aziridination when the ligand bearing the *para*-bromophenyl group **6b** or the 3,5-dimethylphenyl group **6d** was used to prepare the catalyst (Table 7, entries 2 and 3). The reaction of the imine of *para*-methoxybenzaldehyde **8d** was observed to give a slight drop in the induction with ligand **6b** with the *para*-bromophenyl group (entry 5) but an increase in the induction with the ligand **6d** with the 3,5-dimethylphenyl group (entry 6). Like the imine of benzaldehyde **8a**, the imine of *para*-methoxybenzaldehyde **8d** gave the highest asymmetric induction (96% ee) with ligand **6g**, which has the 3,5-dimethyl-4-methoxyphenyl substituent in the 3- and 3′-positions of the VANOL ligand (entry 7).

The data presented in Table 8 show the interactive effects of substituents in both the 3- and 3′-positions and the 7- and 7′-positions of the VANOL ligand on the aziridination reaction of the aryl and alkyl imines **8a** and **8b**, respectively (**7** in Figure 1). When the substituent in the R^7 positions was a bromide, the asymmetric induction was either unchanged or slightly increased (0–3% ee) relative to the 7,7′-unsubstituted ligand **6** (Table 6) for the imine of benzaldehyde **8a** (entries 3–6), except when the R^3 substituents were phenyl, for which the induction drops by 3% (entry 1). For the reactions of the cyclohexyl imine **8b**, the inductions increased by 4–7% ee for all of the different substituents at the R^3 positions when the R^7 substituents were bromide (entries 1, 3, 5 and 6) rather than hydrogen, except for ligand **7d**, which had the R^3 substituents as 3,5-dimethylphenyl and for which the inductions drop by 2% (entry 4). The effect of a *para*-*tert*-butylphenyl substituent at the 7- and 7′-positions significantly enhanced the asymmetric inductions of the aziridination of both the phenyl and cyclohexyl substituted imines **8a** and **8b**. Moreover, they enhanced the inductions of the best substituents in the R^3 positions. For example, the ligand **7q**, with the 3,5-dimethylphenyl groups at position R^3, gave a 5% increase (88 to 93%) in asymmetric induction for the reaction of the cyclohexyl imine **8b** and a 3% increase (95 to 98%) for the phenyl imine **8a** compared to when the *para*-*tert*-butylphenyl substituent was not present (Table 6, entry 6 vs. Table 8, entry 10).

A number of solid-state structures of the boroxinate catalysts containing the VAPOL ligand had been previously reported, which confirmed the presence of a boroxine ring in the catalyst.[2] In contrast, there are no solid-state structures of a VANOL-boroxinate catalyst, although the structure is supported by other spectroscopic data.[4a] It was noted that the boroxinate catalyst formed from the VANOL ligand **6g** tended to crystallize within the NMR tube. We previously found that the boroxinate catalyst generated from VAPOL was particularly prone to crystallization when the catalyst was formed with the MEDAM imine **30a**. Therefore, in an

Table 7 Effect of Ligand **6** on the Aziridination of Imines **8c** and **8d**[a]



8c R = NO_2
8d R = OMe

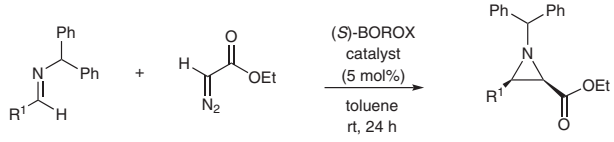
11b
(1.1 equiv)

12c R = NO_2
12d R = OMe

Entry	R	Imine	R^3 in **6**	Ligand	Yield (%)[b]	ee (%)[c]
1	NO_2	**8c**	C_6H_5	**2**	86	89
2	NO_2	**8c**	4-BrC_6H_4	**6b**	86	89
3	NO_2	**8c**	3,5-$Me_2C_6H_4$	**6d**	85	88
4	OMe	**8d**	C_6H_5	**2**	61	87
5	OMe	**8d**	4-BrC_6H_4	**6b**	68	85
6	OMe	**8d**	3,5-$Me_2C_6H_4$	**6d**	54	92
7	OMe	**8d**	3,5-Me_2-4-$MeOC_6H_5$	**6g**	62	96
8	OMe	**8d**	4-$EtOC_6H_4$	**4f**	58	88

[a] Unless otherwise specified, all reactions were carried out in 0.5 M imine in toluene at r.t. for 24 h with **11b** (1.1 equiv). Pre-catalyst prepared as indicated in Scheme 1.
[b] Isolated yield after silica gel chromatography.
[c] Determined by HPLC on a Chiralcel OD-H column.

Table 8 Effect of 3,3′,7,7′-Tetrasubstituted VANOL Ligands on the Aziridination of **8a** and **8b**[a]



8a R^1 = Ph
8b R^1 = C_6H_{11}

11b
(1.1 equiv)

12a R^1 = Ph
12b R^1 = C_6H_{11}

				12a R^1 = Ph		**12b** R^1 = C_6H_{11}	
Entry	R^7 in **7**	R^3 in **7**	Ligand	Yield (%)[b]	ee (%)[c]	Yield (%)[b]	ee (%)[c]
1	Br	C_6H_5	**5b**	89	89	78	85
2	Br	4-*n*-BuC_6H_4	**7j**	87	93	78	85
3	Br	4-FC_6H_4	**7a**	81	94	77	84
4	Br	3,5-$Me_2C_6H_4$	**7d**	82	97	63	86
5	Br	4-$MeOC_6H_4$	**7e**	82	95	75	85
6	Br	3,5-Me_2-4-$MeOC_6H_5$	**7g**	81	98	74	87
7	Ph	4-*n*-BuC_6H_4	**7n**	82	95	84	91
8	4-*t*-BuC_6H_4	C_6H_5	**7o**	85	97	83	93
9	4-*t*-BuC_6H_4	4-*n*-BuC_6H_4	**7p**	87	97	80	90
10	4-*t*-BuC_6H_4	3,5-$Me_2C_6H_4$	**7q**	82	98	83	93
11	4-*t*-BuC_6H_4	3,5-Me_2-4-$MeOC_6H_5$	**7r**	86	96	83	92
12	9-anthracenyl	4-*n*-BuC_6H_4	**7s**	57	90	25[d]	64

[a] Unless otherwise specified, all reactions were run at 0.5 M in imine in toluene on a 0.5 mmol scale with **11b** (1.2 equiv) at r.t., for 24 h and went to 100% completion with 5 mol% catalyst. The pre-catalyst was prepared as indicated in Scheme 1.
[b] Yield of isolated *cis*-aziridine by silica gel chromatography.
[c] Determined by HPLC on a Chiralcel OD-H column.
[d] Reaction time was 48 h.

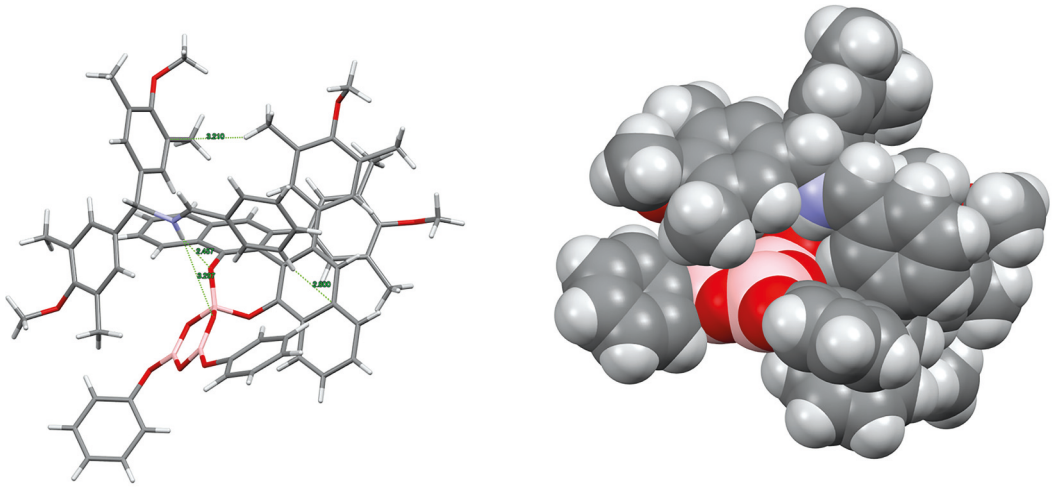


Figure 2 X-ray crystal structure of BOROX-iminium complex **31**

effort to obtain the first X-ray structure of a boroxinate catalyst derived from a VANOL ligand, we prepared the precatalyst from the ligand (*S*)-**6g** as indicated in Scheme 3 and then added 1 equivalent of the MEDAM imine **30a**. The resulting mixture was divided among several NMR tubes under nitrogen with various mixtures of pentane and methylene chloride. Yellow crystals grew in several of the NMR tubes and were found to be of suitable quality for X-ray diffraction analysis. Crystals of this complex could also be grown from a solution prepared from $B(OPh)_3$ instead of $BH_3{\cdot}SMe_2$ and phenol.[2] To confirm that this VANOL boroxinate was indeed capable of catalyzing the aziridination reaction, we carried out the reaction of imine **30a** with ethyl diazoacetate **11b** with 10 mol% precatalyst **6g** and obtained the aziridine **32a** in 93% yield and 99% ee.

The X-ray crystal structure of **31** (Figure 2) confirmed that a boroxinate ring was also generated in the reaction of a VANOL derivative with borane dimethyl sulfide complex, phenol, water and an imine.

There are both similarities and differences in the boroxinate structures of VANOL and VAPOL. As in VAPOL boroxinate complexes, there are a number of noncovalent interactions between the protonated imine substrate and the anionic boroxinate core of VANOL.[2] The strongest interaction is undoubtedly the H-bond between the protonated imine and O-2 of the boroxinate core (H–O 2.457 Å). In contrast to the VAPOL structure, the arene group on the imine carbon does not have a π-π stacking interaction with the naphthalene ring (phenanthrene in the case of VAPOL) of the VANOL ligand **6g**.

Instead, there is a C-H-π interaction (2.800 Å) from the edge of the phenyl ring on the imine carbon and the face of the naphthalene ring. This twist in the orientation of the imine in the binding pocket allows for the formation of a C-H-π interaction (3.210 Å) between one of the arenes on the diarylmethyl substituent on the nitrogen and a methyl group on the aryl ring in the 3-position of the VANOL ligand. This type of interaction is not present in the VAPOL structure.[2]

In conclusion, a series of 22 new VANOL derivatives were prepared and examined as boroxinate catalysts in the asymmetric aziridination of imines with diazoacetate esters. Emphasis was placed on the preparation of ligands that varied in the nature of the substituent in the 3- and 3′-positions since catalysts from these derivatives have not previously been reported. These ligands were prepared by the cycloaddition/electrocyclic ring opening/electrocyclic ring closing cascade (CAEC) and also by an intramolecular enolate/alkyne addition. The asymmetric induction in the aziridination of catalysts generated from these 22 ligands were all screened with imines prepared from both benzaldehyde and cyclohexanecarboxaldehyde. The incorporation of a number of different aryl groups in the 3- and 3′-positions of the VANOL ligand led to catalysts that gave rise to aziridines with slightly improved asymmetric inductions for both imines when compared to the standard phenyl group in the VANOL ligand itself. Exception was found with a 4-cyanophenyl group and 2- and 3-thiophene substituents. The introduction of alkyl groups in the 3- and 3′-positions of VANOL resulted in a catastrophic loss of asymmetric induction in the aziridines. The combination of substituents in both the 3,3′-position and the 7,7′-positions of the VANOL ligand, in general, gave rise to slightly improved outcomes in the aziridination of the imine of benzaldehyde in comparison with those ligands only having substituents in the 3- and 3′-positions and this was especially true for the aziridinations of the imine from cyclohexanecarboxaldehyde (with phenyl substituents in the 7,7′-positions). In addition, the

effect of the variation of the oxygen substituent on the ester of the α-diazoacetate ester was examined in the aziridination reaction and it was found that the yield and asymmetric induction of the aziridines were essentially independent of the nature of the oxygen substituent. Unlike VAPOL, the boroxinate structure in a BOROX catalyst has not been previously confirmed with a VANOL ligand before by X-ray diffraction but has been in the present work with a complex from ligand **6g** and the imine **30a**. The noncovalent binding of the protonated imine **30a** substrate in the BOROX catalyst **31** is similar to that of VAPOL in that the protonated imine is H-bonded to the boroxinate core to O-2, but the orientation of the imine is skewed to produce C–H interactions with the aryl substituent in the 3- and 3′-positions of the VANOL ligand. This was not observed in the VAPOL structure, presumably because the VAPOL ligand had unsubstituted phenyl groups in the 3- and 3′-positions.

Dichloromethane, acetonitrile and triethylamine were distilled from calcium hydride under nitrogen. Toluene, THF, benzene and diethyl ether were distilled from sodium under nitrogen. Hexanes and EtOAc were ACS grade and used as purchased. Other reagents were used as purchased from Aldrich or other commercial sources. Commercially available benzhydrylamine and liquid aldehydes were distilled prior to use. Alkynes were prepared according to the published procedures.[10–13] Ligand **5b** and **7o** were prepared according to the published procedure.[14]

Synthesis of 3-Aryl-1-naphthols (Table 3); Typical Procedure I

3-(3,5-Dimethylphenyl)naphthalen-1-ol (22d)

To a 250 mL flame-dried round-bottom flask was added phenylacetyl chloride **19** (2.64 mL, 20.0 mmol), 1-ethynyl-3,5-dimethylbenzene **20d** (2.60 g, 20.0 mmol) and $(i\text{-PrCO})_2O$ (6.7 mL, 40 mmol) under N_2. The mixture was stirred at 190 °C for 48 h with a gentle nitrogen flow across the top of the condenser. The brown reaction mixture was cooled to below 100 °C (ca. 60 °C, oil bath temperature) and a solution of KOH (4.48 g, 80 mmol) in H_2O (20 mL) was then added slowly. The two-phase mixture was stirred at 100 °C overnight. The mixture was cooled to r.t. and EtOAc (60 mL) was added and the mixture stirred for 10 min before the organic layer was separated. The aqueous layer was extracted with EtOAc (2 × 30 mL) and the combined organic layer was washed with brine (30 mL), dried over $MgSO_4$, filtered through Celite and concentrated to dryness. Purification of the crude product by column chromatography on silica gel (50 mm × 250 mm, CH_2Cl_2/hexanes 1:1 to 2:1 to 1:0) gave **22d**.

Yield: 3.26 g (13.1 mmol, 66%); yellow solid; mp 104–105 °C; R_f = 0.34 (CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.39 (s, 6 H), 5.26 (s, 1 H), 7.01 (s, 1 H), 7.07 (d, J = 1.5 Hz, 1 H), 7.29 (s, 2 H), 7.44–7.52 (m, 2 H), 7.83–7.85 (m, 1 H), 8.13–8.16 (m, 1 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 21.43, 108.59, 118.73, 121.42, 123.53, 125.19, 125.24, 126.81, 128.01, 129.13, 135.00, 138.34, 139.18, 140.92, 151.59.

IR (thin film): 3430br s, 2919s, 1576s, 1456s, 1400s, 1271s cm^{-1}.

HRMS (ESI+): m/z [M + H]$^+$ calcd for $C_{18}H_{17}O$: 249.1279; found: 249.1268.

3-(4-Fluorophenyl)naphthalen-1-ol (22a)

The reaction of phenylacetyl chloride **19** (2.64 mL, 20.0 mmol), 1-ethynyl-4-fluorobenzene **20a** (2.40 g, 20.0 mmol) and $(i\text{-PrCO})_2O$ (6.7 mL, 40 mmol) was performed according to Typical Procedure I. Purification of the crude product by column chromatography on silica gel (50 mm × 250 mm, CH_2Cl_2/hexanes 1:1 to 2:1 to 1:0) gave **22a**.

Yield: 2.54 g (10.6 mmol, 53%); off-white solid; mp 96–97 °C; R_f = 0.30 (CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 5.30 (s, 1 H), 7.02 (d, J = 2.0 Hz, 1 H), 7.11–7.17 (m, 2 H), 7.45–7.53 (m, 2 H), 7.58 (s, 1 H), 7.59–7.64 (m, 2 H), 7.82–7.85 (m, 1 H), 8.14–8.17 (m, 1 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 108.27, 115.61 ($^2J_{CF}$ = 21 Hz), 118.64, 121.42, 123.47, 125.41, 127.02, 127.97, 128.83 ($^3J_{CF}$ = 7.9 Hz), 134.94, 137.03 ($^4J_{CF}$ = 3.3 Hz), 137.91, 151.76, 162.56 ($^1J_{CF}$ = 245.4 Hz).

^{19}F NMR ($CDCl_3$, 283 MHz): δ = –113.77.

IR (thin film): 3399br w, 1507s, 1401s, 1237s cm^{-1}.

HRMS (ESI+): m/z [M + H]$^+$ calcd for $C_{16}H_{12}FO$: 239.0872; found: 239.0884.

3-(4-Bromophenyl)naphthalen-1-ol (22b)

The reaction of phenylacetyl chloride **19** (2.64 mL, 20.0 mmol), 1-bromo-4-ethynylbenzene **20b** (3.62 g, 20.0 mmol) and $(i\text{-PrCO})_2O$ (6.7 mL, 40 mmol) was performed according to Typical Procedure I. Purification of the crude product by column chromatography on silica gel (50 mm × 250 mm, CH_2Cl_2/hexanes 1:1 to 2:1 to 1:0) gave **22b**.

Yield: 2.70 g (9.03 mmol, 45%); off-white solid; mp 168–169 °C; R_f = 0.31 (CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 5.36 (s, 1 H), 7.01 (d, J = 1.5 Hz, 1 H), 7.46–7.54 (m, 4 H), 7.55–7.59 (m, 2 H), 7.59 (s, 1 H), 7.82–7.85 (m, 1 H), 8.14–8.17 (m, 1 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 107.97, 118.70, 121.46, 121.70, 123.68, 125.57, 127.09, 128.03, 128.85, 131.92, 134.92, 137.64, 139.83, 151.88.

IR (thin film): 3355br w, 1576s, 1493s, 1399s, 1265s cm^{-1}.

HRMS (ESI+): m/z [M + H]$^+$ calcd for $C_{16}H_{10}{}^{79}BrO$: 296.9915; found: 296.9906.

3-(4-Methoxyphenyl)naphthalen-1-ol (22e)

The reaction of phenylacetyl chloride **19** (2.64 mL, 20.0 mmol), 1-ethynyl-4-methoxybenzene **20e** (2.64 g, 20.0 mmol) and $(i\text{-PrCO})_2O$ (6.7 mL, 40 mmol) was performed according to Typical Procedure I. Purification of the crude product by column chromatography on silica gel (50 mm × 250 mm, CH_2Cl_2/hexanes 1:1 to 2:1 to 1:0) gave **22e**.

Yield: 2.07 g (8.28 mmol, 41%); pale-brown solid; mp 151–152 °C; R_f = 0.19 (CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 3.85 (s, 3 H), 5.27 (s, 1 H), 6.99 (dd, J = 9.0, 2.0 Hz, 2 H), 7.05 (d, J = 1.0 Hz, 1 H), 7.43–7.51 (m, 2 H), 7.58–7.61 (m, 3 H), 7.82 (d, J = 7.5 Hz, 1 H), 8.12–8.15 (m, 1 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 55.39, 108.26, 114.30, 118.05, 121.40, 123.24, 125.05, 126.84, 127.88, 128.30, 133.43, 135.04, 138.51, 151.65, 159.29.

IR (thin film): 3357br w, 1587s, 1456s, 1401s, 1250s, 1184s cm^{-1}.

HRMS (ESI–): m/z [M – H]$^-$ calcd for $C_{17}H_{13}O_2$: 249.0916; found: 249.0921.

3-(4-Methoxy-3,5-dimethylphenyl)naphthalen-1-ol (22g)

The reaction of phenylacetyl chloride **19** (2.64 mL, 20.0 mmol), 5-ethynyl-2-methoxy-1,3-dimethylbenzene **20g** (3.20 g, 20.0 mmol) and (*i*-PrCO)$_2$O (6.7 mL, 40 mmol) was performed according to Typical Procedure I. Purification of the crude product by column chromatography on silica gel (50 mm × 250 mm, CH_2Cl_2/hexanes 1:1 to 2:1 to 1:0) gave **22g**.

Yield: 3.10 g (11.1 mmol, 56%); light-yellow solid; mp 156–157 °C; R_f = 0.19 (CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.36 (s, 6 H), 3.77 (s, 3 H), 5.33 (s, 1 H), 7.02 (d, *J* = 1.5 Hz, 1 H), 7.31 (s, 2 H), 7.43–7.51 (m, 2 H), 7.57 (s, 1 H), 7.82 (d, *J* = 7.5 Hz, 1 H), 8.13–8.15 (m, 1 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 16.29, 59.84, 108.39, 118.32, 121.44, 123.38, 125.07, 126.79, 127.75, 127.91, 131.18, 134.96, 136.54, 138.68, 151.63, 156.57.

IR (thin film): 3359br s, 2942s, 1576s, 1489s, 1402s, 1230s, 1157s cm^{-1}.

HRMS (ESI–): *m*/*z* [M – H]$^-$ calcd for $C_{19}H_{17}O_2$: 277.1229; found: 277.1224.

3-(Thiophen-2-yl)naphthalen-1-ol (22h)

The reaction of phenylacetyl chloride **19** (3.72 mL, 28.1 mmol), 2-ethynylthiophene **20h** (3.04 g, 28.1 mmol) and (*i*-PrCO)$_2$O (9.33 mL, 56.3 mmol) was performed according to Typical Procedure I. Purification of the crude product by column chromatography on silica gel (50 mm × 250 mm, CH_2Cl_2/hexanes 1:2 to 1:1 to 1:0) gave **22h**.

Yield: 1.66 g (7.35 mmol, 37%); brownish pink solid; mp 128–129 °C; R_f = 0.35 (CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 5.35 (s, 1 H), 7.07–7.11 (m, 2 H), 7.30 (dd, *J* = 5.0, 1.5 Hz, 1 H), 7.36 (dd, *J* = 3.5, 1.5 Hz, 1 H), 7.43–7.51 (m, 2 H), 7.67 (s, 1 H), 7.79–7.82 (m, 1 H), 8.11–8.14 (m, 1 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 107.20, 117.36, 121.51, 123.42, 123.77, 125.02, 125.34, 127.14, 127.84, 128.06, 131.95, 134.91, 144.22, 151.69.

IR (thin film): 3320br s, 1599s, 1401s, 1262s cm^{-1}.

HRMS (ESI–): *m*/*z* [M – H]$^-$ calcd for $C_{14}H_9OS$: 225.0374; found: 225.0377.

3-(Thiophen-3-yl)naphthalen-1-ol (22i)

The reaction of phenylacetyl chloride **19** (2.64 mL, 20.0 mmol), 3-ethynylthiophene **20i** (2.16 g, 20.0 mmol) and (*i*-PrCO)$_2$O (6.7 mL, 40 mmol) was performed according to Typical Procedure I. Purification of the crude product by column chromatography on silica gel (50 mm × 250 mm, CH_2Cl_2/hexanes 1:2 to 1:1 to 1:0) gave **22i**.

Yield: 2.58 g (11.4 mmol, 57%); brownish pink solid; mp 119–120 °C; R_f = 0.32 (CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 5.34 (s, 1 H), 7.06 (d, *J* = 1.5 Hz, 1 H), 7.40 (dd, *J* = 5.5, 3.0 Hz, 1 H), 7.45–7.51 (m, 4 H), 7.65 (s, 1 H), 7.82 (d, *J* = 7.5 Hz, 1 H), 8.14 (d, *J* = 8.0 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 107.84, 117.90, 120.62, 121.43, 123.58, 125.22, 126.31, 126.38, 126.96, 127.88, 133.44, 134.99, 142.05, 151.66.

IR (thin film): 3362br s, 1599s, 1507s, 1418s, 1275s cm^{-1}.

HRMS (ESI–): *m*/*z* [M – H]$^-$ calcd for $C_{14}H_9OS$: 225.0374; found: 225.0382.

Synthesis of 3-Aryl-7-bromo-1-naphthols (Table 4); Typical Procedure II

7-Bromo-3-(4-fluorophenyl)naphthalen-1-ol (25a)

A single-neck round-bottom flask equipped with a condenser was charged with 4-bromo-phenylacetic acid **23** (4.30 g, 20.0 mmol), and $SOCl_2$ (5.3 mL, 73 mmol). The top of the condenser was vented to a bubbler and then into a beaker filled with NaOH (sat. aq.) to trap acidic gases. The mixture was heated to reflux for 1 h in a 90 °C oil bath, and then all of the volatiles were carefully removed by swirling it under high vacuum (1 mmHg) for 1 h with a second liquid N_2 trap to protect the pump. To the flask containing the acyl chloride **24** was added 1-ethynyl-4-fluorobenzene **20a** (2.40 g, 20.0 mmol) and (*i*-PrCO)$_2$O (6.7 mL, 40 mmol) under N_2. The mixture was stirred at 190 °C for 48 h with a gentle nitrogen flow across the top of the condenser. The brown reaction mixture was cooled to below 100 °C (ca. 60 °C, oil bath temperature) and a solution of KOH (4.48 g, 80 mmol) in H_2O (20 mL) was then added slowly. The two-phase mixture was stirred at 100 °C overnight. The mixture was cooled to r.t., EtOAc (60 mL) was added and the mixture was stirred for 10 min before the organic layer was separated. The aqueous layer was extracted with EtOAc (2 × 30 mL) and the combined organic layer was washed with brine (30 mL), dried over $MgSO_4$, filtered through Celite and concentrated to dryness. Purification of the crude product by column chromatography on silica gel (50 mm × 250 mm, CH_2Cl_2/hexanes 1:1 to 2:1 to 1:0) gave **25a**.

Yield: 2.33 g (7.35 mmol, 37%); off-white solid; mp 96–97 °C; R_f = 0.30 (CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 5.27 (s, 1 H), 7.01 (d, *J* = 1.5 Hz, 1 H), 7.14 (t, *J* = 8.7 Hz, 2 H), 7.52 (s, 1 H), 7.53–7.62 (m, 3 H), 7.68 (d, *J* = 8.7 Hz, 1 H), 8.34 (d, *J* = 1.9 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 109.16, 115.81 ($^2J_{CF}$ = 21.3 Hz), 118.47, 119.39, 124.29, 124.61, 128.81 ($^3J_{CF}$ = 7.5 Hz), 129.53, 130.45, 133.34, 136.64 ($^4J_{CF}$ = 3.8 Hz), 138.41, 150.93, 162.68 ($^1J_{CF}$ = 246.3 Hz).

^{19}F NMR ($CDCl_3$, 283 Hz): δ = –113.30.

IR (thin film): 3399br w, 1507s, 1401s, 1237s cm^{-1}.

7-Bromo-3-(3,5-dimethylphenyl)naphthalen-1-ol (25d)

The reaction of 4-bromo-phenylacetic acid **23** (4.30 g, 20.0 mmol), $SOCl_2$ (5.3 mL, 73 mmol), 1-ethynyl-3,5-dimethylbenzene **20d** (2.60 g, 20.0 mmol) and (*i*-PrCO)$_2$O (6.7 mL, 40 mmol) was performed according to Typical Procedure II. Purification of the crude product by column chromatography on silica gel (50 mm × 250 mm, CH_2Cl_2/hexanes 1:1 to 2:1 to 1:0) gave **25d**.

Yield: 3.96 g (12.1 mmol, 61%); off-white solid; mp 110–111 °C; R_f = 0.19 (2:1 CH_2Cl_2/hexanes).

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.39 (s, 6 H), 5.22 (s, 1 H), 7.01 (s, 1 H), 7.07 (d, *J* = 1.5 Hz, 1 H), 7.26 (s, 2 H), 7.55 (dd, *J* = 9.0, 2.0 Hz, 1 H), 7.57 (s, 1 H), 7.69 (d, *J* = 9.0 Hz, 1 H), 8.33 (d, *J* = 2.0 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 21.40, 109.43, 118.53, 119.13, 124.25, 124.60, 125.16, 129.34, 129.55, 130.21, 133.35, 138.43, 139.67, 140.47, 150.72.

IR (thin film): 3509br m, 2918w, 1587s, 1474s, 1404s, 1267s cm^{-1}.

MS: *m*/*z* (%) = 328 (91, ^{81}Br) [M]$^+$, 326 (100, ^{79}Br) [M]$^+$, 202 (42), 163 (20).

Anal calcd for $C_{18}H_{15}BrO$: C, 66.07; H, 4.62. Found: C, 66.00; H, 4.42.

7-Bromo-3-(4-methoxyphenyl)naphthalen-1-ol (25e)

The reaction of 4-bromo-phenylacetic acid **23** (4.30 g, 20.0 mmol), $SOCl_2$ (5.3 mL, 73 mmol), 1-ethynyl-4-methoxybenzene **20e** (2.64 g, 20.0 mmol) and $(i\text{-PrCO})_2O$ (6.7 mL, 40 mmol) was performed according to Typical Procedure II. Purification of the crude product by column chromatography on silica gel (50 mm × 250 mm, CH_2Cl_2/hexanes 1:1 to 2:1 to 1:0) gave **25e**.

Yield: 1.98 g (6.0 mmol, 30%); off-white solid; mp 168–170 °C; R_f = 0.26 (CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 3.85 (s, 3 H), 5.24 (s, 1 H), 6.98–7.00 (m, 2 H), 7.53–7.55 (m, 2 H), 7.56–7.58 (m, 2 H), 7.67 (d, *J* = 9.0 Hz, 1 H), 8.32 (d, *J* = 2.0 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 55.40, 109.13, 114.38, 117.87, 118.96, 124.24, 124.37, 128.27, 129.46, 130.25, 132.99, 133.45, 139.03, 150.82, 159.48.

IR (thin film): 3395br s, 1578s, 1507s, 1402s, 1240s, 1179s cm^{-1};

MS: *m*/*z* (%) = 330 (89, ^{81}Br) [M]$^+$, 328 (100, ^{79}Br) [M]$^+$, 315 (29, ^{81}Br), 313 (31, ^{79}Br), 285 (14), 205 (15).

Anal calcd for $C_{17}H_{13}BrO_2$: C, 62.03; H, 3.98. Found: C, 61.83; H, 3.92.

7-Bromo-3-(4-methoxy-3,5-dimethylphenyl)naphthalen-1-ol (25g)

The reaction of 4-bromo-phenylacetic acid **23** (4.30 g, 20.0 mmol), $SOCl_2$ (5.3 mL, 73 mmol), 5-ethynyl-2-methoxy-1,3-dimethylbenzene **20g** (3.20 g, 20.0 mmol) and $(i\text{-PrCO})_2O$ (6.7 mL, 40 mmol) was performed according to Typical Procedure II. Purification of the crude product by column chromatography on silica gel (50 mm × 250 mm, CH_2Cl_2/hexanes 1:1 to 2:1 to 1:0) gave **25g**.

Yield: 3.56 g (10.0 mmol, 50%); off-white solid; mp 146–148 °C; R_f = 0.22 (CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.35 (s, 6 H), 3.78 (s, 3 H), 5.46 (s, 1 H), 6.98 (d, *J* = 1.5 Hz, 1 H), 7.27 (s, 2 H), 7.51 (s, 1 H), 7.54 (dd, *J* = 8.5, 2.0 Hz, 1 H), 7.67 (d, *J* = 9.0 Hz, 1 H), 8.33 (d, *J* = 2.0 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 16.29, 59.84, 109.29, 118.15, 119.02, 124.28, 124.52, 127.72, 129.49, 130.21, 131.30, 133.38, 136.13, 139.22, 150.80, 156.79.

IR (thin film): 3341br s, 2928s, 1587s, 1485s, 1402s, 1227s, 1157s cm^{-1}.

MS: *m*/*z* (%) = 358 (77, ^{81}Br) [M]$^+$, 356 (80, ^{79}Br) [M]$^+$, 343 (50, ^{81}Br), 341 (52, ^{79}Br), 314 (4, ^{81}Br), 312 (5, ^{79}Br), 202 (28), 189 (49), 171 (34), 100 (100).

Anal calcd for $C_{19}H_{17}BrO_2$: C, 63.88; H, 4.80. Found: C, 63.73; H, 4.72.

7-Bromo-3-(4-butylphenyl)naphthalen-1-ol (25j)

The reaction of 4-bromo-phenylacetic acid **23** (23.7 g, 110 mmol), $SOCl_2$ (29 mL, 398 mmol), 1-butyl-4-ethynylbenzene **20j** (20 g, 127 mmol) and $(i\text{-PrCO})_2O$ (37 mL, 223 mmol) was performed according to Typical Procedure II. Purification of the crude product by column chromatography on silica gel (50 mm × 250 mm, CH_2Cl_2/hexanes 1:3 to 1:2 to 1:1 to 2:1) gave **25j**.

Yield: 26.5 g (74.6 mmol, 68%); light-brown solid; mp 106–109 °C; R_f = 0.21 (2:1 CH_2Cl_2/hexanes).

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 0.94 (t, *J* = 7.5 Hz, 3 H), 1.34–1.43 (m, 2 H), 1.60–1.67 (m, 2 H), 2.65 (t, *J* = 7.5 Hz, 2 H), 5.25 (s, 1 H), 7.07 (d, *J* = 1.5 Hz, 1 H), 7.25–7.28 (m, 2 H), 7.53–7.57 (m, 4 H), 7.69 (d, *J* = 8.5 Hz, 1 H), 8.33 (d, *J* = 2.0 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 13.94, 22.39, 33.58, 35.31, 109.28, 118.29, 119.10, 124.26, 124.57, 127.05, 128.98, 129.54, 130.23, 133.43, 137.78, 139.42, 142.63, 150.82.

IR (thin film): 3260br s, 2926s, 1589s, 1406s, 1254s cm^{-1}.

HRMS (ESI–): *m*/*z* [M – H]$^-$ calcd for $C_{20}H_{18}{}^{79}BrO$: 353.0541; found: 353.0539.

7-Bromo-3-(3,4,5-trimethoxyphenyl)naphthalen-1-ol (25k)

The reaction of 4-bromophenylacetic acid **23** (4.30 g, 20.0 mmol), $SOCl_2$ (5.3 mL, 73 mmol), 5-ethynyl-1,2,3-trimethoxybenzene **20k** (3.84 g, 20.0 mmol) and $(i\text{-PrCO})_2O$ (6.7 mL, 40 mmol) was performed according to Typical Procedure II. Purification of the crude product by column chromatography on silica gel (50 mm × 250 mm, EtOAc/hexanes 1:4 to 1:2) gave **25k**.

Yield: 3.69 g (9.49 mmol, 47%); yellow solid; mp 177–179 °C; R_f = 0.16 (1:2 EtOAc/hexanes).

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 3.90 (s, 6 H), 3.91 (s, 3 H), 5.74 (s, 1 H), 6.80 (s, 2 H), 6.99 (d, *J* = 1.0 Hz, 1 H), 7.50 (s, 1 H), 7.56 (dd, *J* = 8.5, 2.0 Hz, 1 H), 7.69 (d, *J* = 9.0 Hz, 1 H), 8.36 (d, *J* = 2.0 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 56.28, 61.03, 104.71, 109.39, 118.20, 119.26, 124.38, 124.76, 129.47, 130.36, 133.28, 136.73, 139.56, 151.03, 153.53.

IR (thin film): 3413br m, 2938m, 1589s, 1503s, 1406s, 1240s, 1129s cm^{-1}.

MS: *m*/*z* (%) = 390 (14, ^{81}Br) [M]$^+$, 388 (13, ^{79}Br) [M]$^+$, 375 (7, ^{81}Br), 373 (7, ^{79}Br), 236 (4, ^{81}Br), 234 (4, ^{79}Br).

Anal calcd for $C_{19}H_{17}BrO_4$: C, 58.63; H, 4.40. Found: C, 58.39; H, 4.19.

Oxidative Dimerization of 3-Aryl-1-naphthols and Their Deracemization (Table 3 and Table 4): Typical Procedure III

VANOL Derivative (*S*)-6a

Oxidative phenol-coupling: To a flame-dried, three-neck, round-bottom flask equipped with a cooling condenser was added 3-(4-fluorophenyl)naphthalen-1-ol **22a** (952 mg, 4.00 mmol) and mineral oil (5 mL). Airflow was introduced from one side neck via a needle located one inch above the mixture. The airflow rate was about one bubble per second. The mixture was stirred at 165 °C for 24 h. Purification by column chromatography on silica gel (35 mm × 200 mm, CH_2Cl_2/hexanes 2:3) gave racemic **6a** as an off-white solid (752 mg, 1.58 mmol, 79% yield).

Deracemization: The original procedure[7] involves sonification to presumably facilitate reaction. However, it was later found that the deracemization of VAPOL gives the same result whether or not sonification is employed. The following procedure follows the original report: To a round-bottom flask was added (–)-sparteine (754 mg, 3.22 mmol), CuCl (155 mg, 1.57 mmol) and MeOH (25 mL) under an atmosphere of air. The reaction mixture was sonicated in a water bath for 60 minutes with exposure to air. The flask was then sealed with a septum and purged with argon, which was introduced by a needle under the surface for 60 minutes. At the same time, to a flame-dried round-bottom flask was added racemic **6a** (155 mg, 1.57 mmol) and CH_2Cl_2 (100 mL). The resulting solution was purged with argon for 60 minutes under the surface. The green Cu(II)-sparteine solution was then transferred via cannula to the solution of racemic **6a** under argon and then the combined mixture was sonicated for 15 minutes and then allowed to stir at r.t. overnight with an argon balloon attached to the flask, which was covered with aluminum foil. The reaction was quenched by slow addition of sat. aq. $NaHCO_3$ (12 mL), H_2O

(40 mL) and most of the organic solvent was removed under reduced pressure. The residue was then extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layer was dried over $MgSO_4$, filtered through Celite and concentrated to dryness. Purification of the crude product by column chromatography on silica gel (35 mm × 200 mm, CH_2Cl_2/hexanes 2:3) afforded (*S*)-**6a**.

Yield: 281 mg (0.59 mmol, 64%); off-white solid; mp 107–112 °C; R_f = 0.33 (2:1 CH_2Cl_2/hexanes); >99% *ee* (HPLC analysis; Pirkle D-Phenylglycine column; 98:2 hexane/*i*PrOH at 254 nm, flow-rate: 1.0 mL/min): t_R = 20.55 [(*R*)-**6a**, minor], 24.49 [(*S*)-**6a**, major] min; $[\alpha]_D^{20}$ = –193.6 (*c* 1.0, CH_2Cl_2) on >99% *ee* (*S*)-**6a** (HPLC).

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 5.83 (s, 2 H), 6.57–6.61 (m, 4 H), 6.63–6.68 (m, 4 H), 7.29 (s, 2 H), 7.54–7.60 (m, 4 H), 7.77–7.79 (m, 2 H), 8.33–8.35 (m, 2 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 112.40, 114.40 ($^2J_{CF}$ = 21.1 Hz), 122.05, 122.78, 122.93, 125.93, 127.69, 127.77, 130.43 ($^3J_{CF}$ = 8.3 Hz), 134.59, 136.16 ($^4J_{CF}$ = 3.3 Hz), 139.41, 150.42, 161.90 ($^1J_{CF}$ = 244.9 Hz).

^{19}F NMR ($CDCl_3$, 283 Hz): δ = –114.15.

IR (thin film): 3517br s, 3058s, 1512s, 1495s, 1385s, 1221s cm^{-1}.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{32}H_{21}F_2O_2$: 475.1510; found: 475.1504.

VANOL Derivative (*S*)-6b

The synthesis of racemic **6b** was performed according to Typical Procedure III with 3-(4-bromophenyl)naphthalen-1-ol **22b** (1.20 g, 4.00 mmol). Purification by column chromatography on silica gel (35 mm × 250 mm, CH_2Cl_2/hexanes 1:2 to 2:3) gave racemic **6b** as an off-white solid (699 mg, 1.17 mmol, 59% yield). After de-racemization of racemic **6b** (596 mg, 1.00 mmol) with CuCl (168 mg, 1.70 mmol) and (–)-sparteine (819 mg, 3.50 mmol), the crude product was purified by column chromatography on silica gel (35 mm × 200 mm, CH_2Cl_2/hexanes 1:2 to 2:3) to afford (*S*)-**6b**.

Yield: 443 mg (0.74 mmol, 74%); off-white solid; mp 143–148 °C; R_f = 0.33 (2:1 CH_2Cl_2/hexanes); >99% *ee* (HPLC analysis; Chiralcel OD-H column, 98:2 hexane/*i*PrOH at 254 nm, flow-rate: 0.7 mL/min): t_R = 18.72 [(*S*)-**6b**; major], 21.78 [(*R*)-**6b**; minor] min; $[\alpha]_D^{20}$ = –186.8 (*c* 1.0, CH_2Cl_2) on >99% *ee* (*S*)-**6b** (HPLC).

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 5.82 (s, 2 H), 6.48–6.51 (m, 4 H), 7.08–7.11 (m, 4 H), 7.29 (s, 2 H), 7.55–7.61 (m, 4 H), 7.78–7.80 (m, 2 H), 8.32–8.35 (m, 2 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 112.02, 121.11, 122.12, 122.80, 123.03, 126.11, 127.76, 127.89, 130.49, 130.65, 134.58, 139.06, 139.17, 150.48.

IR (thin film): 3505br s, 3052s, 1570s, 1489s, 1385s, 1221s cm^{-1}.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{32}H_{21}{}^{79}Br_2O_2$: 594.9908; found: 594.9921.

VANOL Derivative (*S*)-6d

The synthesis of racemic **6d** was performed according to Typical Procedure III with 3-(3,5-dimethylphenyl)naphthalen-1-ol **22d** (992 mg, 4.00 mmol). Purification by column chromatography on silica gel (30 mm × 250 mm, CH_2Cl_2/hexanes 1:2) gave racemic **6d** as a light-yellow solid (754 mg, 1.52 mmol, 76% yield). After deracemization of racemic **6d** (494 mg, 1.00 mmol) with CuCl (168 mg, 1.70 mmol) and (–)-sparteine (819 mg, 3.50 mmol), the crude product was purified by column chromatography on silica gel (30 mm × 200 mm, CH_2Cl_2/hexanes 1:2) to afford (*S*)-**6d**.

Yield: 160 mg (0.32 mmol, 32%); light-yellow solid; mp 79–83 °C; R_f = 0.39 (2:1 CH_2Cl_2/hexanes); >99% *ee* (HPLC analysis; Chiralcel OD-H column, 99:1 hexane/*i*PrOH at 254 nm, flow-rate: 0.7 mL/min): t_R = 10.14 [(*R*)-**6d**; minor], 16.96 [(*S*)-**6d**; major] min; $[\alpha]_D^{20}$ = –233.9 (*c* 1.0, CH_2Cl_2) on >99% *ee* (*S*)-**6d** (HPLC).

^{1}H NMR ($CDCl_3$, 500 MHz): δ = δ 1.99 (s, 12 H), 5.78 (s, 2 H), 6.33 (d, *J* = 1.0 Hz, 4 H), 6.70 (s, 2 H), 7.31 (s, 2 H), 7.50–7.55 (m, 4 H), 7.74–7.77 (m, 2 H), 8.31–8.34 (m, 2 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 21.05, 113.06, 121.60, 122.64, 122.78, 125.46, 126.82, 127.32, 127.54, 128.19, 134.53, 136.58, 140.13, 141.00, 150.42.

IR (thin film): 3513br s, 2921s, 1597s, 1497s, 1387s, 1277s cm^{-1}.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{36}H_{31}O_2$: 495.2324; found: 495.2332.

VANOL Derivative (*S*)-6e

The synthesis of racemic **6e** was performed according to Typical Procedure III, with 3-(4-methoxyphenyl)naphthalen-1-ol **22e** (590 mg, 2.36 mmol). Purification by column chromatography on silica gel (30 mm × 250 mm, EtOAc/hexanes 1:20 to 1:10) gave racemic **6e** as a yellow solid (362 mg, 0.73 mmol, 62% yield). After deracemization of racemic **6e** (299 mg, 0.60 mmol) with CuCl (101 mg, 1.02 mmol) and (–)-sparteine (491 mg, 2.10 mmol), the crude product was purified by column chromatography on silica gel (35 mm × 200 mm, CH_2Cl_2/hexanes 4:1) to afford (*S*)-**6e**.

Yield: 50 mg (0.10 mmol, 17%); yellow solid; mp 212–215 °C; R_f = 0.42 (CH_2Cl_2); >99% *ee* (HPLC analysis; Chiralpak AS column, 90:10 hexane/*i*PrOH at 254 nm, flow-rate: 0.5 mL/min): t_R = 12.41 [(*S*)-**6e**; major], 22.56 [(*R*)-**6e**; minor] min; $[\alpha]_D^{20}$ = –242.3 (*c* 1.0, CH_2Cl_2) on >99% *ee* (*S*)-**6e** (HPLC).

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 3.68 (s, 6 H), 5.78 (s, 2 H), 6.49–6.53 (m, 4 H), 6.59–6.63 (m, 4 H), 7.30 (s, 2 H), 7.50–7.57 (m, 4 H), 7.75–7.78 (m, 2 H), 8.30–8.33 (m, 2 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 55.14, 112.92, 112.93, 121.78, 122.75, 122.78, 125.43, 127.42, 127.58, 129.94, 132.83, 134.62, 140.30, 150.27, 158.46.

IR (thin film): 3507br s, 2930s, 1514s, 1495s, 1383s, 1246s cm^{-1}.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{34}H_{27}O_4$: 499.1909; found: 499.1902.

VANOL Derivative (*S*)-6g

The synthesis of racemic **6g** was performed according to Typical Procedure III, with 3-(4-methoxy-3,5-dimethylphenyl)naphthalen-1-ol **22g** (1.12 g, 4.00 mmol). Purification by column chromatography on silica gel (35 mm × 250 mm, EtOAc/hexanes 1:20) gave racemic **6g** as a light-yellow solid (590 mg, 1.06 mmol, 53% yield). After deracemization of racemic **6g** (188 mg, 0.34 mmol) with CuCl (58 mg, 0.59 mmol) and (–)-sparteine (278 mg, 1.19 mmol), the crude product was purified by column chromatography on silica gel (20 mm × 200 mm, CH_2Cl_2/hexanes 4:1) to afford (*S*)-**6g**.

Yield: 88 mg (0.16 mmol, 47%); yellow solid; mp 207–210 °C; R_f = 0.32 (CH_2Cl_2); >99% *ee* (HPLC analysis; Chiralcel OD-H column, 99:1 hexane/*i*PrOH at 254 nm, flow-rate: 0.5 mL/min): t_R = 24.40 [(*R*)-**6g**; minor], 27.43 [(*S*)-**6g**; major] min; $[\alpha]_D^{20}$ = –209.2 (*c* 1.0, CH_2Cl_2) on >99% *ee* (*S*)-**6g** (HPLC).

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.94 (s, 12 H), 3.61 (s, 6 H), 5.78 (s, 2 H), 6.32 (s, 4 H), 7.29 (s, 2 H), 7.49–7.56 (m, 4 H), 7.74–7.77 (m, 2 H), 8.30–8.33 (m, 2 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 15.85, 59.69, 113.05, 121.48, 122.62, 122.70, 125.46, 127.37, 127.51, 129.41, 129.44, 134.53, 135.73, 140.41, 150.38, 155.92.

IR (thin film): 3515br s, 2930s, 1570s, 1487s, 1387s, 1225s cm^{-1}.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{36}H_{29}I_2O_4$: 779.0155; found: 779.0159.

VANOL Derivative (*R*)-6h

The synthesis of racemic **6h** was performed according to Typical Procedure III, with 3-(thiophen-2-yl)naphthalen-1-ol **22h** (1.70 g, 7.50 mmol). Purification by column chromatography on silica gel (30 mm × 250 mm, CH_2Cl_2/hexanes 2:3) gave racemic **6h** as a yellow solid (757 mg, 1.68 mmol, 45% yield). After deracemization of racemic **6h** (652 mg, 1.45 mmol) with CuCl (244 mg, 2.46 mmol) and (+)-sparteine (1.19 g, 5.09 mmol), the crude product was purified by column chromatography on silica gel (30 mm × 200 mm, CH_2Cl_2/hexanes 1:1) to afford (*R*)-**6h**.

Yield: 476 mg (1.06 mmol, 73%); off-white foamy solid; mp 157–159 °C; R_f = 0.37 (2:1 CH_2Cl_2/hexanes); >99% *ee* (HPLC analysis; Pirkle D-Phenylglycine column, 98:2 hexane/*i*PrOH at 254 nm, flow-rate: 1.0 mL/min): t_R = 30.75 [(*R*)-**6h**; major], 34.92 [(*S*)-**6h**; minor] min; $[\alpha]_D^{20}$ = +124.9 (*c* 1.0, CH_2Cl_2) on >99% *ee* (*R*)-**6h** (HPLC)

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 5.60 (s, 2 H), 6.68 (dd, *J* = 3.5, 1.0 Hz, 2 H), 6.73 (dd, *J* = 5.0, 1.0 Hz, 2 H), 7.50–7.54 (m, 2 H), 7.56–7.61 (m, 2 H), 7.76 (s, 2 H), 7.86 (d, *J* = 8.0 Hz, 2 H), 8.24–8.26 (m, 2 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 111.44, 121.47, 122.94, 123.29, 125.91, 126.00, 126.04, 127.03, 127.74, 127.96, 133.07, 134.80, 141.52, 151.31.

IR (thin film): 3505br s, 1570s, 1491s, 1387s, 1210s cm^{-1}.

HRMS (ESI–): *m*/*z* [M – H]$^+$ calcd for $C_{28}H_{17}O_2S_2$: 449.0670; found: 449.0660.

VANOL Derivative (*R*)-6i

The synthesis of racemic **6i** was performed according to Typical Procedure III, with 3-(thiophen-3-yl)naphthalen-1-ol **22i** (904 mg, 4.00 mmol). Purification by column chromatography on silica gel (30 mm × 250 mm, CH_2Cl_2/hexanes 1:1) gave racemic **6i** as a light-yellow solid (534 mg, 1.19 mmol, 59% yield). After deracemization of racemic **6i** (360 mg, 0.80 mmol) with CuCl (135 mg, 1.36 mmol) and (+)-sparteine (655 mg, 2.80 mmol), the crude product was purified by column chromatography on silica gel (30 mm × 200 mm, CH_2Cl_2/hexanes 1:1) to afford (*R*)-**6i**.

Yield: 144 mg (0.32 mmol, 40%); off-white solid; >99% *ee* (HPLC analysis; Pirkle D-Phenylglycine column, 98:2 hexane/*i*PrOH at 254 nm, flow-rate: 1.0 mL/min): t_R = 25.76 [(*R*)-**6i**; major], 30.40 [(*S*)-**6i**; minor] min; mp 188–189 °C; R_f = 0.18 (1:1 CH_2Cl_2/hexanes); $[\alpha]_D^{20}$ = +155.1 (*c* 1.0, CH_2Cl_2) on >99% *ee* (*R*)-**6i** (HPLC).

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 5.68 (s, 2 H), 6.62–6.65 (m, 4 H), 6.96 (dd, *J* = 5.0, 3.5 Hz, 2 H), 7.50–7.59 (m, 6 H), 7.81–7.84 (m, 2 H), 8.26–8.29 (m, 2 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 112.45, 121.33, 122.69, 122.83, 123.07, 124.43, 125.71, 127.63, 127.67, 127.94, 134.68, 135.10, 140.46, 150.46.

IR (thin film): 3505br s, 1570s, 1495s, 1379s, 1265s cm^{-1}.

HRMS (ESI–): *m*/*z* [M – H]$^-$ calcd for $C_{28}H_{17}O_2S_2$: 449.0670; found: 449.0685.

VANOL Derivative (*S*)-7a

The synthesis of racemic **7a** was performed according to Typical Procedure III, with 7-bromo-3-(4-fluorophenyl)naphthalen-1-ol **25a** (2.06 g, 6.50 mmol). After cooling to r.t., CH_2Cl_2 (30 mL) was added to the flask and the mixture was stirred until all large chunks had been broken up. The suspension was cooled in a freezer (–20 °C) and then filtered through filter paper. The yellow powder was washed with chilled CH_2Cl_2/hexanes and dried under vacuum to afford a yellow solid (1.19 g). Purification of the product remaining in the mother liquor by column chromatography on silica gel (30 mm × 250 mm, CH_2Cl_2/hexanes 1:1) gave racemic **7a** as a yellow solid (0.25 g). The total yield was 70% (1.44 g, 2.28 mmol). After deracemization of racemic **7a** (632 mg, 1.00 mmol) with CuCl (168 mg, 1.70 mmol) and (–)-sparteine (819 mg, 3.50 mmol), the crude product was purified by column chromatography on silica gel (30 mm × 200 mm, CH_2Cl_2/hexanes 2:3) to afford (*S*)-**7a**.

Yield: 560 mg (0.89 mmol, 87%); off-white solid; mp 152–158 °C; R_f = 0.24 (1:1 CH_2Cl_2/hexanes); >99% *ee* (HPLC analysis; Pirkle D-Phenylglycine column, 98:2 hexane/*i*PrOH at 254 nm, flow-rate: 1.0 mL/min): t_R = 29.55 [(*R*)-**7a**; minor], 35.61 [(*S*)-**7a**; major] min; $[\alpha]_D^{20}$ = –152.7 (*c* 1.0, CH_2Cl_2) on >99% *ee* (*S*)-**7a** (HPLC).

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 5.75 (s, 2 H), 6.54–6.56 (m, 4 H), 6.65–6.69 (m, 4 H), 7.25 (s, 2 H), 7.64 (d, *J* = 1.0 Hz, 4 H), 8.50 (d, *J* = 1.0 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 113.26, 114.58 ($^2J_{CF}$ = 21 Hz), 120.21, 121.99, 123.98, 125.31, 129.36, 130.34 ($^3J_{CF}$ = 8.1 Hz), 131.35, 133.02, 135.64 ($^4J_{CF}$ = 3.3 Hz), 139.79, 149.55, 162.06 ($^1J_{CF}$ = 245.8 Hz).

^{19}F NMR ($CDCl_3$, 283 MHz): δ = –113.46.

IR (thin film): 3517br s, 1512s, 1489s, 1375s, 1235s cm^{-1}.

MS: *m*/*z* (%) = 634 (5, $^{81}Br^{81}Br$) [M]$^+$, 632 (10, $^{81}Br^{79}Br$) [M]$^+$, 630 (7, $^{79}Br^{79}Br$) [M]$^+$, 425 (5), 317 (21, ^{81}Br), 315 (17, ^{79}Br), 289 (12, ^{81}Br), 287 (13, ^{79}Br), 227 (65), 212 (83), 196 (100), 159 (100).

Anal calcd for $C_{32}H_{18}Br_2F_2O_2$: C, 60.79; H, 2.87. Found: C, 60.99; H, 2.72.

VANOL Derivative (*S*)-7d

The synthesis of racemic **7d** was performed according to Typical Procedure III, with 7-bromo-3-(3,5-dimethylphenyl)naphthalen-1-ol **25d** (2.62 g, 8.01 mmol). Purification by column chromatography on silica gel (30 mm × 250 mm, CH_2Cl_2/hexanes 1:3) gave racemic **7d** as a white solid (1.62 g, 2.48 mmol, 65% yield). After deracemization of racemic **7d** (652 mg, 1.00 mmol) with CuCl (168 mg, 1.70 mmol) and (–)-sparteine (819 mg, 3.50 mmol), the crude product was purified by column chromatography on silica gel (30 mm × 200 mm, CH_2Cl_2/hexanes 1:3) to afford (*S*)-**7d**.

Yield: 488 mg (0.75 mmol, 75%); off-white foamy solid; mp 130–134 °C; R_f = 0.19 (1:2 CH_2Cl_2/hexanes); >99% *ee* (HPLC analysis; Pirkle D-Phenylglycine column, 98:2 hexane/*i*PrOH at 254 nm, flow-rate: 1.0 mL/min): t_R = 21.79 [(*S*)-**7d**; major], 24.01 [(*R*)-**7d**; minor] min; $[\alpha]_D^{20}$ = –171.4 (*c* 1.0, CH_2Cl_2) on >99% *ee* (*S*)-**7d** (HPLC).

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.00 (s, 12 H), 5.70 (s, 2 H), 6.28 (s, 4 H), 6.72 (s, 2 H), 7.27 (d, *J* = 0.5 Hz, 2 H), 7.60–7.62 (m, 4 H), 8.48–8.49 (m, 2 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 21.09, 113.92, 119.66, 121.56, 123.82, 125.14, 126.68, 128.51, 129.24, 130.90, 132.95, 136.78, 139.60, 141.41, 149.50.

IR (thin film): 3517br s, 2919s, 1581s, 1487s, 1373s, 1279s cm^{-1}.

HRMS (ESI–): m/z [M – H]$^-$ calcd for $C_{36}H_{27}{}^{79}Br_2O_2$: 649.0378; found: 649.0355.

VANOL Derivative (*S*)-7e

The synthesis of racemic **7e** was performed according to Typical Procedure III, with 7-bromo-3-(4-methoxyphenyl)naphthalen-1-ol **25e** (1.58 g, 4.80 mmol) except that the temperature was 175 °C. Purification by column chromatography on silica gel (30 mm × 250 mm, CH_2Cl_2/hexanes 3:2) gave racemic **7e** as a yellow solid (654 mg, 1.00 mmol, 42% yield). After deracemization of racemic **7e** (548 mg, 0.84 mmol) with CuCl (141 mg, 1.42 mmol) and (–)-sparteine (684 mg, 2.92 mmol), the crude product was purified by column chromatography on silica gel (30 mm × 200 mm, CH_2Cl_2/hexanes 3:2) to afford (*S*)-**7e**.

Yield: 380 mg (0.58 mmol, 69%); light-yellow solid; mp 147–150 °C; R_f = 0.24 (2:1 CH_2Cl_2/hexanes); >99% *ee* (HPLC analysis; Chiralcel OD-H column, 90:10 hexane/*i*PrOH at 254 nm, flow-rate: 0.5 mL/min): t_R = 4.68 [(*R*)-7e; minor], 6.65 [(*S*)-7e; major] min; $[\alpha]_d^{20}$ = –182.6 (*c* 1.0, CH_2Cl_2) on >99% *ee* (*S*)-**7e** (HPLC).

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 3.68 (s, 6 H), 5.70 (s, 2 H), 6.51–6.52 (m, 4 H), 6.57–6.59 (m, 4 H), 7.25 (s, 2 H), 7.60–7.62 (m, 4 H), 8.46–8.47 (m, 2 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 55.17, 113.09, 113.81119.63, 121.71, 123.82, 125.28, 129.28, 129.85, 130.96, 132.26, 133.06, 140.70, 149.41, 158.74.

IR (thin film): 3503br s, 2930m, 1514s, 1487s, 1375s, 1248s cm^{-1}.

HRMS (ESI–): m/z [M – H]$^-$ calcd for $C_{34}H_{23}O_4{}^{79}Br_2$: 652.9963; found: 652.9937.

VANOL Derivative (*S*)-7g

The synthesis of racemic **7g** was performed according to Typical Procedure III, with 7-bromo-3-(4-methoxy-3,5-dimethylphenyl)naphthalen-1-ol **25g** (2.50 g, 7.00 mmol). Purification by column chromatography on silica gel (20 mm × 200 mm, CH_2Cl_2/hexanes 3:2) gave racemic **7g** as a light-yellow solid (990 mg, 1.39 mmol, 40% yield). After deracemization of racemic **7g** (712 mg, 1.00 mmol) with CuCl (168 mg, 1.70 mmol) and (–)-sparteine (819 mg, 3.50 mmol), the crude product was purified by column chromatography on silica gel (30 mm × 200 mm, CH_2Cl_2/hexanes 3:2) to afford (*S*)-**7g**.

Yield: 526 mg (0.74 mmol, 74%); light-yellow solid; mp 203–206 °C; R_f = 0.33 (CH_2Cl_2); >99% *ee* (HPLC analysis; Pirkle D-Phenylglycine column, 98:2 hexane/*i*PrOH at 254 nm, flow-rate: 1.0 mL/min): t_R = 44.60 [(*R*)-**7g**; minor], 49.09 [(*S*)-**7g**; major] min; $[\alpha]_D^{20}$ = –176.4 (*c* 1.0, CH_2Cl_2) on >99% *ee* (*S*)-**7g** (HPLC).

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.95 (s, 12 H), 3.61 (s, 6 H), 5.70 (s, 2 H), 6.28 (s, 4 H), 7.25 (d, *J* = 0.5 Hz, 2 H), 7.60–7.62 (m, 4 H), 8.47–8.48 (m, 2 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 15.89, 59.70, 113.93, 119.64, 121.43, 123.75, 125.12, 129.21, 129.29, 129.68, 130.94, 132.96, 135.20, 140.85, 149.48, 156.20.

IR (thin film): 3513br s, 2930s, 1577s, 1483s, 1375s, 1225s cm^{-1}.

HRMS (ESI–): m/z [M – H]$^-$ calcd for $C_{38}H_{31}{}^{79}Br_2O_4$: 709.0589; found: 709.0590.

VANOL Derivative (*S*)-7j

The synthesis of racemic **7j** was performed according to Typical Procedure III, with 7-bromo-3-(4-butylphenyl)naphthalen-1-ol **25j** (5.09 g, 14.3 mmol). After cooling to r.t., CH_2Cl_2 (30 mL) and hexanes (30 mL) were added to the flask and the mixture was stirred until all large chunks had been broken up. The suspension was cooled in a freezer (–20 °C) and then filtered through filter paper. The yellow powder was washed with chilled CH_2Cl_2/hexanes and dried under vacuum to afford a yellow solid (2.42 g). Purification of the product remaining in the mother liquor by column chromatography on silica gel (30 mm × 250 mm, CH_2Cl_2/hexanes 1:2) gave racemic **7j** as an off-white solid (1.25 g). The total yield was 62% (3.67 g, 5.18 mmol). After deracemization of racemic **7j** (6.75 g, 9.54 mmol) with CuCl (1.61 g, 16.3 mmol) and (–)-sparteine (7.81 g, 33.4 mmol), the crude product was purified by column chromatography on silica gel (50 mm × 250 mm, CH_2Cl_2/hexanes 1:3) to afford (*S*)-**7j**.

Yield: 5.38 g (7.60 mmol, 80%); off-white foamy solid; mp 85–88 °C; R_f = 0.19 (1:2 CH_2Cl_2/hexanes); >99% *ee* (HPLC analysis; Pirkle D-Phenylglycine column, 98:2 hexane/*i*PrOH at 254 nm, flow-rate: 1.0 mL/min): t_R = 23.71 [(*S*)-**7j**; major], 28.67 [(*R*)-**7j**; minor] min; $[\alpha]_D^{20}$ = –187.5 (*c* 1.0, CH_2Cl_2) on >99% *ee* (*S*)-**7j** (HPLC).

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 0.88 (t, *J* = 7.5 Hz, 6 H), 1.25–1.30 (m, 4 H), 1.46–1.51 (m, 4 H), 2.46 (t, *J* = 7.5 Hz, 4 H), 5.68 (s, 2 H), 6.52 (dd, *J* = 6.5, 2.0 Hz, 4 H), 6.76 (d, *J* = 8.0 Hz, 4 H), 7.29 (s, 2 H), 7.59–7.65 (m, 4 H), 8.46–8.48 (m, 2 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 13.89, 22.20, 33.45, 35.12, 113.79, 119.66, 121.74, 123.92, 125.29, 127.64, 128.57, 129.32, 130.92, 133.07, 136.94, 141.11, 141.66, 149.39.

IR (thin film): 3519br s, 2928s, 2857s, 1561s, 1487s, 1375s cm^{-1}.

HRMS (ESI–): m/z [M – H]$^-$ calcd for $C_{40}H_{35}{}^{79}Br_2O_2$: 705.1004; found: 705.0973.

Susuki Coupling for the Synthesis of VANOL Derivatives (*S*)-7n to (*S*)-7s (Table 5); Typical Procedure IV

VANOL Derivative (*S*)-7o

Benzene, EtOH and Na_2CO_3 (aq. 2 M) were purged (>10 min) with inert gas (Ar or N_2) prior to use. To a 25 mL round-bottom flask was added (*S*)-**5b** (60 mg, 0.10 mmol), tetrakis(triphosphine)palladium (12 mg, 0.010 mmol), benzene (1 mL) and Na_2CO_3 (aq. 2 M, 0.5 mL) under argon. To the stirred mixture was added 4-*tert*-butylphenylboronic acid **26a** (71 mg, 0.40 mmol) and EtOH (0.5 mL). The mixture was stirred at 90 °C for 14 h with an argon balloon attached to the condenser. After cooling to r.t., the mixture was partitioned between EtOAc (10 mL) and brine (5 mL). The organic layer was separated, dried over $MgSO_4$, filtered through Celite and concentrated to dryness. Purification of the crude product by column chromatography on silica gel (20 mm × 250 mm, CH_2Cl_2/hexanes 1:2) gave (*S*)-**7o**.

Yield: 29 mg (0.041 mmol, 41%); white solid; mp >300 °C; R_f = 0.21 (1:2 CH_2Cl_2/hexanes); $[\alpha]_D^{20}$= +29.2 (c 1.0, CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.39 (s, 18 H), 5.89 (s, 2 H), 6.67 (dd, *J* = 8.5, 1.5 Hz, 4 H), 6.96–7.00 (m, 4 H), 7.06–7.10 (m, 2 H), 7.34 (d, *J* = 1.0 Hz, 2 H), 7.51–7.55 (m, 4 H), 7.73–7.76 (m, 4 H), 7.84 (d, *J* = 1.5 Hz, 4 H), 8.56 (d, *J* = 1.0 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 31.39, 34.60, 113.11, 120.45, 121.80, 123.24, 125.86, 126.64, 127.09, 127.11, 127.50, 128.21, 128.90, 133.66, 138.11, 138.31, 140.25, 140.58, 150.55, 150.61.

IR (thin film): 3517br s, 2961s, 1559s, 1456s, 1387s, 1267s cm^{-1}.

HRMS (ESI–): m/z [M – H]$^-$ calcd for $C_{52}H_{45}O_2$: 701.3420; found: 701.3448.

VANOL Derivative (*S*)-7p

The reaction of (*S*)-**7j** (284 mg, 0.40 mmol), tetrakis(triphosphine)palladium (46 mg, 0.040 mmol), benzene (4 mL), Na_2CO_3 (aq. 2 M, 4 mL), 4-*tert*-butylphenylboronic acid (285 mg, 1.60 mmol) and EtOH (2 mL) was performed according to Typical Procedure IV. Purification of the crude product by column chromatography on silica gel (30 mm × 200 mm, CH_2Cl_2/hexanes 2:5) gave (*S*)-**7p**.

Yield: 162 mg (0.199 mmol, 50%); off-white solid; mp >260 °C; R_f = 0.22 (1:2 CH_2Cl_2/hexanes); $[\alpha]_D^{20}$ = –31.7 (*c* 1.0, CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 0.89 (t, *J* = 7.5 Hz, 6 H), 1.27–1.32 (m, 4 H), 1.39 (s, 18 H), 1.49–1.52 (m, 4 H), 2.47 (t, *J* = 7.5 Hz, 2 H), 5.84 (s, 2 H), 6.58 (dd, *J* = 6.5, 2.0 Hz, 4 H), 6.78 (d, *J* = 8.0 Hz, 4 H), 7.36 (d, *J* = 1.0 Hz, 2 H), 7.52 (dd, *J* = 6.5, 2.0 Hz, 4 H), 7.74 (dd, *J* = 6.5, 2.0 Hz, 4 H), 7.83–7.84 (m, 4 H), 8.54 (m, 2 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 13.91, 22.24, 31.40, 33.52, 34.59, 35.15, 113.30, 120.48, 121.61, 123.18, 125.84, 126.98, 127.08, 127.57, 128.14, 128.69, 133.69, 137.53, 138.09, 138.18, 140.60, 141.26, 150.48, 150.49.

IR (thin film): 3499br s, 2957s, 1559s, 1456s, 1388s, 1267s cm^{-1}.

HRMS (ESI–): *m*/*z* [M – H]$^-$ calcd for $C_{60}H_{61}O_2$: 813.4672; found: 813.4709.

VANOL Derivative (*S*)-7q

The reaction of (*S*)-**7d** (261 mg, 0.40 mmol), tetrakis(triphosphine)palladium (46 mg, 0.040 mmol), benzene (4 mL), Na_2CO_3 (aq. 2 M, 4 mL), 4-*tert*-butylphenylboronic acid (285 mg, 1.60 mmol) and EtOH (2 mL) was performed according to Typical Procedure IV. Purification of the crude product by column chromatography on silica gel (30 mm × 200 mm, CH_2Cl_2/hexanes 2:5) gave (*S*)-**7q**.

Yield: 145 mg (0.191 mmol, 48%); off-white solid; mp 170–185 °C; R_f = 0.19 (1:2 CH_2Cl_2/hexanes).

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.38 (s, 18 H), 2.01 (s, 12 H), 5.82 (s, 2 H), 6.36 (d, *J* = 0.5 Hz, 4 H), 6.71 (s, 2 H), 7.33 (d, *J* = 0.5 Hz, 2 H), 7.52 (dd, *J* = 6.5, 2.0 Hz, 4 H), 7.75 (dd, *J* = 7.0, 2.0 Hz, 4 H), 7.82–7.83 (m, 4 H), 8.55 (d, *J* = 0.5 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 21.10, 31.39, 34.59, 113.41, 120.24, 121.36, 123.07, 125.84, 126.82, 126.86, 127.03, 128.06, 128.22, 133.58, 136.62, 137.95, 138.12, 140.17, 140.90, 150.49, 150.65.

IR (thin film): 3519br s, 2961s, 1597s, 1495s, 1387s, 1267s cm^{-1}.

HRMS (ESI–): *m*/*z* [M – H]$^-$ calcd for $C_{56}H_{53}O_2$: 757.4046; found: 757.4055.

VANOL Derivative (*S*)-7r

The reaction of (*S*)-**7g** (214 mg, 0.30 mmol), tetrakis(triphosphine)palladium (35 mg, 0.030 mmol), benzene (3 mL), Na_2CO_3 (aq. 2 M, 1.5 mL), 4-*tert*-butylphenylboronic acid (214 mg, 1.20 mmol) and EtOH (1.5 mL) was performed according to Typical Procedure IV. Purification of the crude product by column chromatography on silica gel (30 mm × 200 mm, CH_2Cl_2/hexanes 3:2) gave (*S*)-**7r**.

Yield: 63 mg (0.077 mmol, 26%); off-white solid; mp 172–178 °C; R_f = 0.40 (CH_2Cl_2); $[\alpha]_D^{20}$ = –40.8 (*c* 1.0, CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.39 (s, 18 H), 1.96 (s, 12 H), 3.62 (s, 6 H), 5.84 (s, 2 H), 6.36 (s, 4 H), 7.32 (s, 2 H), 7.53 (dd, *J* = 6.5, 2.0 Hz, 4 H), 7.76 (dd, *J* = 6.5, 2.0 Hz, 4 H), 7.82–7.83 (m, 4 H), 8.55–8.56 (m, 2 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 15.89, 31.39, 34.59, 59.90, 113.44, 120.22, 121.26, 123.02, 125.85, 126.91, 127.03, 128.04, 129.42, 129.49, 133.60, 135.79, 137.96, 138.12, 140.34, 150.50, 150.64, 155.9.

IR (thin film): 3519br s, 2959s, 1559s, 1489s, 1389s, 1223s cm^{-1}.

HRMS (ESI–): *m*/*z* [M – H]$^-$ calcd for $C_{58}H_{57}O_4$: 817.4257; found: 817.4262.

VANOL Derivative (*S*)-27

To a flame-dried 250 mL round-bottom flask was added (*S*)-**7j** (1.42 g, 2.00 mmol) and anhydrous THF (15 mL). The resulting mixture was cooled to 0 °C and NaH (176 mg, 60% in mineral oil, 4.40 mmol) was added. The mixture was stirred at 0 °C for 15 minutes and MeI (0.8 mL, 12.8 mmol) was added. The mixture was warmed to r.t. and stirred for additional 24 h. NH_4Cl (sat. aq. 4 mL) was added to the mixture and the organic solvent was removed by rotary evaporation. The residue was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layer was washed with $Na_2S_2O_3$ (sat. aq. 2 × 5 mL), brine (5 mL), and dried over $MgSO_4$, filtered through Celite and concentrated to dryness. Purification of the crude product by column chromatography on silica gel (20 mm × 320 mm, CH_2Cl_2/hexanes 1:4) gave (*S*)-**27**.

Yield: 1.30 g (1.76 mmol, 88%); white foamy solid; mp 75–77 °C; R_f = 0.29 (1:2 CH_2Cl_2/hexanes); $[\alpha]_D^{20}$ = –85.4 (*c* 1.0, CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 0.91 (t, *J* = 7.5 Hz, 6 H), 1.28–1.33 (m, 4 H), 1.49–1.53 (m, 4 H), 2.45–2.49 (m, 4 H), 3.63 (s, 6 H), 6.63 (dd, *J* = 6.5, 2.0 Hz, 4 H), 6.74 (d, *J* = 8.0 Hz, 4 H), 7.50 (s, 2 H), 7.57 (dd, *J* = 8.5, 2.0 Hz, 2 H), 7.71 (d, *J* = 8.5 Hz, 2 H), 8.33 (d, *J* = 2.0 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 13.91, 22.24, 33.58, 35.10, 61.14, 120.02, 124.84, 125.25, 126.37, 127.64, 128.10, 128.72, 129.82, 129.90, 132.99, 137.66, 140.65, 141.17, 153.39.

IR (thin film): 2955s, 2928s, 2857s, 1561s, 1480s, 1352s, 1105s cm^{-1}.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{42}H_{41}{}^{79}Br_2O_2$: 735.1473; found: 735.1495.

VANOL Derivative (*S*)-7n

To a flame-dried 25 mL round-bottom flask were added (*S*)-**27** (184 mg, 0.25 mmol), tetrakis(triphosphine)palladium (29 mg, 0.025 mmol) and DME (1.7 mL) under argon. To the stirred mixture were added phenyboronic acid (107 mg, 0.88 mmol) and Na_2CO_3 (aq. 2 M, 0.7 mL). The mixture was stirred at 90 °C for 14 h with an argon balloon attached. After cooling to r.t., the mixture was filtered through a pad of Celite and washed with CH_2Cl_2. After removal of the solvent, the residue was dissolved in CH_2Cl_2 (20 mL) and washed with NH_4Cl (sat. aq. 5 mL) and brine (5 mL). The organic layer was separated, dried over $MgSO_4$, filtered through Celite and concentrated to dryness. The residue was purified by column chromatography (silica gel, 20 mm × 250 mm, CH_2Cl_2/hexanes 1:2). The purified and concentrated product was dissolved in CH_2Cl_2 (4 mL) and cooled to 0 °C, BBr_3 (1 M in CH_2Cl_2, 1.5 mL, 1.5 mmol) was added dropwise to the mixture at 0 °C. The mixture was stirred at r.t. overnight with an argon balloon attached to the flask. The mixture was then cooled to 0 °C and H_2O (8 mL) was added dropwise. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layer was dried over $MgSO_4$, filtered through Celite and concentrated to dryness. Purification of the crude product by column chromatography on silica gel (20 mm × 260 mm, CH_2Cl_2/hexanes 1:2) gave (*S*)-**7n**.

Yield: 130 mg (0.185 mmol, 74% isolated yield over two steps); light-yellow solid; mp 225–226 °C; R_f = 0.26 (1:1, CH_2Cl_2/hexanes); $[\alpha]_D^{20}$ = –86.8 (*c* 1.0, CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 0.89 (t, *J* = 7.5 Hz, 6 H), 1.27–1.32 (m, 4 H), 1.47–1.54 (m, 4 H), 2.47 (t, *J* = 7.5 Hz, 4 H), 5.84 (s, 2 H), 6.59 (d, *J* = 8.0 Hz, 4 H), 6.78 (d, *J* = 8.0 Hz, 4 H), 7.36–7.40 (m, 4 H), 7.48–7.52 (m, 4 H), 7.78–7.88 (m, 8 H), 8.55 (d, *J* = 0.5 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 13.90, 22.23, 33.51, 35.15, 113.36, 120.75, 121.63, 123.15, 127.02, 127.41, 127.44, 127.59, 128.24, 128.69, 128.89, 133.81, 137.46, 138.25, 140.78, 141.10, 141.33, 150.53.

IR (thin film): 3503br s, 2928s, 1559s, 1489s, 1387s, 1215s cm^{-1}.

HRMS (ESI–): *m*/*z* [M – H]$^-$ calcd for $C_{52}H_{45}O_2$: 701.3420; found: 701.3411.

VANOL Derivative (*S*)-7s

To a flame-dried 25 mL round-bottom flask were added (*S*)-**27** (184 mg, 0.25 mmol), tetrakis(triphosphine)palladium (29 mg, 0.025 mmol) and DME (1.7 mL) under argon. To the stirred mixture were added anthracene-9-boronic acid (195 mg, 0.88 mmol) and Na_2CO_3 (aq. 2 M, 0.7 mL). The mixture was stirred at 90 °C for 14 h with an argon balloon attached. After cooling to r.t., the mixture was filtered through a pad of Celite and washed with CH_2Cl_2. After removal of the solvent, the residue was dissolved in CH_2Cl_2 (20 mL) and washed with NH_4Cl (sat. aq. 5 mL) and brine (5 mL). The organic layer was separated, dried over $MgSO_4$, filtered through Celite and concentrated to dryness. The residue was purified by column chromatography (silica gel, 20 mm × 250 mm, CH_2Cl_2/hexanes 1:2). The purified and concentrated product was dissolved in CH_2Cl_2 (4 mL) and cooled to 0 °C, BBr_3 (1 M in CH_2Cl_2, 1.5 mL, 1.5 mmol) was added dropwise to the mixture at 0 °C. The mixture was stirred at r.t. overnight with an argon balloon attached to the flask. The mixture was then cooled to 0 °C and H_2O (8 mL) was added dropwise. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layer was dried over $MgSO_4$, filtered through Celite and concentrated to dryness. Purification of the crude product by column chromatography on silica gel (20 mm × 260 mm, CH_2Cl_2/hexanes 1:2) gave (*S*)-**7s**.

Yield: 120 mg (0.133 mmol, 53% isolated yield over two steps); light-yellow solid; mp 170–172 °C; R_f = 0.15 (1:2 CH_2Cl_2/hexane); $[\alpha]_D^{20}$ = –497.9 (c 1.0, CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 0.96 (t, *J* = 7.5 Hz, 6 H), 1.35–1.40 (m, 4 H), 1.56–1.62 (m, 4 H), 2.57 (t, *J* = 7.5 Hz, 4 H), 5.87 (s, 2 H), 6.69 (d, *J* = 8.0 Hz, 4 H), 6.89 (d, *J* = 8.0 Hz, 4 H), 7.30–7.34 (m, 2 H), 7.40–7.50 (m, 8 H), 7.61 (dd, *J* = 8.5, 2.0 Hz, 2 H), 7.72 (d, *J* = 8.5 Hz, 2 H), 7.82 (d, *J* = 8.5 Hz, 2 H), 7.98 (d, *J* = 8.5 Hz, 2 H), 8.04–8.09 (m, 4 H), 8.42 (d, *J* = 1.0 Hz, 2 H), 8.53 (s, 2 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 13.97, 22.34, 33.63, 35.26, 113.59, 121.84, 122.91, 125.10, 125.14, 125.17, 125.44, 125.51, 126.76, 126.95, 127.64, 127.69, 128.35, 128.47, 128.82, 130.42, 130.53, 131.07, 131.45, 131.49, 133.94, 136.03, 136.94, 137.63, 141.11, 141.41, 150.54 (one sp^2 C not located).

IR (thin film): 3520br s, 3052m, 2928s, 1559s, 1456s, 1387s cm^{-1}.

HRMS (ESI–): *m*/*z* [M – H]$^-$ calcd for $C_{68}H_{53}O_2$: 901.4046; found: 901.4084.

Cycloaromatization Promoted by Potassium *t*-Butoxide (Scheme 2); Typical Procedure V

3-Cyclohexyl-1-naphthol 29m

To an oven-dried 100 mL round-bottom flask was added K*t*OBu (1.347 g, 12.00 mmol, 1.200 equiv) and THF (20 mL). *o*-(Cyclohexylethynyl)acetophenone **28m** (2.264 g, 10.00 mmol) was added in one portion at r.t. and the reaction mixture was heated to 80 °C under N_2 atmosphere. After 2 h, the reaction mixture was acidified with 1 M H_2SO_4 (50 mL) at 0 °C and then extracted with EtOAc (3 × 50 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/EtOAc 20:1 to 10:1) to obtain **29m**.

Yield: 2.124 g (9.380 mmol, 94%); white solid; mp 100–101 °C; R_f = 0.41 (hexanes/EtOAc 8:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.25–1.55 (m, 6 H), 1.76–2.00 (m, 5 H), 2.57 (tt, *J* = 11.5, 3.2 Hz, 1 H), 6.31 (s, 1 H), 6.69 (d, *J* = 1.4 Hz, 1 H), 7.28–7.38 (m, 1 H), 7.51 (dddd, *J* = 25.4, 8.1, 6.8, 1.3 Hz, 2 H), 7.78–7.93 (m, 1 H), 8.27 (dd, *J* = 8.4, 1.3 Hz, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 26.28, 27.01, 34.32, 44.74, 109.29, 117.62, 121.54, 123.29, 124.65, 126.52, 127.58, 135.03, 146.32, 151.14.

HRMS (ESI–): *m*/*z* [M – H]$^-$ calcd. for $C_{16}H_{17}O$: 225.1279; found: 225.1296.

3-Butyl-1-naphthol 29n

Naphthol **29n** was prepared from *o*-(butylethynyl)acetophenone **28n** (2.003 g, 10.00 mmol) by Typical Procedure V. The crude product was purified by column chromatography (silica gel, hexanes/EtOAc 40:1 to 9:1) to give **29n**.

Yield: 1.889 g (9.430 mmol, 94%); yellow liquid; R_f = 0.45 (hexanes/EtOAc 8:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.92 (td, *J* = 7.3, 1.1 Hz, 3 H), 1.37 (qd, *J* = 7.5, 1.9 Hz, 2 H), 1.65 (tt, *J* = 9.0, 6.8 Hz, 2 H), 2.55–2.76 (m, 2 H), 5.14 (s, 1 H), 6.67 (d, *J* = 1.3 Hz, 1 H), 7.21 (d, *J* = 1.6 Hz, 1 H), 7.35–7.50 (m, 2 H), 7.72 (dt, *J* = 7.6, 1.4 Hz, 1 H), 8.02–8.13 (m, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 13.99, 22.37, 33.33, 35.81, 110.08, 119.23, 121.28, 122.77, 124.38, 126.42, 127.19, 134.82, 140.85, 151.10.

HRMS (ESI–): *m*/*z* [M – H]$^-$ calcd. for $C_{14}H_{15}O$: 199.1123; found: 199.1129.

3,3′-Cy_2VANOL (±)-6m

VANOL derivative (±)-**6m** was prepared from 3-cyclohexyl-1-naphthol **28m** (6.64 mL, 29.3 mmol) by Typical Procedure III, with heating at 165 °C for 36 h. The crude product was purified by column chromatography (silica gel, CH_2Cl_2/hexanes: 1:3 to 1:1) to give (±)-**6m**.

Yield: 3.360 g (7.460 mmol, 51%); off-white solid; mp 196–198 °C; R_f = 0.41 (hexanes/EtOAc 8:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.74–1.38 (m, 8 H), 1.52–1.81 (m, 12 H), 2.20 (tt, *J* = 11.8, 3.3 Hz, 2 H), 5.19 (s, 2 H), 7.42–7.58 (m, 6 H), 7.83 (dt, *J* = 8.3, 0.8 Hz, 2 H), 8.22 (ddd, *J* = 8.3, 1.3, 0.6 Hz, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 26.01, 26.78, 26.81, 33.71, 36.09, 41.42, 112.75, 117.92, 122.44, 122.70, 124.78, 127.11, 127.23, 134.96, 146.15, 149.80.

HRMS (ESI–): *m*/*z* [M – H]$^-$ calcd. for $C_{32}H_{33}O_2$: 449.2481; found: 449.2519.

3,3′-Bu$_2$VANOL (±)-6n

VANOL derivative **6n** was prepared from 3-butyl-1-naphthol **29n** (6.822 g, 34.10 mmol) by Typical Procedure III with heating at 165 °C for 24 h. The crude product was purified by column chromatography (silica gel, CH_2Cl_2/hexanes: 1:3 to 1:2) to give (±)-**6n**.

Yield: 3.360 g (7.550 mmol, 44%); yellow semisolid; R_f = 0.39 (hexanes/EtOAc 8:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.86 (t, *J* = 7.4 Hz, 6 H), 1.30 (qd, *J* = 7.3, 2.0 Hz, 4 H), 1.60 (p, *J* = 7.6 Hz, 4 H), 2.52 (qt, *J* = 14.8, 7.8 Hz, 4 H), 5.41 (s, 2 H), 7.52–7.59 (m, 4 H), 7.64 (ddd, *J* = 8.2, 6.8, 1.3 Hz, 2 H), 7.92 (d, *J* = 8.3 Hz, 2 H), 8.36 (d, *J* = 8.3 Hz, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 13.97, 22.62, 32.22, 33.32, 113.42, 120.00, 122.73, 122.80, 124.95, 127.21, 127.29, 134.95, 140.41, 150.20.

HRMS (ESI–): *m*/*z* [M – H]$^-$ calcd. for $C_{28}H_{29}O_2$: 397.2168; found: 397.2189.

Deracemization of 3,3′-DialkylVANOL Derivatives (Scheme 2); Typical Procedure VI

(*R*)-3,3′-Cy$_2$VANOL (*R*)-6m

To a 100 mL round-bottom flask was added (+)-sparteine (0.81 mL, 3.5 mmol, 3.5 equiv), CuCl (168 g, 1.70 mmol) and MeOH (27 mL) under an atmosphere of air. The reaction mixture was sonicated in a water bath for 60 minutes with exposure to air. The flask was then sealed with a septum and purged with argon, which was introduced by a needle under the surface for 60 minutes. At the same time, to a 250 mL flame-dried round-bottom flask was added racemic **6m** (451 mg, 1.00 mmol) and CH_2Cl_2 (54 mL). The resulting solution was purged with argon for 60 minutes under the surface. The green Cu(II)-sparteine solution was then transferred via cannula to the solution of racemic **6m** under argon and then the combined mixture was sonicated for 15 minutes and then allowed to stir at r.t. overnight with an argon balloon attached to the flask, which was covered with aluminum foil. The reaction was quenched by slow addition of $NaHCO_3$ (sat. aq. 15 mL), H_2O (40 mL) and most of the organic solvent was removed under reduced pressure. The residue was then extracted with CH_2Cl_2 (30 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered through Celite and concentrated to dryness. Purification of the crude product by column chromatography on silica gel (CH_2Cl_2/hexanes 1:2) gave the product (*R*)-**6m**.

Yield: 315 mg (0.699 mmol, 70%); off-white foamy solid; mp 196–198 °C; >99% ee (HPLC analysis; Pirkle D-Phenylglycine column, 98:2 hexane/iPrOH at 254 nm, flow-rate: 1.0 mL/min): t_R = 8.69 [(*R*)-**6m**; major], 10.36 [(*S*)-**6m**; minor] min.

3,3′-Bu$_2$VANOL (*R*)-6n

Typical Procedure VI was followed with (±)-3,3′-*n*-Bu$_2$VANOL **6n** (1.568 g, 3.930 mmol). Purification of the crude product by column chromatography on silica gel (CH_2Cl_2/hexanes 1:2) gave the product (*R*)-**6n**.

Yield: 293 mg (0.735 mmol, 19%); off-yellow foamy semi-solid; 95% ee (HPLC analysis; Pirkle D-Phenylglycine column, 98:2 hexane/iPrOH at 254 nm, flow-rate: 1.0 mL/min): t_R = 8.73 [(*R*)-**6n**; major], 10.37 [(*S*)-**6n**; minor] min.

Catalytic Asymmetric Aziridination of Benzhydryl Imines with Ethyl Diazoacetate (Tables 6–8); Typical Procedure for the Preparation of Aziridine 12a Mediated by a Catalyst Prepared from Ligand 7q (Table 8, entry 10)[5]

A 25 mL pear-shaped, single-necked Schlenk flask that had its 14/20 joint replaced with a threaded high vacuum Teflon valve was flame-dried (with a stir bar in it) and cooled to r.t. under N_2 and charged with **7q** (19.0 mg, 0.025 mmol) and triphenylborate (29 mg, 0.10 mmol). The mixture was dissolved in anhydrous toluene (1 mL). After the addition of H_2O (0.45 mL, 0.025 mmol), the Teflon valve was closed and the flask was heated at 80 °C for 1 h. Toluene was carefully removed by exposing to high vacuum (0.1 mmHg) by slight cracking of the Teflon valve. After removal of the solvent, the Teflon valve was completely opened and the flask was heated to 80 °C under high vacuum for 30 min. To the Schlenk flask containing the catalyst were added imine **8a** (136 mg, 0.50 mmol) and anhydrous toluene (1 mL). The reaction mixture was stirred at r.t. for 5 minutes and then ethyl diazoacetate (62 μL, 0.6 mmol) was added via syringe. The Teflon valve was closed and the reaction mixture was stirred at r.t. for 24 h. The mixture was then diluted with hexanes (5 mL) and transferred to a 25 mL round-bottom flask. Rotary evaporation of the solvent followed by exposure to high vacuum (0.5 mmHg) for 30 minutes gave the crude mixture as an off-white solid. The conversion was determined from the ^{1}H NMR spectrum of the crude reaction mixture by integration of the aziridine ring methine protons relative to either the imine methine proton or the H on the imine carbon. The *cis*/*trans* ratio was determined to be >100:1 from the ^{1}H NMR spectrum of the crude reaction mixture by integration of the ring methine protons for each aziridine. The *cis* (*J* = 6–8 Hz) and the *trans* (*J* = 1–3 Hz) coupling constants were used to differentiate the two isomers. The yields of the acyclic enamine products were determined to be <1% from the ^{1}H NMR spectrum of the crude reaction mixture by integration of the N-H proton of the enamine relative to the aziridine ring methine protons with the aid of the isolated yield of the *cis*-aziridine. The crude product was purified by column chromatography on silica gel (35 mm × 400 mm, EtOAc/hexanes 1:19) to afford **12a**.

Yield: 146 mg (0.41 mmol, 82%); white solid; mp 126–127 °C; R_f = 0.13 (1:9 EtOAc/hexanes); 98% *ee* (HPLC; Chiralcel OD-H column, 222 nm, 90:10 hexane/*i*PrOH, flow rate: 0.7 mL/min): t_R = 4.42 [(2*S*,3*S*)-**12a**; minor], 8.17 [(2*R*,3*R*)-**12a**; major] min; $[\alpha]_D^{20}$ = +36.2 (*c* 1.0, CH_2Cl_2) on 98% *ee* (2*R*,3*R*)-**12a**.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 0.96 (t, *J* = 7.0 Hz, 3 H), 2.65 (d, *J* = 7.0 Hz, 1 H), 3.19 (d, *J* = 7.0 Hz, 1 H), 3.93 (s, 1 H), 3.90–3.94 (m, 2 H), 7.14–7.20 (m, 2 H), 7.20–7.26 (m, 5 H), 7.30–7.34 (m, 2 H), 7.37–7.40 (m, 2 H), 7.46–7.49 (m, 2 H), 7.57–7.60 (m, 2 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 13.93, 46.38, 48.03, 60.55, 77.71, 127.19, 127.21, 127.31, 127.40, 127.54, 127.75, 127.78, 128.48, 135.03, 142.38, 142.52, 167.72 (one sp^2 C not located).

IR (thin film): 3031w, 2982w, 1738s, 1456m, 1204s cm^{-1}.

MS: *m*/*z* (%) = 357 (0.05) [M]$^+$, 190 (46), 167 (100), 117 (61).

Procedure for Growing Crystals of the Boroxinate/Imine complex 31 (Scheme 3)

To a flame-dried 25 mL Schlenk flask flushed with argon was added activated 4Å MS (bead) and 10 mL pentane at least 4 h prior to the preparation of the catalyst. To a 25 mL flame-dried Schlenk flask flushed with argon was added (*S*)-**6g** (28 mg, 0.05 mmol), BH_3·SMe_2 (100 μL, 0.2 mmol) (2 M in toluene) and phenol (15 mg, 0.15 mmol), followed by addition of distilled toluene (1.5 mL) and then H_2O (1.8 μL, 0.1 mmol). The flask was sealed, and then placed in an 85 °C oil bath. After 1 hour, a vacuum (0.2 mmHg) was applied carefully for 45

minutes while the flask was still heated at 85 °C. The prepared catalyst was allowed to cool to r.t. under argon. At the same time, NMR tubes (2 to 3 for parallel experiments) were taken from the oven and immediately capped with either a plastic cap or a sealed cap depending on the type of the NMR tube. These NMR tubes were then connected to vacuum, flame-dried and cooled under argon. To the Schlenk flask containing the prepared catalyst flushed with argon was then added *N*-MEDAM phenyl imine **30a** (20 mg, 0.05 mmol), the Teflon cap was switched with a medium-size rubber septum, followed by the addition of distilled CH_2Cl_2 (1.5 mL) through the septum to give a light-brown solution. To this solution was carefully added dried pentane until a cloudy suspension appeared (ca. 4–6 mL), to which was added CH_2Cl_2 again (0.2 mL). The solution was then transferred to the prepared NMR tube by syringe (the smaller the diameter of the needle, the better) in the amounts of 1.5 mL, 2 mL and full for the parallel experiments, the empty space in each NMR tube was then filled with pentane to the top (Note: if a plastic cap was used for the NMR tube, after transferring, the cap was replaced with a new one). The NMR tubes were wrapped with parafilm and covered with aluminum foil, then set for a week or longer to let the crystals grow. These crystals could also be prepared from $B(OPh)_3$ instead of $BH_3{\cdot}SMe_2$ and phenol. One of these crystals was submitted to X-ray analysis and the result has been deposited with the Cambridge Crystallographic Data Centre.

CCDC 1946429 contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.

Asymmetric Aziridination of Imine 30a with a Catalyst Prepared from Ligand (*S*)-6g (Table 3)

The reaction was performed in a flame-dried 25 mL Schlenk flask. The flask was charged with (*S*)-**6g** (10 mol%, 0.025 mmol, 14 mg) followed by addition of $B(OPh)_3$ (40 mol%, 0.1 mmol, 29 mg) and H_2O (10 mol%, 0.025 mmol, 0.45 μL). The mixture was dissolved in toluene (0.0125 M, 2 mL) and heated at 85 °C for 1 hour. The Teflon cap of the Schlenk flask was opened carefully to remove the solvent, and high vacuum (1 mmHg) was applied for 30 minutes at 85 °C. To the Schlenk flask, MEDAM imine **30a** (1.0 equiv 0.25 mmol, 97 mg) and toluene (0.125 M, 2 mL) were added and the resulting mixture was stirred at r.t. for 10 minutes. The reaction was carried out by addition of ethyl diazoacetate (1.1 equiv 0.275 mmol, 34 μL) and stirring at r.t. for 24 h. The mixture was diluted with hexane (5 mL) and transferred to a 50 mL round-bottom flask and the Schlenk flask was rinsed with CH_2Cl_2 (6 mL). After the evaporation of the solvent an off-white solid was obtained as the crude mixture of the reaction. The NMR yield and conversion were determined based on the ^{1}H NMR spectrum of the crude reaction mixture by using triphenylmethane as the internal standard. The conversion and the NMR yield were 99%. The crude product was purified by using column chromatography on silica gel with a 90:10 mixture of hexanes and EtOAc to give the pure product.

Yield: 93% isolated yield; off-white solid; 99% *ee* (HPLC; Chiralcel, OD-H column, 226 nm 99:1 hexane/*i*PrOH, flow rate 0.7 mL/min): R_t = 6.47 (minor enantiomer), 9.67 (major enantiomer) min.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.39 (d, *J* = 7.4 Hz, 2 H), 7.27–7.16 (m, 5 H), 7.12 (s, 2 H), 3.94 (p, *J* = 6.5 Hz, 2 H), 3.69 (d, *J* = 8.3 Hz, 3 H), 3.64 (s, 3 H), 3.13 (d, *J* = 6.8 Hz, 1 H), 2.58 (d, *J* = 6.8 Hz, 1 H), 2.27 (s, 6 H), 2.21 (s, 6 H), 1.00 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 168.06, 156.08, 155.92, 137.99, 137.83, 135.30, 130.65, 130.63, 127.87, 127.81, 127.75, 127.41, 127.25, 77.05, 60.55, 59.62, 59.56, 48.24, 46.28, 29.73, 16.29, 16.22, 14.06.

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Supporting Information

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