structures of the Group 1 complexes of (S)-[(Ph(Me)-CH)(PhCH$_2$)NH] reveal the amido ligand adopts a "butterfly in flight" configuration in which the phenyl groups are almost perpendicular to each other,[8] and as such can be viewed as having significant steric bulk with the charge concentrated on the N$^-$ ion. This is less likely to give stable mixed-anion complexes, and can be contrasted to [{[PhN(H)]$_2$(*t*BuO)Li-NaK · (tmen)$_2$}$_2$] and [{(MeOPh)N(H)}$_2$(*t*BuO)NaLi$_2$], both of which are derived from primary amines.

Experimental Section

1: (S)-α-(Ph(Me)CH)(PhCH$_2$)NH (5 mmol, 1.05 g) was added dropwise to a chilled (−78 °C) suspension of *t*BuOK (15mmol, 1.55 g) in hexane (20 mL). *n*BuLi (5.5 mmol, 3.2 mL, 1.6 M in hexane) was added dropwise resulting in the formation of a bright red suspension. The reaction mixture was stirred and allowed to warm to room temperature over 2 h during which time the suspension darkened to a deeper red. Hexane was removed in vacuo and THF added (ca. 20 mL) which with gentle warming allowed complete dissolution. The ligand tmen (10 mmol, 1.51 mL) was added, then the solvent was reduced in vacuo by approximately a third and the mixture was placed in the freezer at −20 °C overnight. This resulted in a crop of red needlelike crystals which were isolated and then washed with hexane. Yield 57 % (1.7 g). M.p. 131–132 °C; elemental analysis $C_{31}H_{48}NK_3O_4$ (%); calcd: C 60.5, H 7.8, N 2.3; found: C 61.1, H 7.5, N 2.1; ^{1}H NMR ([D$_8$]THF, 25 °C, 300 MHz): $\delta = 7.21$ (d, $J = 7.9$ Hz, 2H; *o*-H), 6.90 (brs, 2H; *o*-H), 6.81 (t, $J = 7.7$ Hz, 2H; *m*-H), 6.72 (t, $J = 7.6$ Hz, 2H; *m*-H), 6.19 (m, 2H, *p*; PhC*H*), 6.06 (t, $J = 7.1$ Hz, 1H; *p*-H), 3.57 (m, 4H; THF), 1.89 (s, 3H; Me), 1.73 (m, 4H; THF), 0.96 (s, 18H; *t*Bu); ^{13}C NMR ([D$_8$]THF, 25 °C, 75.5 MHz): $\delta =$ 146.33 (*q*C), 145.78 (*q*C), 129.14 (*o*C), 129.09 (*o*C), 129.00 (*o*C), 128.70 (*m*C), 127.35 (*m*C), 127.32 (*m*C), 119.16 (Ph*C*H), 115.81 (*p*C), 114.41 (Ph*C*Me), 105.75 (*p*C), 37.5 (*t*Bu), 12.35 (Me).

Crystallographic data for **1**: Data collected on an Enraf Nonius Kappa CCD at 123 K. Crystal mounted under oil. $C_{31}H_{48}NK_3O_4$, $M_r = 615.01$, monoclinic, space group $P2_1/c$ (no. 14), red acicular crystal measuring $0.30 \times 0.24 \times 0.10$ mm, $a = 10.7096(5)$, $b = 16.4210(8)$, $c = 19.8427(9)$ Å, $\beta = 91.875(2)^\circ$, $V = 3487.7(2)$ Å3, $Z = 4$, $\rho_{calcd} = 1.171$ g cm^{-3}, $\lambda(Mo_{K\alpha}) = 0.71073$ Å, $\mu(Mo_{K\alpha}) = 4.23$ cm^{-1}, 42594 reflections measured, 8661 unique, 3936 were observed ($I > 3.00\sigma(I)$), $R = 0.043$, $R_w = 0.051$, GoF 1.30. The structure was solved by direct methods with all H atoms placed in idealized positions ($r = 0.95$ Å). The aza-allylic anion is disordered in the crystal, as indicated by the occupancy of Me on C1 and C8 of 50:50. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-147738. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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Catalytic Asymmetric Aziridination with Arylborate Catalysts Derived from VAPOL and VANOL Ligands[**]

Jon C. Antilla and William D. Wulff[*]

The ring opening of chiral aziridines is a potent method for the synthesis of optically active amines.[1] The driving force of this process derives from the ring strain of the aziridine and this can be used to extend the ring opening to a variety of nucleophiles to produce difuncational amines with vicinal chiral centers. Since no general method for catalytic asymmetric aziridination exists,[2] chiral aziridines have been largely made from materials in which the chiral centers already exist.[1d] Given the synthetic and strategic advantages of asymmetric catalysis we began a program to find a chiral catalyst for asymmetric aziridination, and recently reported

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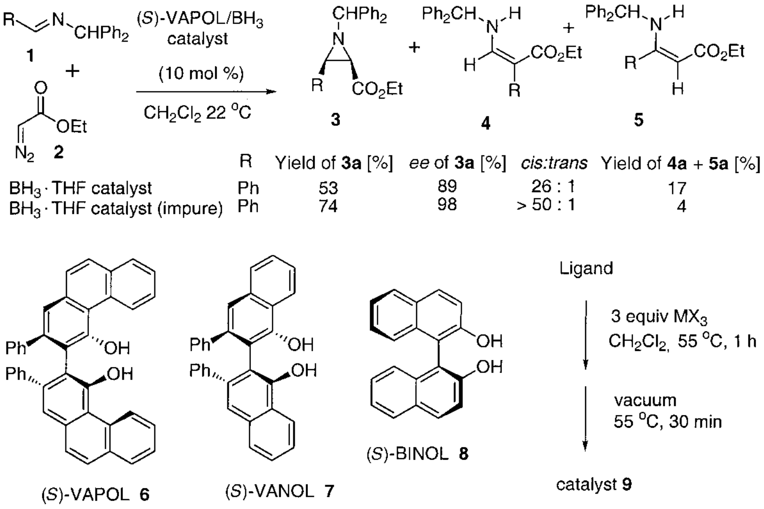
[**] This work was supported by the National Institutes of Health and was performed at the University of Chicago. VAPOL = 2,2′-diphenyl-[3,3′-biphenanthrene]-4,4′-diol, VANOL = 3,3′-diphenyl-[2,2′-binaphthalene]-1,1′-diol.

Supporting information for this article is available on the WWW under http://www.wiley-vch.de/home/angewandte/ or from the author.

the first catalyst that is generally applicable for a range of substrates.[3] This methodology involves the addition of ethyl diazoacetate (EDA) to imines mediated by a catalyst prepared from the VAPOL ligand and the $BH_3 \cdot THF$ complex.[4] We have since found that the success of the reaction is dependent on the purity of the $BH_3 \cdot THF$ complex used to generate the catalyst. This observation led to the present report of the development of a catalyst that is not only more reliable, but which can be extended to previously unreactive substrates, gives increased chemical yields, and greatly increased diastereoselectivity while maintaining high asymmetric inductions. It was also found that the vaulted biaryl ligand VANOL[4c, 5] is equally effective for this process whereas the 1,1′-binaphth-2-ol (BINOL) ligand fails to give significant asymmetric induction.



Scheme 1. Synthesis of aziridine **3a** and the catalyst **9**. MX_3 = triphenylborate.

A catalyst prepared from VAPOL and a sample of $BH_3 \cdot THF$ that is greater than 98% pure gives the aziridine **3a** in 89% *ee* from the addition of ethyl diazoacetate to the imine **1a**. However, batches of $BH_3 \cdot THF$ that are not so pure can lead to a catalyst with a much improved profile: up to 98% *ee*, d.r. ≥50:1, and improved yields as well as a significantly reduced level of side products (Scheme 1). One of the impurities that we identified in the commercially available samples of $BH_3 \cdot THF$, especially in aged ones, was tributylborate. This observation prompted a study of catalysts prepared from the VAPOL ligand and a variety of borate esters, and the results are given in Table 1. Indeed, it was found that a catalyst prepared from tributylborate gave results nearly identical with the best observed with impure $BH_3 \cdot THF$. Lower asymmetric induction was seen with trimethyl- and triethylborate while higher induction was seen with triisopropylborate, although the rate was much slower with the latter. The performance of aluminum and gallium ethoxides were far inferior to any of the borate esters, and in the case of aluminum this may be attributed to poor solubility. The optimal catalyst was that prepared from triphenylborate, which gave an 81% yield of **3a** in 95% *ee* and with a d.r. ≥50:1 in favor of the *cis* isomer.

A comparison of catalysts prepared from triphenylborate and the biaryl ligands BINOL, VANOL, and VAPOL was undertaken. The BINOL-derived catalyst gave very low induction (20% *ee*) for the addition of ethyl diazoacetate to the imine **1a** (Table 1, entry 11) as well as significantly reduced *cis*/*trans* selection and an increased proportion of the noncyclized products **4** and **5**. In contrast, the catalysts prepared from the VANOL and VAPOL ligands and triphenylborate were found to be essentially equally effective with remarkably small variation between the two catalysts for all of the substrates (Table 2). In all other reactions that we have previously examined the VANOL and VAPOL ligands have always led to disparate levels of induction.[4] In the present case, the asymmetric inductions track nearly identically with each substrate and only small differences are seen. For some reactions slightly higher inductions were observed with the VANOL catalyst while for others the higher induction was

Table 1. Asymmetric aziridination of imine **1a** (R = Ph) with catalysts **9**.[a]

Entry	Metal complex	Catalyst	*t* [h]	Conversion[b]	Yield of *cis*-**3a** [%][c]	*ee* of *cis* **3a** [%][d]	*cis*:*trans* of **3a**[e]	Yield of **4a** [%][f]	Yield of **5a** [%][f]
1	$BH_3 \cdot THF$	**9a**[g]	20	100	53	89	26:1	11.1	6.3
2	$BH_3 \cdot THF$	**9a**[g, h]	3	100	58	91	21:1	15	5.3
3	$B(OnBu)_3$	**9b**[i]	10	100	72	96	44:1	3	2.4
4	$B(OnBu)_3$	**9b**[i, j]	2	100	71	96	>50:1	4.8	5.0
5	$B(OiPr)_3$	**9c**[k]	92	41	20	97	>50:1	1.3	1.0
6	$B(OMe)_3$	**9d**	20	92	74	91	35:1	3.6	2.5
7	$B(OEt)_3$	**9e**	20	67	51	92	30:1	3.2	2.3
8	$Al(OEt)_3$	**9f**	20	16	–	–	5:1	6.0	
9	$Ga(OEt)_3$	**9g**	20	84	29	30	7:1	16.2	12.3
10	$B(OPh)_3$	**9h**	1	100	81	95	>50:1	4.3	1.4
11	$B(OPh)_3$	**9h**[l]	3	100	61	20	17:1	12.6	9.0

[a] Unless otherwise specified, all reactions were run in dichloromethane (0.5 M in the imine) with 0.1 mmol of (*S*)-VAPOL at 22 °C with 1.1 equiv of ethyl diazoacetate with respect to **1a** and 10 mol% of the catalyst. [b] Determined by ^1H NMR spectroscopy. [c] Isolated after puriifcation by chromatography on silica gel. [d] Determined by HPLC on a Chiralcel OD-H column. [e] Ratio calculated by integration of the methine protons from the *cis*- and *trans*-aziridines. [f] Determined by ^1H NMR spectroscopy of the crude reaction mixture by integration of the signals relative to those of *cis*-**3a**. [g] $BH_3 \cdot THF$ contained less than 2% $B(OnBu)_3$. [h] Catalyst prepared at 0 °C for 24 h. [i] 5 mol% of the catalyst. [j] Syringe pump addition of imine (in 1 mL of CH_2Cl_2) to a solution of the catalyst and ethyl diazoacetate over 1 h and with stirring for an additional 1 h. [k] Catalyst prepared from 1 equiv of borate and 1 equiv of (*S*)-VAPOL. [l] (*S*)-BINOL was used as the ligand to give **3a** with the same configuration as (*S*)-VAPOL.

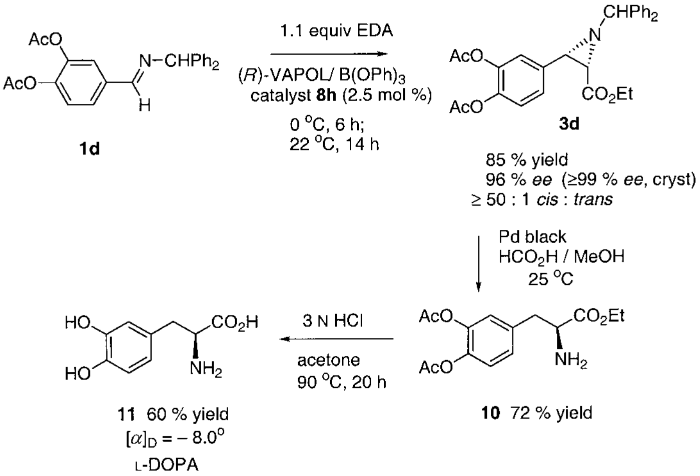
Table 2. Asymmetric aziridination with VAPOL and VANOL catalysts prepared from B(OPh)$_3$.[a]

Entry	Imine	R	Ligand	t [h]	Yield of *cis*-**3** [%][b]	*ee* of *cis*-**3** [%][c]	*cis*-:*trans*-**3**[d]	Yield of **4** [%][e]	Yield of **5** [%][e]
1	**1a**	Ph	(*S*)-VAPOL	48	77[f]	95	> 50:1	4.4	1.7
2			(*S*)-VANOL	0.5	85	96	> 50:1	3.3	1.0
3	**1b**	*p*-BrC$_6$H$_4$	(*S*)-VAPOL	5	91[g]	98	> 50:1	3.4	2.2
4			(*S*)-VANOL	1	85	98	> 50:1	8	3
5	**1c**	*o*-MeC$_6$H$_4$	(*S*)-VAPOL	14	69	94	40:1	11.1	7.1
6			(*S*)-VANOL	16	65	91	> 50:1	6	4
7	**1d**	3,4-(OAc)$_2$C$_6$H$_3$	(*R*)-VAPOL	20	85[f, h]	96	> 50:1	< 1	< 1
8			(*S*)-VANOL	5	83	97	> 50:1	< 1	< 1
9	**1e**	2-furyl	(*R*)-VANOL	16	55[i]	93	> 50:1	< 1	< 1
10	**1f**	1-naphthyl	(*S*)-VAPOL	12	87	92	> 50:1	3.8	0.3
11	**1g**	*n*-propyl	(*S*)-VAPOL	20	54[j]	91	> 50:1	8.3	9.2
12			(*S*)-VANOL	5	60	90	> 50:1	6.7	9.2
13	**1h**	*tert*-butyl	(*S*)-VAPOL	12	78	91	40:1	< 1	< 1
14			(*S*)-VANOL	5	77[k]	97	> 50:1	< 1	< 1
15	**1i**	*c*-C$_6$H$_{11}$	(*S*)-VAPOL	8	74	94	38:1	< 1	< 1

[a] Unless otherwise specified, all reactions were run in dichloromethane containing 0.5 M imine at 22 °C with 1.1 equiv of ethyl diazoacetate with respect to imine **1a** and 10 mol% of the catalyst. [b] Isolated after puriifcation by chromatography on silica gel. [c] Determined by HPLC on a Chiralcel OD-H column. [d] Ratio calculated by integration of the methine protons from *cis*- and *trans*-aziridines. [e] Determined by ^{1}H NMR spectroscopy of the crude reaction mixture by integration of the signals relative to those of *cis*-**3**. [f] Reaction with 2 mol% of the catalyst (entry 1) or 2.5 mol% (entry 7) and 1.0 M of the imine. [g] Reaction in toluene:dichloromethane (1:1). [h] Reaction was run at 0 °C for 4 h and then 16 h at 22 °C. [i] Reaction conditions: toluene, 0 °C for 16 h. [j] Reaction conditions: toluene, 0 °C for 4 h, then 22 °C for 16 h. [k] Reaction conditions: toluene, 0 °C for 4 h, then 22 °C for 1 h.

observed with the VAPOL catalyst. What is remarkable is that for both ligands and for all substrates the asymmetric induction for all combinations falls in the range of 90–98% *ee*. The chemical yields of **3** for each catalyst are similar and both are generally higher that the yields observed with the BH$_3$·THF complex. The reaction times indicated in Table 2 are not indicative of rate since the times were not optimized and in some cases different catalyst loadings were employed. The diastereoselectivites are very high for both catalysts but the VANOL catalyst gave a selectivity of greater than 50:1 for every substrate. The diastereoselectivity is one of the greatest differences between the catalysts generated from triphenylborate and the BH$_3$·THF complex. For example, the *cis*:*trans* selectivity for the imine **1c** derived from *ortho*-methylbenzaldehyde was 3:1 for the catalyst prepared from VAPOL and the BH$_3$·THF complex,[3] while it was 40:1 with the corresponding catalyst derived from the triphenylborate catalyst. Another dramatic difference is that the imines prepared from pivaldehyde and 1-naphthylaldehyde are unreactive with the catalyst prepared from VAPOL and BH$_3$·THF, whereas these substrates react with similar rates using the triphenylborate catalyst to give asymmetric inductions and chemical yields similar to those observed for the other substrates. Finally, the rates of the reaction could not be increased by the slow addition of the imine with the VAPOL–borate catalyst as was found to be the case with the VAPOL–borane catalyst.[3]

An application of the VAPOL–triphenylborate catalyst in the synthesis of L-3,4-dihydroxyphenylalanine (L-DOPA) is illustrated in Scheme 2. The reaction of imine **1d** with ethyl diazoacetate in the presence of 2.5 mol% of the catalyst derived from (*R*)-VAPOL and triphenylborate led to the formation of the aziridine **3d** in 85% yield and in 96% *ee* on a multigram scale. The optical purity could be improved to greater than 99% *ee* with a single crystallization of the product from hexane:dichloromethane (10:1; the first crop gave 85% recovery).[6] Hydrogenation of the nitrogen–benzylic bond occurred with cleavage of the benzhydral group to give the amino ester **10** in 72% yield. After hydrolysis of the three ester linkages L-DOPA was obtained in 60% yield with an optical rotation of $[\alpha]_D = -8.0°$. This rotation corresponds to 98% *ee*, and thus very little if any epimerization occurred during the hydrolysis.[7]



Scheme 2. Synthesis of L-DOPA.

Further studies on the mechanism, scope, and synthetic applications of this asymmetric catalytic aziridination reaction will be reported in due course.

Experimental Section

3d: (*R*)-VAPOL (174 mg, 0.323 mmol) was added to a flame-dried flask cooled under argon and then dissolved in CH$_2$Cl$_2$ (6 mL). After the addition of triphenylborate (281 mg, 0.969 mmol) the mixture was heated to 55 °C for 1 h and then a vacuum (0.5 mm Hg) was applied for 30 min with the temperature maintained at 55 °C. The catalyst was dissolved in CH$_2$Cl$_2$ (3.0 mL) and transferred by syringe to a 50-mL flame-dried flask which was previously charged with a stirring bar and filled with argon. A solution of imine **3d** (5.00 g, 12.9 mmol) in CH_2Cl_2 (10 mL) was added by syringe to the catalyst solution at 0 °C. Stirring the mixture for 10 min gave an orange solution to which was rapidly added ethyl diazoacetate (1.484 mL, 14.2 mmol) by syringe. Some bubbling was noted after the addition. The reaction was allowed to proceed for 6 h at 0 °C and then for 14 h at room temperature (22 °C). The reaction mixture was transferred to a 500-mL flask, diluted with hexanes (250 mL), and then the volatiles were removed under vacuum to give the crude aziridine **3d** as an off-white solid. The ^{1}H NMR spectrum of this material revealed **3d** with *cis*:*trans* $\geq$ 50:1 and indicated that $<$1 % of **4d** and **5d** were formed. Purification of **3d** by column chromatography on silica gel with a mixture of ethyl acetate:hexanes (3:7) gave aziridine **3d** (5.20 g, 11 mmol) as a white solid in 85 % yield. The optical purity of this material was determined to be 96 % *ee* by HPLC analysis (OD-H column). Crystallization from hexanes:CH_2Cl_2 (10:1, 300 mL) gave **3d** (4.43 g) with 99 % *ee*. A second crop was taken but found to be only 90 % *ee*. Spectral data for **3d**: m.p. 141–143 °C (hexanes:CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.99$ (t, $J = 7$ Hz, 3H), 2.24 (s, 3H), 2.25 (s, 3H), 2.68 (d, $J = 7$ Hz, 1H), 3.18 (d, $J = 7$ Hz, 1H), 3.95 (s, 1H), 3.95 (m, 2H), 7.07 (d, $J = 9$ Hz, 1H), 7.19 (m, 1H), 7.28 (m, 7H), 7.45 (d, $J = 7$ Hz, 2H), 7.81 (d, $J = 7$ Hz, 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 13.84$, 20.64, 46.57, 47.03, 60.89, 77.49, 122.75, 122.78, 126.05, 127.18, 127.30, 127.45, 127.61, 128.55, 128.65, 133.97, 141.35, 141.57, 142.21, 167.45 168.07, 168.24; IR (thin film) 3030 (w), 2980 (w), 1770 (s), 1731 (s), 1600 cm^{-1} (m); MS (EI): *m*/*z* (relative intensity): 474 (21) [M+1], 306 (12), 195 (10), 167 (100); *m*/*z* calcd for $C_{28}H_{27}NO_6$: 474.1903, found 474.1903. Elemental analysis calcd for $C_{28}H_{27}NO_6$: C 71.02, H 5.75, N 2.96; found: C 71.23, H 5.88, N 2.94. $[\alpha]^{23}_{D} = -17.3°$, ($C = 1$ from CH_2Cl_2) taken on 99 % *ee* material (HPLC). Further experimental details can be found in the Supporting Information.

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[5] The VANOL ligand was prepared according to the same procedure that has been reported for the VAPOL ligand.[4c]

[6] A second crop was taken but had only approximately 90 % *ee*.

[7] The optical rotation of an authentic sample of L-DOPA was found to be $[\alpha]_D = -8.2°$.

Stereoselective Synthesis of R_P- and S_P-Dithymidine Phosphorothioates via Chiral Indolooxazaphosphorine Intermediates Derived from Tryptophan[**]

Yixin Lu and George Just*

The use of phosphorothioates as DNA analogues useful in antisense-based therapy is well established[1] and led to the development of Vitravene as the first antisense drug.[2] Several other phosphorothioate oligonucleotides (PS-Oligos) are in clinical trials. Although Stec et al. described an elegant oxathiaphospholane-based approach[3] for preparing diastereomerically pure phosphorothioates, it has not been used for large-scale production of PS-Oligos, which are still used as a mixture of about 10^6 diastereomers. The use of cyclic *N*-acylphosphoramidites as promising monomers for the stereocontrolled synthesis of phosphorothioates was recently reported by Beaucage et al.[4]

Previously, we developed cyclic phosphoramidites[5] such as sugar-derived oxazaphosphorinanes,[5b,c] indolooxazaphosphorines (**a**),[5e, f] and indoleimidazoles[5i] for the stereoselective synthesis of PS-Oligos. Here we report on the use of promising indolooxazaphosphorine precursors derived from tryptophan which do not require a difficult chromatographic separation and may form the basis of a practical process.

As demonstrated in the indolooxazaphosphorine approach,[5f] chiral auxiliary **a** led to the stereoselective synthesis of phosphorothioate in solution. When it was applied to solid-phase synthesis, a β-elimination caused rearrangement to give

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