An examination of VANOL, VAPOL, and VAPOL derivatives as ligands for asymmetric catalytic Diels–Alder reactions[1]

Douglas P. Heller, Daniel R. Goldberg, Hongqiao Wu, and William D. Wulff

Abstract: Several derivatives of the vaulted biaryl ligand VAPOL were prepared and evaluated as chiral ligands for aluminum Lewis acids in the catalytic asymmetric Diels–Alder reactions of methyl acrylate and methacrolein with cyclopentadiene. The substituents on VAPOL were introduced into the 6- and 6′-positions in an effort to further extend the chiral pocket of the major groove, which contains the phenol functions at the 4- and 4′-positions. The set of four new ligands that have been prepared have the following groups introduced into the 6- and 6′-positions of VAPOL: bromide, methyl, phenyl and 3,5-di-*t*-butylphenyl. All of these ligands give lower asymmetric inductions than the unsubstituted VAPOL for the Diels–Alder reactions of both methyl acrylate and methacrolein. The positive cooperativity of added carbonyl compounds on the autoinduction in the Diels–Alder reaction of methyl acrylate and cyclopentadiene were also investigated with the VANOL and VAPOL ligands as well as the 6,6′-dibromo and 6,6′-diphenyl derivatives of VAPOL. Only the reaction with VAPOL showed any significant positive cooperativity. The reaction with VANOL was sluggish at −78 °C, but at higher temperatures, the reaction did exhibit positive cooperativity that was similar to that of VAPOL. Finally, no positive cooperativity was observed with the VAPOL ligand for the reaction of methacrolein and cyclopentadiene.

Key words: Diels–Alder, asymmetric catalysis, vaulted biaryl ligands, VANOL, VAPOL.

Résumé : On a préparé plusieurs dérivés du ligand voûté VAPOL et on les a évalués comme ligands chiraux pour des acides de Lewis dérivés de l'aluminium à utiliser dans des réactions de Diels–Alder asymétrique catalytique de l'acrylate de méthyle et de la méthacroléine avec le cyclopentadiène. On a introduit des substituants sur les positions 6 et 6′ du VAPOL dans le but d'agrandir la poche chirale de la cannelure principale qui comporte les fonctions phénols dans les positions 4 et 4′. Dans l'ensemble des quatre nouveaux ligands qui ont été préparés, on a introduit les groupes suivants dans les positions 6 et 6′ du VAPOL: bromure; méthyle; phényle et 3,5-di-tert-butylphényle. Chacun de ces ligands conduit à des inductions asymétriques inférieures à celle observé avec le VAPOL non substitué, tant pour les réactions de Diels-Alder de l'acrylate de méthyle que celles de la méthacroléine. On a aussi étudié la coopération positive des composés carbonyles ajoutés sur l'autoinduction de la réaction de l'acrylate de méthyle et du cyclopentadiène à l'aide de ligands VANOL et VAPOL ainsi qu'avec les dérivés 6,6′-dibromo et 6,6′-diphényl du VAPOL. Seule la réaction avec le VAPOL a montré une coopération positive significative. La réaction avec le VANOL était lente à −78°C, mais à des températures plus élevées, la réaction présente une coopération positive semblable à celle du VAPOL. Enfin, on n'a observé aucune coopération positive avec le ligand VAPOL pour la réaction de la méthacroléine avec le cyclopentadiène.

Mots clés : Diels–Alder, catalyse asymétrique, ligands biaryles voûtés, VANOL, VAPOL.

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This manuscript is dedicated to Dr. Alfred Bader. Dr. Bader is many things to many people and included among them he is an entrepreneur, a lover of the arts, a champion of young scientists, and above all, a generous and gracious human being. When I was a beginning assistant professor in the early 1980s, he awarded me one of his young chemist awards. This was a greatly appreciated and needed boast to my program. A gift of $5000 was a significant sum in those days considering my start-up package was $25 000. His call came out of the blue one day when I was home in bed with a nasty fever. Having failed to reach me at work, he tracked me down at home and what I remember from my delirious state is my wife saying someone named Alfred Bader was on the phone. I think that I thanked him at the time, and if I didn't, I would certainly like to thank him now.

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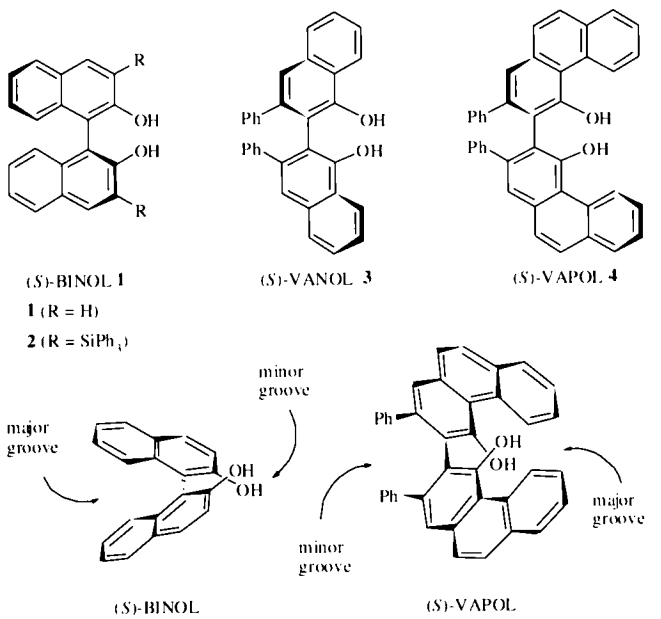
Scheme 1.

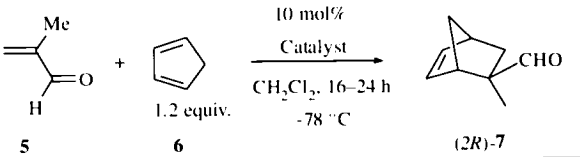


Introduction

One of the most widely used and successful ligands in asymmetric catalysis is 1,1′-binaphth-2,2′-ol, or BINOL 1 (1). In most applications, catalysts are generated from BINOL by the formation of covalent bonds to the two phenol functions with either a transition metal or a main group atom. In many applications it has been found that improved induction results from these catalysts if substituents are introduced in the 3- and 3′-positions of BINOL (such as **2**) (2). This is particularly true for catalysts that have only one BINOL ligand bound to the metal center (2). In the absence of substituents at the 3- and 3′-positions, the BINOL ligand provides a much smaller chiral pocket for the metal center since the phenol functions project into the minor groove of BINOL rather than the major groove (Scheme 1). Our approach to this problem is to design biaryls in which the phenol functions are projected into the major groove of the ligand (Scheme 1). To this end, we simply envisioned an extension of the aromatic system of BINOL out into the region of the phenol functions and as a result ultimately synthesized the vaulted biaryl ligands VANOL **3** and VAPOL **4** (3). These ligands have been demonstrated to be particularly successful in catalytic asymmetric Diels–Alder (4), aziridination (5), Mannich (6) reactions, as well as in Baeyer–Villiger oxidations (7) and imine amination reactions (8).

We have reported that a catalyst prepared from VAPOL and diethylaluminum chloride is effective in providing high asymmetric inductions in the reactions of methacrolein and methyl acrylate with cyclopentadiene (Table 1) (4). A comparison of a series of catalysts prepared from diethyl aluminum chloride and ligands **1**–**4** reveals that only the VAPOL-derived catalyst offers significant asymmetric induction in the reaction with methacrolein (Table 1) (4*a*). The data from a corresponding set of boron catalysts prepared from bromoborane dimethyl sulfide complex revealed that these catalysts are slower and that VANOL gave the catalyst with the superior enantioselectivities (4*b*). Based on the data in

Table 1. Diels–Alder reaction of methacrolein and cyclopentadiene.



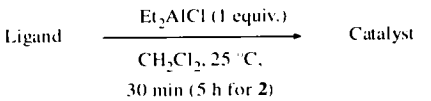
5 **6** (2*R*)-**7**

Ligand	Yield **7** (%)	exo–endo	ee% **7** (exo)[a]
(*S*)-BINOL	99	97:3	23
(*S*)-**2**	69	92:8	20
(*S*)-VANOL	84	93:7	5
(*S*)-VAPOL	100	98:2	91.4 (93.6)[b]

Note: All reactions use 1.0 mol/L in methacrolein.

[a]ee% was measured by conversion to chiral acetals as described in the experimental section.

[b]ee% in parentheses was measured by GC as described in the experimental section.



Scheme 2.

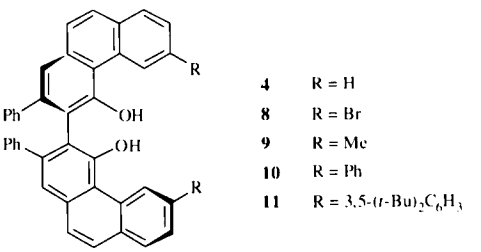
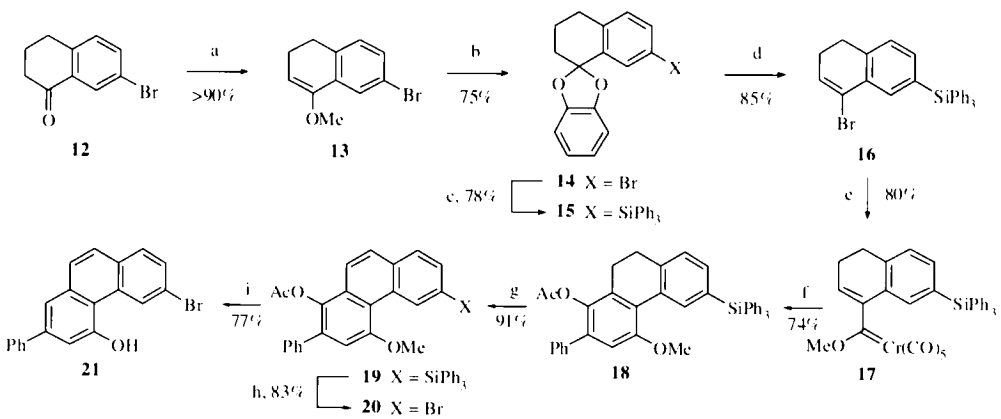


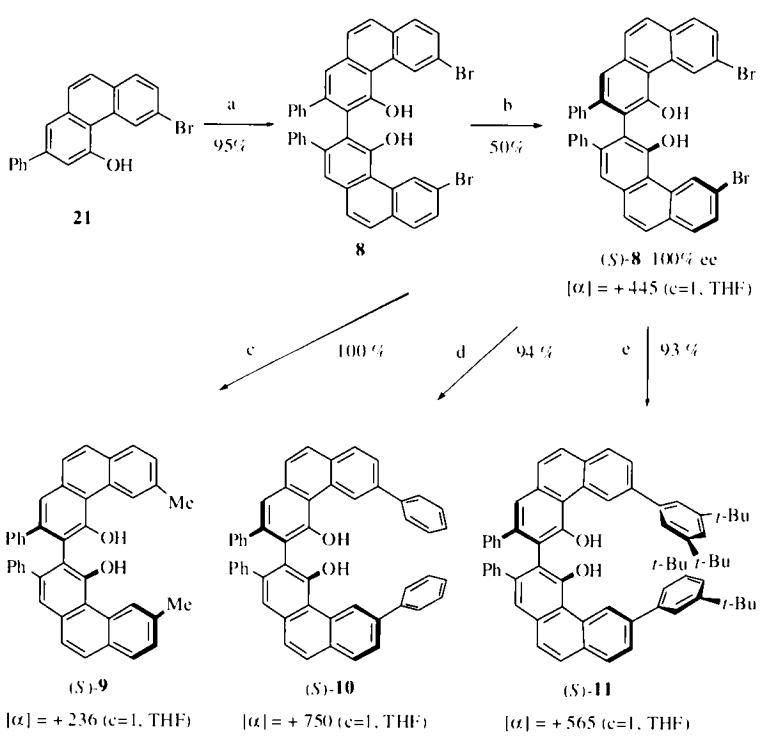
Table 1, we set out to prepare and evaluate the set of 6,6′-disubstituted VAPOL ligands **8**–**11** (Scheme 2) as precursors to aluminum catalysts in the asymmetric catalytic Diels–Alder reaction and to compare their selectivity profile with that of the unsubstituted VAPOL ligand **4**. Substituents in the 6- and 6′-positions would be expected to increase the size of the major groove of the VAPOL ligand (Scheme 1) and as a result, the asymmetric induction observed in reactions mediated by catalysts generated from these ligands. In addition, catalysts generated from the VANOL ligand **3** will be evaluated for the Diels–Alder reactions, given the recent findings that the VANOL ligand is equally as effective as the VAPOL ligand in asymmetric catalytic aziridination reactions and superior to the VAPOL ligand in Baeyer–Villiger reactions (7).

The retrosynthesis of the VAPOL derivatives **8**–**11** was envisioned to involve, first, the initial preparation of the 6,6′-dibromoVAPOL **8** and then after subsequent resolution, the utilization of this dibromo derivative as the intermediate through which the other derivatives will be prepared. The synthesis of the 6,6′-dibromo-VAPOL **8** was modeled after the original method that we developed for the synthesis of the VAPOL ligand (3) and involves the oxidative phenol coupling of the phenanthrol **21** (Scheme 3), whose synthesis in turn would involve the benzannulation reaction of the carbene complex **17** with phenylacetylene as the key step (Scheme 4). The synthesis of the alkenyl bromide **16** neces-

Scheme 3. (*a*) $HC(OMe)_3$, MeOH, cat CSA, benzene, reflux; (*b*) catechol, cat TsOH, benzene, reflux; (*c*) *i*. *n*-BuLi, THF, −78 °C, *ii*. Ph_3SiCl; (*d*) BBr_3, CH_2CL_2; (*e*) *i*. 2 equiv. *t*-BuLi, THF, −78 °C, *ii*. $Cr(CO)_6$, *iii*. MeOTf, CH_2CL_2; (*f*) *i*. PhC / CH, THF, 60 °C, 21 h, *ii*. Ac_2O, NEt_3, THF, 60 °C; (*g*) NBS, cat benzoyl peroxide, benzene, reflux; (*h*) Br_2, CH_2CL_2, reflux; (*i*) EtSH, $AlCl_3$, CH_2CL_2.



Scheme 4. (*a*) 195 °C, air; (*b*) *i*. (−)-sparteine, $CuCl_2$-$2H_2O$, MeOH–CH_2CL_2, *ii*. extract into hexane; (*c*) MeMgBr, cat Ni(II)(dpe)Cl_2, ether, reflux; (*d*) $PhB(OH)_2$, cat $Pd(PPh_3)_4$, benzene, aq. Na_2CO_3, reflux; (*e*) 3,5-(*t*-Bu)$_2C_6H_3B(OH)_2$, cat $Pd(PPh_3)_4$, benzene, aq. Na_2CO_3, reflux.



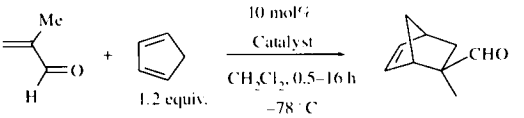
sary for the synthesis of the carbene complex **17** begins with 7-bromo-α-tetralone **12**, as indicated in Scheme 4. After evaluation of several methods for the conversion of ketones to alkenyl bromides, we found that the best procedure for the tetralone **12** was the method reported by Napolitano (9) involving the intermediacy of a catechol ketal, which was reported for α-tetralone in 40% overall yield. As reported by Napolitano for α-tetralone, we found that the direct conversion of 7-bromo-α-tetralone **12** to the catechol ketal **14** was inefficient. On a small scale, the direct reaction of **12** with catechol gave minimal yields of **14** and on a large scale this conversion failed completely. However, excellent yields of **14** could be obtained if **12** was first converted to the methyl enol ether **13**. The bromide function in the alkenyl bromide **16** is necessary for the preparation of the carbene complex **17**, but prior to the formation of the alkenyl bromide **16** by treatment of the ketal with boron tribromide the aryl bromide function in **14** was protected as its triphenylaryl silane **15**. The carbene complex **17** could then be generated by the standard Fischer procedure from **16** and chromium hexacarbonyl in 80% yield. The benzannulation of the carbene complex **17** with phenyl acetylene was carried out in two steps, (*i*) the reaction with phenylacetylene and (*ii*) the protection of the phenol function as its acetate. One attempt to carry out this transformation concurrently by the addition of acetic anhydride and triethylamine at the beginning of the reaction met with failure. Thus, this overall transformation must be carried in sequential steps. In the next step, oxida-

tion of the B ring with NBS under free-radical conditions afforded phenanthrene **19** in 91% yield. Initial attempts at this oxidation with palladium on carbon or DDQ were unsuccessful. One might wonder why we waited until after the benzannulation reaction to aromatize. We could have, for example, oxidized the compound **16** and carried the naphthyl system into the benzannulation. We chose this order because the benzannulation of alkenyl carbene complexes with alkynes is much less susceptible to side-product formation than aryl complexes (10). The triphenylsilyl group was then "deprotected" to the bromide by treatment with bromine, which after considerable optimization was found to be best achieved with two equivalents of bromine to give **20** in 83% yield. The monomer **21** was finally generated by the reaction of **20** with ethanethiol and aluminum chloride (3). It is critical to control the time of this reaction since prolonged times can lead to the reduction of the bromide in the product **21**. Since trace amounts of this reduced monomer would lead to cross-coupled products in the oxidative phenol coupling step, it was necessary to rigorously purify the monomer **21** by column chromatography.

The oxidative phenol coupling follows the procedure developed for the synthesis of VAPOL and VANOL (3). Melting **21** in the presence of air and heating at 195 °C until the monomer **21** was consumed gave racemic 6,6′-dibromo-VAPOL **8** in 95% yield. This compound was deracemized with (−)-sparteine and copper (II) according to a procedure originally reported by Kocovsky (11), which has recently been improved by our laboratory (12). This procedure gave 6,6′-dibromo-VAPOL **8** that was substantially enantioenriched (>90% ee). The optical purity could be easily improved by extracting with hexane. The racemates of VAPOL **4** and Br_2-VAPOL **8** are both substantially less soluble than the optically pure material. Thus, the pure enantiomer of **8** (>99% ee) could be easily obtained by stirring the enantioenriched **8** with enough hexane to leave only a small amount of residue undissolved. The hexane solution is decanted to leave the solid and then the hexane is removed to leave the optically pure ligand **8**. This ligand could also be crystallized from hexane and ethyl acetate to give X-ray quality crystals, which have two molecules of ethyl acetate per molecule of **8**. The conversion of the 6,6′-dibromo-VAPOL ligand **8** to the corresponding dimethyl derivative **9** was accomplished in 100% yield by the nickel-catalyzed coupling of **8** with methyl magnesium bromide (6 equiv.) (13). The two aryl-substituted VAPOL ligands **10** and **11** were prepared from the dibromide **8** by Suzuki coupling reactions in 94% and 93% yields, respectively (14).

The results from the asymmetric catalytic Diels–Alder reactions of methacrolein and cyclopentadiene with catalysts generated from VAPOL **4** and the VAPOL derivatives **8–11** are shown in Table 2. All of the VAPOL derivatives with substituents in the 6- and 6′-positions give lower asymmetric inductions than VAPOL. The best of these is the bis-(3,5-di-*t*-butylphenyl) derivative, which gives a 62% ee for the reaction. Interestingly, the diphenyl derivative **10** gives the product **7** with the opposite sense of induction to all of the other ligands. The catalyst was prepared in each case by treating the ligand with 1 equiv. of ethylaluminum dichloride at RT. The completion of catalyst formation was determined by ^{1}H NMR and it was found that for the ligands **4**, **8**, and **9** the

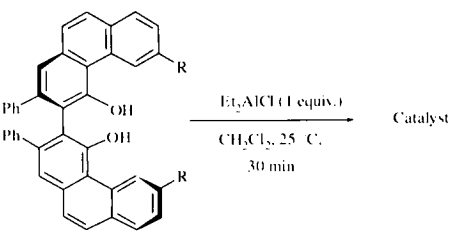
Table 2. Effect of vaulted biaryl catalysts on the reaction of **5** and **6**.



5 **6** (2*R*)-**7**

Ligand	R	Yield **7** (%)[a]	exo–endo[b]	ee% **7** (exo)[b]
(*S*)-**4**	H	>95	27	93
(*S*)-**8**	Br	>95	8.3	18
(*S*)-**9**	Me	>95	14.4	30
(*S*)-**10**	Ph[c]	76	11.7	−41
(*S*)-**11**	3,5-(*t*-Bu)$_2$C$_6$H$_3$[c]	>95	8.4	62

Note: All reactions use 0.5–1.0 mol/L in methacrolein.
[a]Determined by ^{1}H NMR with ligand as internal standard.
[b]Determined by GC of acetals prepared from (2*R*,4*R*)(−)pentanediol.
[c]Catalyst was prepared at 55 °C for 24 h.

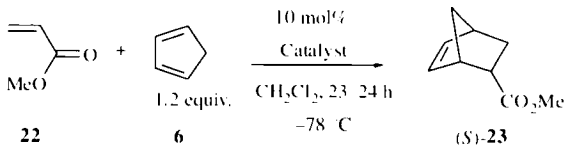


VAPOL was completely consumed within 30 min. However, for the more hindered ligands **10** and **11**, the complete consumption of the ligand required heating at 55 °C for 24 h.

Catalysts prepared from VAPOL-derived ligands **8–11** were also examined with the reaction of methyl acrylate and cyclopentadiene (Table 3). These reactions were slower than those with methacrolein but all are complete in 24 h except for the catalyst generated from the VANOL ligand, which only gave a 28% yield of the product **23** after 24 h. As with the reactions with methacrolein, all of the derivatives of VAPOL gave lower asymmetric inductions than VAPOL itself. Thus, for both sets of reactions it appears that the VANOL ligand does not provide a large enough chiral pocket. Furthermore, all of the 6,6′-substituted VAPOL derivatives form aluminum catalysts where either the bound substrate does not exist in a single conformation or the substrate does not have one of its faces sufficiently differentially shielded. The VAPOL ligand seems to be optimal for this particular aluminum catalyst.

The effect of solvents on the reaction of methyl acrylate with cyclopentadiene that is catalyzed by the VAPOL-derived catalyst is shown in Table 4. There was no reaction at all in THF and in ether the reaction was very sluggish giving only a 23% yield after 24 h with 10 mol% catalyst. Clearly, the best solvent for this reaction is toluene, which gives the product in 100% yield and 97% ee, whereas methylene chloride gives 87% yield and 82% ee. It was very curious indeed to find that if the reaction in methylene chloride was stopped after 15 min, the product was isolated with 48% ee. Furthermore, if the reaction was carried out by addition of only 10% of the dienophiles at the beginning of the reaction followed by slow addition of the remaining dienophiles, the asymmetric induction for **23** was higher at the end of the

Table 3. Effect of vaulted biaryl catalysts on the reaction of **22** and **6**.



22 **6** (*S*)-**23**

Ligand	R	Yield **23** (%)[a]	endo–exo[b]	ee% **23** (exo)[b]
(S)-**4**	H	87	112	82
(S)-**8**	Br	>95	51	16
(S)-**9**	Me	>95	92	28
(S)-**10**	Ph[c]	>95	129	35
(S)-**11**	3,5-(*t*-Bu)$_2$C$_6$H$_3$[c]	>95	44	29
(S)-**3**	VANOL	28	34	21

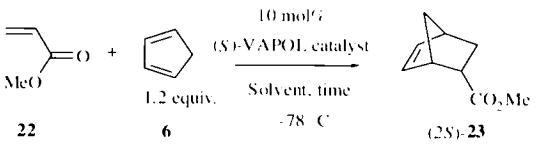
Note: All reactions use 0.5–1.0 mol/L in **22**. Unless otherwise specified the catalyst was prepared as indicated in Table 2.

[a]Determined by ^{1}H NMR with ligand as internal standard.

[b]Determined with a chiral GC column (J & W Cyclodex-B).

[c]Catalyst was prepared at 55 °C for 24 h.

Table 4. Solvent effect on the reaction of **22** and **6**.



22 **6** (2*S*)-**23**

Entry	Solvent	Time (h)	Yield **23** (%)[a]	endo–exo[b]	ee% **23** (exo)[b]
1	CH_2Cl_2	24	87	112	82
2	CH_2Cl_2	0.25[c]	21	—	48
3	CH_2Cl_2	24[d]	80	—	89.4
4	Toluene	24	100	99	96.6
5	THF	24	0	—	—
6	Et_2O	24	23	—	—

Note: All reactions use 0.5–1.0 mol/L in **22**. Unless otherwise specified the catalyst was prepared as indicated in Table 2.

[a]Determined by ^{1}H NMR with ligand as internal standard.

[b]Determined with a chiral GC column (J & W Cyclodex-B).

[c]Reaction stopped at 20% conversion.

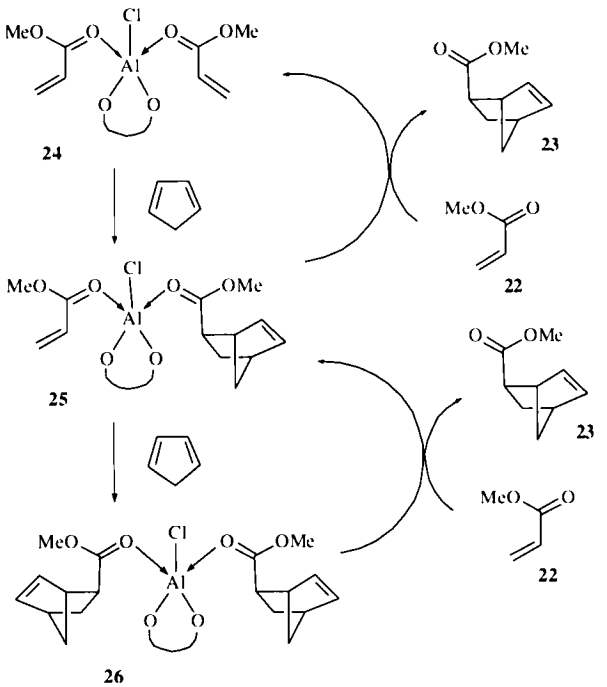
[d]10% of **22** was added at the beginning of the reaction and the rest was added slowly by syringe pump over 2.5 h.

reaction. We had observed this same type of behaviour for the reaction of methacrolein and cyclopentadiene (4*a*). We interpreted this as an asymmetric autoinduction (15) and have investigated this in some detail for the reaction of methyl acrylate and cyclopentadiene (4*c*). We chose the reaction of methyl acrylate and cyclopentadiene over that of methacrolein and cyclopentadiene since the former reacts much slower and it would be easier to follow the time course of the reaction. Also, the asymmetric induction was lower for the reaction with methyl acrylate and thus changes in induction would be more easily detected and monitored over a greater range. It is also for this reason that we chose to investigate the reaction of methyl acrylate in methylene chloride rather than in toluene.

Our explanation for the autoinductive effect observed for these reactions is illustrated in Scheme 5 for the reaction of methyl acrylate with cyclopentadiene (4*c*). It was proposed that the aluminum in the chiral catalyst could coordinate to the carbonyl group of two molecules of the starting material as in **24**, two molecules of the product as in **26**, or one molecule of each as in **25**. The fact that the particular asymmetric autoinduction we observed involves an increase in the asymmetric induction as the reaction progresses can then be accounted for if the Diels–Alder reaction of the complex **25** with one molecule of methyl acrylate and one molecule of product coordinated to the aluminum occurs with a higher selectivity than complex **24** with two molecules of starting material coordinated to the aluminum. At the beginning of the reaction there was little or no product and thus the great majority of the reaction flux will be through complex **24**. As more and more of the product is formed, more of the flux will occur through complex **25** and thus the asymmetric induction will continue to climb as the reaction progresses. In fact we have previously reported that the asymmetric induction for the reaction of methyl acrylate with cyclopentadiene is 48% ee after 20% completion and slowly rises during the course of the reaction until its culmination at 82% ee when the reaction is complete (Table 4 and ref. 4*c*).

It was reasoned that if complex **25** gives higher induction than **24** because of the greater steric size of the product com-

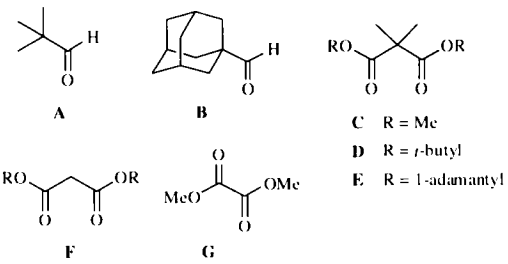
Scheme 5.



pared with that of the starting material, then one might be able to avoid the low asymmetric induction at the beginning of the reaction by the addition of a "dummy" carbonyl compound that is physically larger than methyl acrylate. This expectation was borne out in a series of experiments involving the carbonyl compounds indicated in Scheme 6. This study has been already communicated and some of this data is included in Table 5 (4*c*). As can be seen from the data in the first three entries, the addition of 0.5 equiv. of pivaldehyde at the beginning of the reaction increased the asymmetric induction at the end of the reaction from 82% to 96% ee. The larger adamantyl aldehyde B increased the induction still further to 98.5% ee. It was unexpected to find that 1,3-dicarbonyl compounds were even more effective. The di-*t*-butylmalonate D increased the induction to greater than 99% ee (Table 5, entry 5). These effects were more visible at higher temperatures. For example, the malonate E can increase the induction from 37% ee to 85% ee at 0 °C with 0.5 equiv. of E and to 92% ee with 1.0 equiv. This is quite remarkable when considering that the presence of this additive allows the temperature of the reaction to be increased by 80 °C and at the same time increases the induction from 82% ee to 92% ee. Since our initial report (4*c*) and as mentioned above, we have found that substantially increased asymmetric induction can be achieved in toluene as solvent. The asymmetric induction can be increased from 82% ee in CH_2Cl_2 to 97% ee in toluene at –78 °C (Table 5, entries 1 and 20). However, the additive effect is hardly observable in toluene. The reaction at 0 °C in toluene shows only a slight increase in induction from 46% ee to 58% ee in the presence of 0.5 equiv. of the malonate E.

The phenomenon of increased asymmetric induction with the addition of product mimics was termed "positive cooperativity" (4*c*). The strong effect that carbonyl additives had on the autoinduction for the reaction of methyl acrylate and cyclopentadiene with a catalyst generated from the VAPOL

Scheme 6.

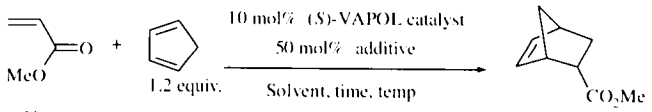


ligand prompted the study outlined in Table 6 to probe the extent to which added carbonyl compounds would exhibit positive cooperativity with the substituted VAPOL ligands **8** and **10** and with the VANOL ligand. These reactions were screened with 0.5 equiv. of the di-*t*-butyl malonate D added at the beginning of the reaction. Remarkably, the addition of malonate D had essentially no effect on the asymmetric induction with catalyst generated from 6,6′-dibromo-VAPOL **8** or from 6,6′-diphenyl-VAPOL **10**. Perhaps the major groove of these ligands (Scheme 1) is too hindered to allow for the coordination of two carbonyl groups at the same time. It was also found that the asymmetric induction from the VANOL-derived catalyst was not sensitive to the addition of the malonate D (Table 6, entries 8 and 9). In this case however, the yields were quite low with and without the additive. At this point we do not know if the structure of the active catalyst is the same from VAPOL and VANOL and, in fact, the ^1H NMR spectrum of the catalyst generated from Et_2AlCl and VAPOL reveals that there appears to be a mixture of several different species. In light of this fact, it is remarkable that very high asymmetric inductions can be achieved with this catalyst mixture for the reaction with methyl acrylate in toluene (Table 5, entry 20) or in CH_2Cl_2 in the presence of additives A-D (Table 5, entries 2–5).

The sluggishness of the reaction with the VANOL catalyst prompted a study of the effect of temperature on this catalyst to find conditions under which the reaction could be driven to completion and at the same time to determine the extent of any positive cooperativity with added carbonyl compounds leading to increased asymmetric induction. As the data in Table 7 shows, it was found that reasonable yields of the product could be observed in 24 h with 10 mol% catalyst if the temperature was raised to –40 °C and that at –20 °C the reaction was complete in the same time period. It is interesting to note that the VANOL and VAPOL ligands gave nearly identical results at –40 °C (Table 7, entry 7 vs. Table 5, entry 7) and at 0 °C (Table 7, entry 11 vs. Table 5, entry 13). In contrast to the VAPOL-derived ligands **8** and **10** (Table 6), the VANOL catalyst was significantly affected by the addition of additives. The degree of the effect of the malonate D was about the same as that on the VAPOL catalyst at 0 °C but the effect was less for the VANOL catalyst at –40 °C.

An investigation of the Diels–Alder reactions of cyclopentadiene with the *t*-butyl, *n*-propyl, and ethyl esters of acrylic acid was undertaken to compare the results with those of methyl acrylate. It was thought that if the steric bulk of the two carbonyls coordinated to the aluminum were important to the asymmetric induction of the Diels–Alder reaction (Scheme 5) then perhaps adjusting the size of the alkoxy group of the acrylate ester could have a similar ef-

Table 5. Effect of additives on the reaction of **22** and **6**.



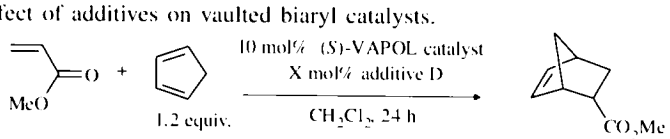
22 **6** (2*S*)-**23**

Entry	Solvent	Additive	Temp (°C)	Yield **23** (%)[a]	endo–exo[b]	ee% **23** (exo)[b]
1	CH_2CL_2	None	–78	87	99	82
2	CH_2CL_2	A	–78	80	99	96
3	CH_2CL_2	B	–78	60	99	98.5
4	CH_2CL_2	C	–78	49	99	98
5	CH_2CL_2	D	–78	76	99	>99
6	CH_2CL_2	F	–78	<30	—	—
7	CH_2CL_2	None	–40	76	99	47
8	CH_2CL_2	B	–40	80	99	88
9	CH_2CL_2	C	–40	80	98	90
10	CH_2CL_2	D	–40	100	99	92
11	CH_2CL_2	E	–40	100	98	93
12	CH_2CL_2	G	–40	85	92	45
13	CH_2CL_2	None	0	84	99	37
14	CH_2CL_2	D	0	67	94	69
15	CH_2CL_2	E	0	90	95	85
16	CH_2CL_2	E[c]	0	80	99	92
17	CH_2CL_2	None	25	100	92	33
18	CH_2CL_2	D	25	80	99	56
19	CH_2CL_2	E	25	80	93	49
20	Toluene	None	–78	100	99	97
21	Toluene	E	–78	100	99	96
22	Toluene	None	0	77	99	46
23	Toluene	E	0	100	—	58

Note: All reactions use 0.5–1.0 mol/L in **22**. Unless otherwise specified the catalyst was prepared as indicated in Table 2. Reaction time for all reactions was 24 h except for those at 0 °C, which was 2 h and those at RT, which was 1 h.

[a]Determined by ^{1}H NMR with ligand as internal standard.
[b]Determined with a chiral GC column (J & W Cyclodex-B).
[c]100 mol% additive.

Table 6. Effect of additives on vaulted biaryl catalysts.



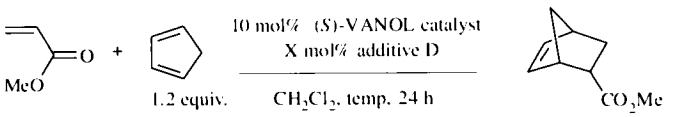
22 **6** (2*S*)-**23**

Entry	Ligand	X	Yield **23** (%)[a]	endo–exo[b]	ee% **23** (exo)[b]
1	**4**(*R*)-VAPOL	0	99	>100	82[c]
2	**4**(*R*)-VAPOL	50	94	>100	98[c]
3	**4**(*S*)-VAPOL	50	86	>100	99
4	**8**(*S*)-Br_2VAPOL	0	99	65	15
5	**8**(*S*)-Br_2VAPOL	50	95	56	16
6	**10**(*S*)-Ph_2VAPOL	0	99	122	35
7	**10**(*S*)-Ph_2VAPOL	50	58	145	31
8	**3**(*S*)-VANOL	0	28	34	21
9	**3**(*S*)-VANOL	50	11	42	17

Note: All reactions use 0.5–1.0 mol/L in **22**. Unless otherwise specified the catalyst was prepared as indicated in Table 2.

[a]Determined by ^{1}H NMR with ligand as internal standard.
[b]Determined with a chiral GC column (J & W Cyclodex-B).
[c](2*R*)-**23** was obtained.

Table 7. Reaction of **22** and **6** with a VANOL catalyst.



22 **6** (2*S*)-**23**

Entry	X	Temp (°C)	Yield **23** (%)[a]	endo–exo[b]	ee% **23** (exo)[b]
1	0	–78	28	34	21
2	50	–78	11	42	17
3	0	–60	25	47	19
4	50	–60	10	50	24
5	0	–50	38	132	39
6	50	–50	41	100	57
7	0	–40	74	38	42
8	50	–40	75	74	54
9	0	–20	100	30	35
10	50	–20	100	31	57
11	0	0	97	22	29
12	50	0	95	Nd[c]	60

Note: All reactions use 0.5–1.0 mol/L in **22**. Unless otherwise specified the catalyst was prepared as indicated in Table 2.

[a]Determined by ^{1}H NMR with ligand as internal standard.

[b]Determined with a chiral GC column (J & W Cyclodex-B).

[c]Not determined.

fect. As expected, the asymmetric induction observed for the ethyl and *n*-propyl esters (Table 8, entries 6 and 9) were greater than that for the methyl ester (Table 5, entry 1). However, the trend does not continue to the *t*-butyl ester as the induction with this substrate falls to 9% ee (Table 8, entry 1). While the reaction of the *t*-butyl ester was unresponsive to any positive cooperativity effect with any additive (B–E), it was found that both the ethyl and *n*-propyl esters responded to carbonyl additives to a degree very similar to that of methyl acrylate (Table 8 vs. Table 5).

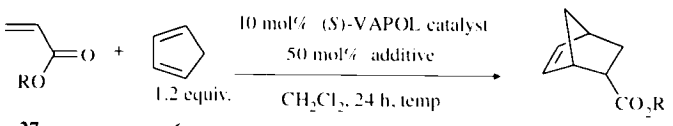
Finally, the reaction of methacrolein and cyclopentadiene was investigated in the presence of carbonyl additives to look for positive cooperativity effects. The data in Table 9 suggests that this reaction is unaffected by the presence of adamantyl aldehyde B or the di-*t*-butyl malonate D. The asymmetric induction for this reaction in CH_2Cl_2 is higher at –78 °C (93.6% ee) than it is for the same reaction with methyl acrylate (82% ee). Nonetheless, the addition of either B or D to the reaction would have been expected to produce measurable increases in induction if the positive cooperativity effect was in play here. Furthermore, no significant positive cooperativity effect was observed if the reaction temperature was raised to –40 °C or even to 0 °C where the asymmetric induction of the reaction itself was 16.9% and 5.1% ee, respectively. This lack of a positive cooperativity effect for the reaction of methacrolein and cyclopentadiene was surprising since this reaction, like the reaction of methyl acrylate, exhibits autoinduction. The degree of autoinduction for methacrolein is not as strong as that for methyl acrylate. For example, the reaction of methacrolein and cyclopentadiene has been reported to give an 81% ee after 30% conversion under conditions where an 88% ee was observed at the end of the reaction (4*a*).

The results of the present studies suggest that the VAPOL ligand appears to be optimal in forming a catalyst with diethylaluminum chloride to effect asymmetric Diels–Alder reactions with methacrolein and methyl acrylate with cyclopentadiene. Catalyst derived from the 6,6′-disubstituted VAPOL derivatives **8**, **9**, **10**, and **11** all gave reduced enantioselectivities for both of these reactions. The VANOL ligand gave lower enantioselectivities and slower rates as well. Since this is a smaller ligand, the lower rates may be due to a different catalyst structure. It was also found that carbonyl additives displayed positive cooperativity with the VAPOL catalyst on the autoinduction for the reaction with methyl acrylate but not with the substituted VAPOL catalysts derived from **8** and **10** or with the catalyst derived from the VANOL ligand. In contrast, no positive cooperativity with carbonyl additives was observed with the VAPOL catalyst on the autoinduction in the reaction of methacrolein and cyclopentadiene.

Experimental

Syntheses were performed under dry argon unless otherwise stated. THF and ether were distilled from sodium benzophenone ketyl. Methylene chloride, 1,2-dichloroethane, and acetonitrile were distilled from CaH_2. Toluene was distilled from sodium. Methacrolein was distilled from CaO. Methyl acrylate and pivaldehyde were distilled from $MgSO_4$. Cyclopentadiene was freshly cracked from dicyclopentadiene over 4 Å MS. Whatman glass-backed TLC plates (part #4861–820, 250 mm thickness, K6F Silica gel) were used for reported R_f values, except in those noted cases in which Macherey–Nagel plastic-backed TLC plates (Polygram® Sil N-HR/UV$_{254}$, 250 mm thickness) were used. IR spectra were taken on a Nicolet 20SXB FTIR spectrometer. Melting points were taken on a Hoover Unimelt apparatus and are uncorrected. Mass spectra were run on a VG Analytical 70–70EQ Double Focusing Hybrid MS (EI @ 70 eV).

Table 8. Effect of ester substituent on the reaction of **27** and **6**.



27 6 (2S)-28

Entry	R	Additive	Temp (°C)	Yield **28** (%)[a]	endo–exo[b]	ee% **28** (exo)[b]
1	*t*-butyl	None	–78	63	96	9
2		B	–78	Trace	—	—
3		C	–78	0	—	—
4		D	–78	32	96	19
5		E	–78	0	—	—
6	*n*-propyl	None	–78	33	99	92
7		B	–78	25	99	>99
8		C	–78	52	99	98
9	ethyl	None	–78	58	99	94
10		None	–40[c]	90	97	60
11		C	–40	72	98	92
12		D	–40[c]	100	Nd[d]	87
13		None	0[e]	100	93	33
14		C	0[e]	100	95	69

Note: All reactions use 0.5–1.0 mol/L in **22**. Unless otherwise specified the catalyst was prepared as indicated in Table 2.

[a]Determined by ^{1}H NMR with ligand as internal standard.
[b]Determined with a chiral GC column (J & W Cyclodex-B).
[c]The reaction time was 30 h.
[d]Not determined because of obscured integral.
[e]The reaction time was 2 h.

Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tennessee.

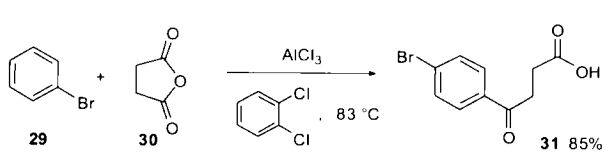
Chiral HPLC was done with a Pirkle covalent D-phenylglycine Rexchrom™ Regis column. Pump: Waters M-45 (ser. # 5615); operating pressure: 3100 psi (1 psi = 6.894 757 kPa); flow rate: 2.0 mL/min; solvent: 7:3 (*v*/*v*) hexane–isopropanol; detector (254 nm): Waters 440 Absorbance detector (ser. #07249); integrator: Spectra-Physics SP4270 (ser. #092–132).

Capillary GC was done on a Varian Star 3600 outfitted with an Alltech Econocap SE-54 column for nonchiral applications and a J & W Scientific Cyclodex-B column for chiral applications using helium carrier gas and FID detection.

Optical rotations were taken on a PerkinElmer Model 141 instrument using the sodium D line (589 nm). For ligand sample preparation, a 20 mg sample was dissolved in 2 mL THF. Concentration: 1 g/100 mL; temperature: 23 °C; path length: 1 dm; $[\alpha]_D = (100)\ a_{obs}$.

Preparation of 7-bromo-α-tetralone 12 (16)

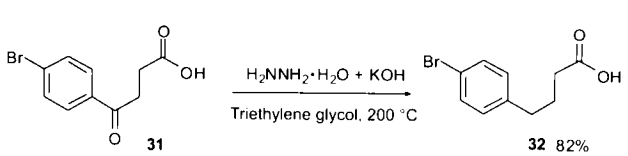
Friedel–crafts acylation of bromobenzene



29 30 31 85%

A 1 L three-necked round-bottomed (RB) flask was fitted with a mechanical stirrer and was connected to an oil bubbler. It was charged with bromobenzene **29** (60.5 mL, 573 mmol), succinic anhydride **30** (37.6, 376 mmol), and *o*-dichlorobenzene (113 mL), and mechanically stirred. Aluminum trichloride (107 g, 804 mmol) was added in portions over 30 min. The solution turned rust red in colour and emitted a whitish smoke. It was warmed to 83 °C for 6 h, cooled to RT, and then poured into a mixture of HCl–ice in a 2 L Erlenmeyer flask whereupon a white curdish precipitate came out of solution. The precipitate was dissolved in ether, the entire contents were transferred in portions to a large separatory funnel, and the aqueous layer was removed. Concentration of the ether layer by distillation afforded crystals of product, which were suction filtered and then finely divided and spread out to dry in a pan in a 110 °C oven for two days. Yield: 82 g white-pinkish solid (85% yield). On a larger scale, it was not practical to dissolve the crude product in ether. In this case, crude product was allowed to oven dry directly, which took longer.

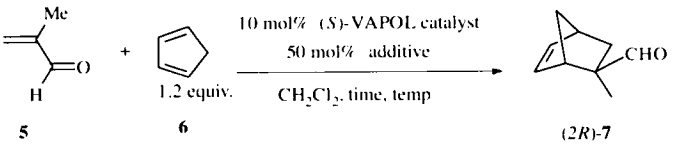
Wolff–Kischner reduction of 31



31 32 82%

A 1 L three-necked flask was equipped with a thermometer and a condenser–receiving flask. KOH (45 g, 804 mmol) and triethylene glycol (350 mL) were added and mechanically stirred. The mixture was warmed to 100 °C with a heating mantle to dissolve the KOH. It was then cooled to

Table 9. Effect of additives on the reaction of **5** and **6**.



5 6 (2*R*)-7

Entry	Additive	Time	Temp (°C)	Yield **7** (%)[a]	exo–endo[b]	ee% **7** (exo)[b]
1	None	0.5 h	–78	51	93	93.6
2	B	0.5 h	–78	65	94	94.6
3	D	0.5 h	–78	53	92	93.7
4	None	1 h	–40	73	80	16.9
5	D	1 h	–40	80	81	17.3
6	None	15 min	0	84	71	5.1
7	D	15 min	0	80	77	10.8

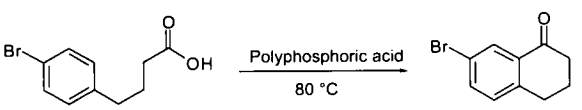
Note: All reactions use 0.5–1.0 mol/L in **5**. Unless otherwise specified the catalyst was prepared as indicated in Table 2.

[a]Determined by ^{1}H NMR with ligand as internal standard.

[b]Determined with a chiral GC column (Astec B-MB column) after reduction to the alcohol with $NaBH_4$.

80 °C, whereupon 68 g (265 mmol) of the keto acid **31** from the previous step and 34 mL of hydrazine monohydrate (702 mmol) were added. After stirring at 90–100 °C for 1 h, the mixture was warmed by a heating mantle to 200 °C and stirred at that temperature for 1 h. Liquid was distilled off into the receiving flask. The solution was cooled to near RT and poured into 400 mL of H_2O. Aq HCl (6 N, 220 mL) was added, which precipitated out a white suspension, and an oil settled on the bottom. On sitting overnight the oil solidified. The solid was filtered, then dissolved in ether (it was exceedingly soluble in ether), dried over $MgSO_4$, filtered, and left to crystallize in a crystallizing dish on air evaporation of ether to afford 52.98 g of **32** as a light tan solid (82% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.96 (quintet, 2H), 2.38 (t, 2H, J = 7.4 Hz), 2.64 (t, 2H), 7.04 (d, 2H, J = 8.2 Hz), 7.38 (d, 2H, J = 8.2 Hz), acid proton not reported.

Cyclization of carboxylic acid (32)

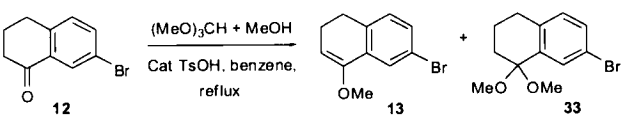


32 **12** 75%

This reaction was run in open air. Polyphosphoric acid (PPA, 250 g) was warmed in a 1 L Erlenmeyer flask to 70 °C. The bromoaryl carboxylic acid **32** (52.98 g, 218 mmol) was melted at 50 °C and then added to the PPA and the mixture was swirled with a glass rod for a few minutes while keeping the temp between 70 and 90 °C. Additional PPA (200 g) was added and the mixture was kept at 80 °C for 1 h and swirled occasionally and it became a dark orange color. Heat was removed and ice was added, which turned the mixture yellowish. The mixture was extracted three times with ether (1 × 200 mL, 2 × 100 mL). The combined ether layers were washed sequentially with 200 mL H_2O, 100 mL 5% aq KOH, 100 mL H_2O, 100 mL 3% aq HOAc, 100 mL 5% aq $NaHCO_3$, and 100 mL H_2O, then dried over $MgSO_4$ and filtered into a crystallizing dish. Air evaporation of ether afforded 36.8 g of clear blocky crystals covered with an orange thin film (75% yield). The product could be crystallized from MeOH to yield colourless crystals: mp 75 to 76 °C (lit. value (16) mp 71–73 °C). R_f = 0.23 (hexane–EtOAc, 9:1). IR (neat film, NaCl, cm^{-1}): 2946 (w), 1676 (s), 1585 (m), 1221 (m), 1190 (m). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.10 (quintet, 2H, J = 6.3 Hz), 2.62 (t, 2H, J = 6.5 Hz), 2.88 (t, 2H, J = 6.0 Hz), 7.12 (d, 1H, J = 8.13 Hz), 7.53 (dd, 1H, J = 8.2, 1.9 Hz), 8.11 (d, 1H, J = 1.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 22.9, 29.0, 38.6, 120.5, 129.8, 130.5, 133.9, 135.9, 143.0, 196.8.

Preparation of the catechol ketal 14 from 7-bromo-α-tetralone (12)

Preparation of methyl vinyl ether (13)

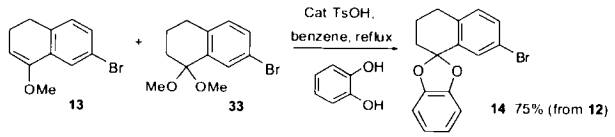


12 **13** **33**

A 250 mL three-necked RB flask equipped with a side arm adapter, to which was connected a condenser and receiving flask, was charged with 7-bromotetralone **12** (20 g, 88.8 mmol), trimethyl orthoformate (25 mL, 228.5 mmol), *p*-toluenesulfonic acid monohydrate (980 mg, 5.15 mmol), methanol (23 mL), and benzene (60 mL). The magnetically stirred solution was warmed under N_2 to gentle reflux for 40 h so that solvent distilled very slowly over into the receiving flask. After cooling to RT, it was partitioned between 500 mL ether and 250 mL satd. aq $NaHCO_3$. The organic layer was removed by separatory funnel and washed with 1 × 150 mL satd. aq $NaHCO_3$ and 1 × 150 mL brine, then dried over $MgSO_4$ and filtered. Solvent was removed in vacuo to afford 22 g of an orange oil, which was used in the next step without purification.

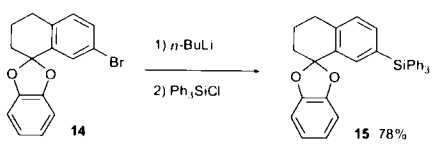
Conversion of 13 to ketal 14

A 250 mL three-necked RB flask equipped as described in the last step was charged with 22 g of the crude starting material **13**, catechol (11.75 g, 106.7 mmol), *p*-toluenesulfonic acid monohydrate (150 mg, 0.79 mmol), and benzene (150 mL) and was brought to reflux under N_2 for 4 h so that



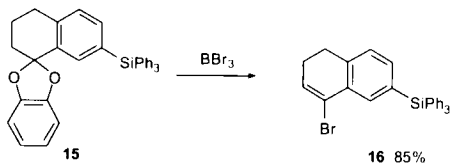
solvent distilled slowly into the receiving flask. After cooling to RT, 1.5 mL triethylamine was added. The mixture was partitioned between 200 mL ether and 100 mL water. The organic layer was removed by separatory funnel, washed with 1 × 100 mL H_2O, 2 × 75 mL 10% aq NaOH, 1 × 100 mL brine, then dried over $MgSO_4$, and filtered. The solvent was removed in vacuo to afford 27 g of a light tan crude product. The product was purified in portions by SiO_2 chromatography (hexane eluent) to yield 21 g of the white crystalline product **14** (75% yield): mp 101–104 °C. R_f = 0.45 (hexane–EtOAc, 9:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.03–2.10 (m, 2H), 2.22–2.26 (m, 2H), 2.82 (t, 2H, J = 6.3 Hz), 6.81–6.88 (m, 4H), 7.04 (d, 1H, J = 8.3 Hz), 7.41 (dd, 1H, J = 8.3, 2.1 Hz), 7.68 (d, 1H, J = 2.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 19.8, 28.4, 34.0, 108.6, 114.4, 120.0, 121.5, 129.3, 130.4, 132.7, 136.4, 137.1, 147.0. EI-MS m/z (%): 318 [M^+] (69, ^{81}Br), 316 [M^+] (69, ^{79}Br), 301 (16), 299 (17), 290 (16), 288 (17), 209 (22), 207 (22), 128 (100), 107 (36). Anal. calcd. for $C_{16}H_{13}O_2Br$: C 60.59, H 4.10; found: C 60.24, H 4.13.

Synthesis of the catechol ketal of 7-triphenylsilyl-α-tetralone (15)



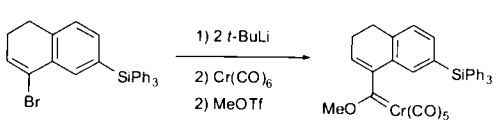
A 250 mL RB flask was charged with aryl bromide **14** (2.04 g, 6.4 mmol) and covered with Ar. It was dissolved in 50 mL THF and then cooled to –78 °C. t-BuLi in pentane (7.8 mL, 1.7 mol/L, 13.2 mmol) was added over 10 min whereupon the solution turned brown. After stirring at –78 °C for 40 min, a solution of triphenylsilylchloride (2.08 g, 7.1 mmol) in 20 mL THF was added dropwise over 5 min. After stirring an additional 1.25 h, the cold bath was removed. Over the next few hours the colour evolved from a dark blue, to a greenish olive, to a light brown, and finally to a clear light orange. The solution was stirred for 20 h at RT. Satd. aq $NaHCO_3$ (3 mL) was added and the THF was removed by rotory evaporator to leave a gummy residue. The residue was partitioned between 100 mL ether and 100 mL satd. aq $NaHCO_3$. The organic layer was washed with brine and then dried over $MgSO_4$. Purification by SiO_2 chromatography (hexanes–EtOAc, 9:1) afforded 2.5 g of a clear, colourless waxy oil, which foamed up under high vacuum (78% yield). On runs of larger scale, a white solid crystallized out on removal of solvent: mp 125.8–128 °C. R_f = 0.375 (hexane–EtOAc, 9:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.05–2.09 (m, 2H), 2.25–2.29 (m, 2H), 2.87 (t, 2H, J = 6.2 Hz), 6.64–6.75 (m, 4H, catechol protons), 7.16 (d 1H, J = 7.6 Hz), 7.75 (s, 1H), 7.24–7.63 (m, 16 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 20.1, 28.8, 34.6, 108.1, 115.0, 121.1, 127.8, 128.2, 129.5, 133.8, 134.1, 136.2, 136.36, 136.44, 137.2, 139.2, 147.2, (one sp^2 C not located). EI-MS m/z (%): 497 [M^++1] (43), 496 [M^+] (100), 416 (27), 339 (22), 259 (38), 181 (17).

The preparation of vinyl bromide 16 (9)



A 500 mL RB flask was charged with starting material **15** (5.0 g, 10.08 mmol) and was covered with Ar. Methylene chloride (200 mL) was added to dissolve the solid and the solution was cooled to between –30 and –35 °C. A 1 mol/L solution of BBr_3 (10.25 mL, 10.15 mmol) in CH_2Cl_2 was added over 5 min. The reaction was slowly warmed to –15 °C over 3 h and then to 0 °C over 2 h, after which time it was stored overnight at –15 °C. Satd. aq $NaHCO_3$ (10 mL) was added and the mixture was concentrated until ~50 mL CH_2Cl_2 remained. Hexane (300 mL) was added and the solution was washed sequentially with 1 × 150 mL H_2O, 1 × 100 mL 10% aq NaOH, 1 × 150 mL 5% aq KOH, 1 × 150 mL H_2O, then dried over $MgSO_4$, and filtered. The crude product was purified by SiO_2 chromatography (hexane–EtOAc, 9:1) to give 4.0 g of **16** as a white crystalline solid (85% yield): mp 146–148 °C. R_f = 0.38 (hexane–EtOAc, 9:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.36 (dt, 2H, J = 4.8, 8.0 Hz), 2.84 (t, 2H, J = 8.0 Hz), 6.38 (t, 1H, J = 4.8 Hz), 7.05 (d, 1H, J = 7.3 Hz), 7.33 (t, 6H, J = 7.1 Hz), 7.38 (t, 3H, J = 7.0 Hz), 7.50 (d, 1H, J = 7.3 Hz), 7.53 (d, 6H, J = 7.1 Hz), 7.74 (s, 1H). ^{13}C NMR (75MHz, $CDCl_3$) δ: 25.3, 27.6, 121.6, 126.9, 127.9, 129.6, 130.7, 132.38, 132.45, 134.2, 136.3, 136.5, 137.9. EI-MS m/z (%): 469 [M^++1] (33, ^{81}Br), 468 [M^+] (97, ^{81}Br), 467 [M^++1] (36, ^{79}Br), 466 [M^+] (100, ^{79}Br), 391 (83), 389 (86), 312 (30), 259 (55), 181 (40), 105 (30). Anal. calcd. for $C_{28}H_{23}SiBr$: C 71.97, H 4.92; found: C 71.81, H 5.09.

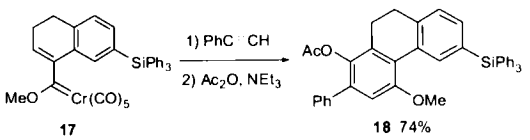
Synthesis of chromium carbene complex (17)



A 100 mL RB flask with a stir bar was charged with vinyl bromide **16** (3.0 g, 6.42 mmol) and then covered with Ar. THF was added (32 mL) and after the solid dissolved the solution was cooled to –78 °C. A 1.7 mol/L solution of t-BuLi in pentane (12.84 mmol, 7.6 mL) was added over 5–10 min. The solution was stirred at –78 °C for 15 min, was warmed to 0 °C for 10 min, and was then transferred by cannula into a separate flask containing a stirred slurry of $Cr(CO)_6$ (1.41 g, 6.42 mmol) in 39 mL of THF under Ar. After stirring at RT for 1.7 h the solvent was removed by rotary evaporator and then high vacuum (19 h) to afford a light brown foam. The foam was dissolved in 45 mL argon-sparged (AS) CH_2Cl_2 under Ar and then cooled to 0 °C. Methyl triflate (1.09 mL, 9.63 mmol) was added over 5 min. The mixture was warmed to RT and stirred for 55 min. The deep red so-

lution was then concentrated down to a few mL of volume by rotary evaporator, applied to the top of a SiO_2 column, and eluted with hexane–EtOAc (9:1), which after removal of solvent afforded 3.2 g of carbene complex **17** as a red solid (80% yield). R_f = 0.275 (hexane–EtOAc, 9:1). IR (neat film, NaCl, cm^{-1}): 2062 (m), 1988 (w), 1940 (s). ^1H NMR (300 MHz, CD_2Cl_2) δ: 2.47 (m, 2H), 2.86 (m, 2H), 4.14 (br s, 3H, methoxy), 5.76 (t, 1H, J = 4.5 Hz), 7.38 (t, 6H, J = 7.0 Hz), 6.78 (s, 1H), 7.52 (d, 6H, J = 7.6 Hz), 7.24–7.57 (m, 5H). ^{13}C NMR (75 MHz, CD_2Cl_2) δ: 22.7, 27.8, 66.1, 123.4, 128.3, 128.6, 129.7, 130.0, 130.1, 132.2, 134.3, 135.9, 136.4, 136.6, 137.8, 216.5 (CO), 225.1 (CO), 358.6 (carbene C). MS (FAB, nitrobenzyl alcohol) *m/z* (%): 622 [M^+] (3), 594 [M^+ – CO] (5), 483 (44), 482 (87), 467 (37), 452 (18), 259 (100).

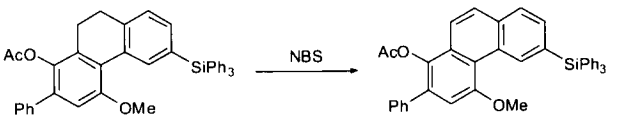
The benzannulation reaction of complex 17 with phenylacetylene (3)



17 **18** 74%

Carbene complex **17** (3.2 g, 5.15 mmol) was dissolved in 150 mL of THF in a 250 mL single-necked RB flask, which had the joint replaced with a threaded high-vacuum Teflon stopcock. Phenylacetylene (0.85 mL, 7.72 mmol) was added and the solution was deoxygenated by the freeze-pump-thaw method (3 cycles, –196 °C and 20 °C). The flask was charged with Ar at RT and then sealed and warmed at 60 °C for 21 h. After cooling to RT, triethylamine (1.79 mL, 12.87 mmol) and 1.19 mL acetic anhydride (12.6 mmol) were added. The flask was resealed and warmed to 60 °C for 8 h and then stirred at RT overnight. The crude mixture was concentrated down to a few mL of volume by rotorary evaporator, applied to the top of a SiO_2 column, and eluted with hexane–EtOAc 9:1). The product fraction was collected (R_f = 0.22, hexane–EtOAc (9:1)) as well as a more polar yellow band, which was the arene chromium tricarbonyl complex of the product. This yellow compound was dissolved in $CHCl_3$ and stirred overnight in open air to remove the chromium. This was then passed through a short SiO_2 pad to filter off the green flocculent chromium byproduct. The resulting product was combined with the earlier collected product to afford 2.3 g of a white crystalline solid (74% yield); mp 228–229.5 °C. IR (neat film, NaCl, cm^{-1}): 3067 (w), 3048 (w), 2933 (w), 1761 (ms), 1460 (m), 1428 (m), 1367 (m), 1211 (s), 1186 (s), 1108 (ms), 1059 (m), 701 (vs). ^1H NMR (500 MHz, $CDCl_3$) δ: 2.07 (s, 3H), 2.78 (t, 2H, J = 6.4 Hz), 2.50–2.85 (m, 2H), 3.56 (s, 3H), 6.76 (s, 1H), 7.21–7.29 (m, 2H), 7.31–7.39 (m, 14H), 7.58 (d, 6H, J = 7.0 Hz), 8.51 (s, 1H). ^{13}C NMR (75MHz, $CDCl_3$) δ: 20.5, 23.1, 28.9, 55.4, 111.6, 123.8, 127.0, 127.5, 127.8, 128.8, 129.4, 131.1, 131.5, 133.1, 134.1, 134.6, 135.1, 136.5, 136.9, 138.0, 138.5, 139.6, 154.7, 169.4. EI-MS *m/z* (%): 604 [M^+ + 2] (10), 603 [M^+ + 1] (27), 602 [M^+] (51), 562 (15), 561 (48), 560 [M^+ – ketene] (100), 483 (14), 259 Ph_3Si^+ (73), 230 (19), 181 (14). Anal. calcd. for $C_{41}H_{34}O_3Si$: C 81.70, H 5.64; found: C 81.53, H 5.62.

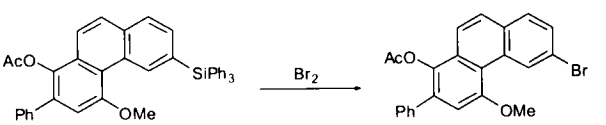
Aromatization of the B-ring of intermediate (18)



18 **19** 91%

A 500 mL RB flask was charged with starting material **18** (2.17g, 3.6 mmol), N-bromosuccinimide (673 mg, 3.78 mmol), benzoyl peroxide (89 mg, 0.36 mmol), and benzene (200 mL). The magnetically stirred solution was refluxed for 9 h. Upon cooling, the solution was filtered through a short plug of Al_2O_3 and then purified by SiO_2 chromatography (hexane–EtOAc, 5:1) to afford 1.97 g of **19** as a white crystalline solid (91% yield); mp 237 to 238 °C. R_f = 0.31 (hexane–EtOAc, 4:1). IR (neat film, NaCl, cm^{-1}): 3066 (w), 3048 (w), 2922 (w), 1763 (m), 1428 (m), 1197 (s), 1108 (ms), 1049 (mw). ^1H NMR (500 MHz, $CDCl_3$) δ: 2.14 (s, 3H), 3.61 (s, 3H), 6.98 (s, 1H), 7.28–7.39 (m, 11H), 7.47 (d, 2H, J = 7.3 Hz), 7.63 (d, 6H, J = 7.2 Hz), 7.73 (m, 4H), 7.83 (d, 1H, J = 7.8 Hz), 9.89 (s, 1H). ^{13}C NMR (75MHz, $CDCl_3$) δ: 20.7, 55.4, 109.6, 120.5, 120.8, 127.6, 127.9, 128.4, 128.8, 129.1, 129.5, 132.0, 132.8, 132.9, 133.0, 133.2, 134.6, 136.6, 136.9, 137.3, 137.8, 138.0, 156.6, 169.7, (1C not located). EI-MS *m/z* (%): 602 [M^+ + 2] (8), 601 [M^+ + 1] (15), 600 [M^+] (30), 560 (21), 559 (45), 558 [M^+ – ketene] (100), 481 (8), 465 (10), 387 (10), 260 (17), 259 Ph_3Si^+ (66,), 230 (19), 181 (14), 220 (15), 181 (8).

Bromo-desilylation of phenanthrene (19)

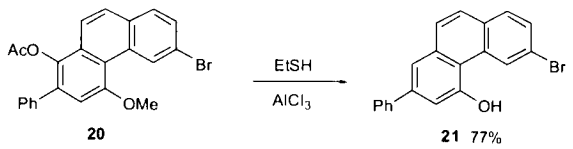


19 **20** 83%

A 100 mL RB flask with a stir bar was charged with phenanthrene **19** (342 mg, 0.57 mmol), CH_2Cl_2 (20 mL), and 5.1 mL of a 0.3 mol/L solution of Br_2 in CH_2Cl_2 (1.54 mmol). The mixture was brought to reflux for 3.5 h and then stirred at RT for 20 h. A small amount of SiO_2 was poured into the reaction mixture. Solvent was removed in vacuo to adsorb the crude reaction material on the silica. This SiO_2 adsorbate was applied to the top of a silica gel column and eluted with hexane–EtOAc (4:1) to afford 199 mg of **20** as a white solid (83% yield). The desired product elutes from the column after an orange impurity elutes. On scaling up the reaction, it was more efficacious to use slightly less Br_2 (~2 equiv.) to avoid this separation. Melting point 203.5–205 °C. R_f = 0.36 (hexane–EtOAc, 4:1). IR (neat film, NaCl, cm^{-1}): 2922 (w), 1761 (ms), 1589 (mw), 1440 (m), 1368 (m), 1212 (m), 1196 (vs), 1048 (m). ^1H NMR (300 MHz, $CDCl_3$) δ: 2.17 (s, 3H), 4.11 (s, 3H), 7.13 (s, 1H), 7.32–7.44 (m, 4 H), 7.56 (d, 1H, J = 7.9 Hz), 7.61 (dd, 1H, J = 7.6, 1.4 Hz), 7.64–7.68 (m, 1H), 7.70 (d, 2H, J = 9.5 Hz), 9.84 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 20.7, 55.9, 109.6, 120.5, 121.1, 127.7, 127.8, 127.9, 128.4, 128.6, 129.0, 129.4, 129.6, 130.0, 131.1, 132.7, 134.9, 136.5, 137.7, 156.4, 169.6. EI-MS *m/z* (%): 423 [M^+ + 1] (5,

^{81}Br), 422 [M$^+$] (18, ^{81}Br), 421 [M$^+$ + 1] (5, ^{79}Br), 420 [M$^+$] (19, ^{79}Br), 381 (23), 380 (99), 379 (25), 378 (100), 365 (14), 363 (14), 300 (19), 298 (14), 284 (32).

Reduction of 20 to the phenanthrol 21 (3)

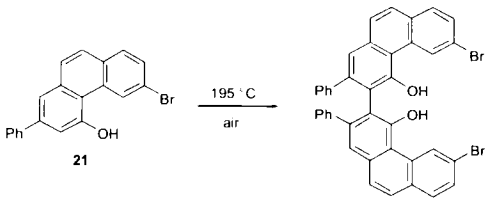


20 **21** 77%

A 200 mL RB flask with stir bar was charged with freshly sublimed $AlCl_3$ (405 mg, 3.03 mmol), CH_2Cl_2 (100 mL), and ethanethiol (0.475 mL, 6.4 mmol). Caution: flask needs to be openly vented to allow gases to escape on addition of ethanethiol. A gentle stream of N_2 was directed down into the open neck of the flask. After stirring for 5 min at RT, starting material (421 mg, 1.0 mmol) was added, which turned the mixture orange. The flask was then sealed with a septum and punctured with a needle connected to an N_2 bubbler. The mixture was stirred 9 h. The solution turned murky within 2 to 3 h after the addition of the starting material. The solution was carefully quenched with satd. aq $NaHCO_3$ (caution: vent flask to open air) and then partitioned between 50 mL H_2O and 100 mL ether. The aqueous layer was removed by separatory funnel and re-extracted with 50 mL ether. The combined organic layers were washed with 50 mL brine, dried over $MgSO_4$, filtered, and then stripped of volatiles. Trituration from CH_2Cl_2–hexane afforded a white powder that was contaminated with a small amount (ca. 5%) of a compound that resulted from reduction of the bromide in **21**. Repeated trial runs of this reaction indicated that the amount of this impurity increased with reaction times greater than 8 to 9 h. Reaction glassware was deodorized from the stench of EtSH by immersion in dilute aqueous bleach solution. Pure product was isolated by SiO_2 chromatography (hexane–EtOAc, 5:1). It elutes just before the bromine-reduced impurity. Yield: 270 mg (77%) of light peach-coloured powder, which could be crystallized to colourless needles by slow evaporation from ether; mp 178 to 179 °C (ether). R_f = 0.29 (hexane–EtOAc, 4:1). Note: the phenananthrol monomer **21** as well as the phenanthrol dimers described below are prone to decomposition as evidenced by their turning yellow and orange on handling. Chromatography should be done expeditiously. They should not be stored as solutions (especially CH_2Cl_2) open to air. They are more stable as solids. A useful method for crashing out solid is to dissolve the compound in CH_2Cl_2, add hexane, and then slowly remove solvent on a rotory evaporator. IR (neat film, NaCl, cm^{-1}): 3335 (br), 3052 (w), 2921 (w), 1587 (w), 1393 (w). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.76–6.10 (variable) (s, 1H, **OH**), 7.20 (d, 2H, J = 5.9 Hz), 7.35 (t, 1H, J = 7.2 Hz), 7.44 (t, 2H, J = 7.5 Hz), 7.61–7.69 (m, 6H), 9.77 (s, 1H). ^{13}C NMR (75MHz, CD_2Cl_2) δ: 112.6, 117.8, 119.7, 121.0, 127.5, 127.9, 128.17, 128.23, 129.3, 129.9, 131.3, 131.5, 131.9, 135.7, 140.2, 155.5 (2C not located). EI-MS *m/z* (%): 351 [M$^+$ + 1] (24, ^{81}Br), 350 [M$^+$] (99, ^{81}Br), 349 [M$^+$ + 1] (24, ^{79}Br), 348 [M$^+$] (100, ^{79}Br), 270 (32), 269 (54), 268 (26), 241 (47), 239 (46), 120 (26).

Synthesis of (*S*)-6,6′-dibromo-2,2′-diphenyl-3,3′-bis(phenanthren-4-ol) 8 (3)

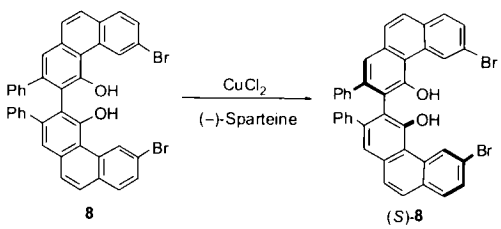
Oxidative coupling of 21



21 **8** 95%

Phenanthrene **21** (310.8 mg, 0.89 mmol) was added to a 25 × 150 mm test tube containing a micro stir bar. It was heated for a total of 14 h at 195 °C during which time it solidified to a dark brown cake. Heating was interrupted briefly after ca. 6 h to wash down sublimed starting material from the sides of the test tube with a small amount of EtOAc. (Care should be exercised in evaporating of the last of this EtOAc as it tends to spray the reaction mixture along the sides of the test tube.) The crude brown product was obtained (303 mg, 97% crude yield), which NMR indicated was the dimerized product **8** contaminated with ~5%–10% unreacted starting material. This material was used in the next step without purification. HPLC retention times for the two enantiomers: 11.33 and 17.45 min.

Deracemization of 8

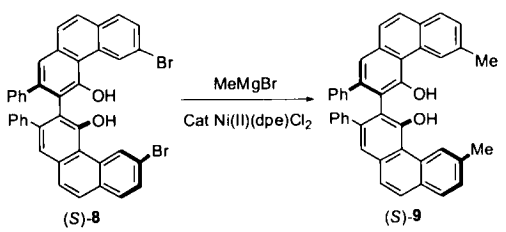


8 (*S*)-**8**

A sample of $CuCl_2$·$2H_2O$ (73 mg, 0.428 mmol) was dissolved under Ar in 6.7 mL AS MeOH in a 100 RB flask. A solution of 200 mg (–)-sparteine (0.853 mmol) in 13 mL AS MeOH was added by cannula, which turned the solution a murky lime green. The solution was stirred for 0.5 h at RT. In a separate flask, 213 mg of the crude biphenanthrol **8** (~0.31 mmol) was partially dissolved in 10 mL AS CH_2Cl_2. This solution was transferred by cannula into the reaction mixture with concurrent addition of 10 mL AS MeOH. The remaining undissolved starting material was dissolved in 6.5 mL AS CH_2Cl_2 and transferred into the reaction flask with concurrent addition of 6.5 mL AS MeOH. The mixture turned black. It was stirred for 24 h, quenched with 1 mL conced HCl, and then partitioned between 50 mL H_2O and 50 mL CH_2Cl_2. The organic layer was dried over $MgSO_4$ and filtered, then adsorbed onto a small amount of SiO_2 and chromatographed (hexane–EtOAc, 5:1) to afford 108 mg of (*S*)-**8** as a white or pale yellow solid (50% yield). R_f = 0.38 (hexane–EtOAc, 4:1). The optical purity of **8** was determined to be >98% ee by chiral HPLC analysis on Pirkle D-phenyl glycine column with 70:30 mixture of hexane–*i*PrOH at 2 mL/min. The chiral HPLC retention time of (*S*)-**8** was 16.9 min. X-ray quality crystals were grown by dissolving a

sample in a minimum amount of hot EtOAc, allowing this to cool to RT, and then layering with hexane, which produced clear faintly pale green crystals. Crystallography as well as ^{1}H NMR indicated the crystal contained two equiv. of EtOAc. Absolute configuration is assigned to the (*S*)-isomer by analogy with the parent molecule VAPOL, which upon deracemization with (–)-sparteine–$CuCl_2$ affords (*S*)-(+)-VAPOL (12). On scaling up the reaction, the material obtained from the chromatography column was not always enantiopure. In this case the enantiopurity was upgraded by stirring the scalemic powder for 1 h in enough hexane to allow a small amount to remain undissolved. The decanted hexane was found to contain enantiopure material. $[\alpha]_D$ + 445° (*c* 1.0, THF). IR (neat film, NaCl, cm^{-1}): 3482 (s), 3139 (w), 3052 (w), 3027 (w). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.60 (s, 2H), 6.64 (d, 4H, *J* = 7.5 Hz), 6.94 (t, 4H, *J* = 7.6 Hz), 7.05 (t, 2H, *J* = 7.3 Hz), 7.40 (s, 2H), 7.65 (d, 2H, *J* = 8.7 Hz), 7.69 (d, 2H, *J* = 8.3 Hz), 7.75 (t, 4H, *J* = 9.5 Hz), 9.91 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 116.0, 117.1, 121.3, 123.2, 126.9, 127.4, 127.6, 128.6, 128.8, 129.4, 129.6, 131.27, 131.35, 131.42, 135.3, 139.5, 142.2, 153.3. EI-MS *m/z* (%): 699 [M^+ + 1] (23, ^{81}Br), 698 [M^+] (65, ^{81}Br), 697 [M^+ + 1] (48, ^{81}Br^{79}Br), 696 [M^+] (100, ^{81}Br^{79}Br), 695 [M^+ + 1] (26, ^{79}Br, ^{79}Br), 694 [M^+] (41, ^{79}Br, ^{79}Br), 618 (22), 616 (18), 536 (5), 268 (72), 239 (27), 149 (42). Anal. calcd. for $C_{40}H_{24}O_2Br_2 \cdot 2(C_4H_8O_2)$: C 6.07, H 4.62; found: C 66.16, H 4.57.

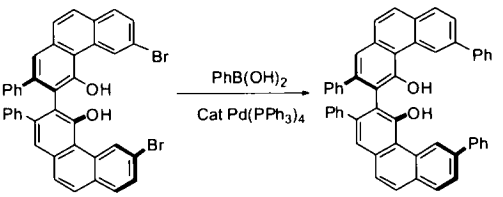
Coupling of (S)-8 with methyl Grignard reagent — Synthesis of (S)-9 (13)



(*S*)-**8** (*S*)-**9**

The optically pure dibromide (*S*)-**8** (10 mg, 14.4 μmol) and Ni(II)dpeCl_2 (1 mg,1.9 μmol) were added to a 5 mL RB flask and then covered with Ar. Ether (3 mL) was added via syringe and the solution was cooled to 0 °C. A 3 mol/L solution (29 μL) of CH_3MgBr in ether (86.4 μmol) was added dropwise. The solution was stirred for 0.5 h and was then warmed to reflux for 20.5 h. Additional ether (3 mL) was added during the reflux period to replace evaporated solvent. On cooling to RT, 3 mL of 10% aq HCl was added and the reaction mixture was partitioned between 20 mL ether and 5 mL H_2O. The organic layer was washed with brine and then dried over $MgSO_4$. Solvent was removed in vacuo to afford 7.6 mg (93% yield) of (*S*)-**9** as a pale tan solid that was pure by proton NMR. Chiral HPLC retention time: 23.3 min. $[\alpha]_D$ + 236° (*c* 1.0, THF). R_f = 0.34 (hexane–EtOAc, 9:1, plastic plate). IR (neat film, NaCl, cm^{-1}): 3480 (s), 3054 (w), 2922 (m). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.60 (s, 6H), 6.60 (s, 2H), 6.64 (d, 4H, *J* = 7.8 Hz), 6.92 (t, 4H, *J* = 7.5 Hz), 7.03 (t, 2H, *J* = 7.5 Hz), 7.38 (s, 2H), 7.74 (d, 2H, *J* = 8.2 Hz), 7.80 (d, 2H, *J* = 7.9 Hz), 9.54 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 22.5, 115.6, 117.9, 123.2, 126.1, 126.7, 127.5, 127.9, 128.3, 128.6, 128.8, 129.1, 130.4, 130.7, 135.5, 136.8, 139.8, 141.4, 153.5. EI-MS *m/z* (%): 568 [M^+ + 2] (10), 567 [M^+ + 1] (44), 566 [M^+] (100), 552 (7), 475 (7), 383 (11), 283 (30), 255 (8).

Coupling of (*S*)-8 with phenyl boronic acid — Synthesis of (*S*)-10 (14)

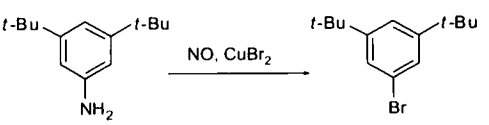


(*S*)-**8** (*S*)-**10**

Ethanol, aq Na_2CO_3 (2 mol/L), and benzene were sparged (>10 min) with inert gas (Ar or N_2) prior to use. A 25 mL RB flask was charged with $Pd(PPh_3)_4$ (2.3 mg, 2.2 μmol) and optically pure (*S*)-**8** (25 mg, 35.9 μmol). The flask was filled with Ar and 1.5 mL benzene and aq Na_2CO_3 (0.75 mL, 2 mol/L) was added by syringe. A solution of phenyl boronic acid (10.9 mg, 89.7 μmol) in 0.5 mL EtOH was added. The mixture was refluxed for 7 h and then stirred overnight at RT. The reaction mixture was diluted with 30 mL ether and washed with 25 mL brine containing a pipette tipful of HCl. The organic layer was dried over $MgSO_4$, filtered, adsorbed onto a small amount of SiO_2, and chromatographed (hexane–EtOAc, 9:1) to afford 23.4 mg of (*S*)-**10** as a white solid film (94% yield). $[\alpha]_D$ 749.5° (*c* 1.0, THF). R_f = 0.25 (hexane–EtOAc, 9:1, plastic plate). Chiral HPLC retention time: 22.4 min. IR (neat film, NaCl, cm^{-1}): 3481 (s), 3058 (w), 2923 (m), 2852 (w). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.66 (d, 6H), 6.94 (t, 4H, *J* = 7.6 Hz), 7.04 (t, 2H, *J* = 7.1 Hz), 7.27, (t, 2H, *J* = 7.1 Hz), 7.39 (t, 6H), 7.64 (d, 2H, *J* = 8.7 Hz), 7.76 (d, 4H, *J* = 7.4 Hz), 7.81 (d, 2H, *J* = 8.5 Hz), 7.87 (d, 2H, *J* = 7.5 Hz), 7.96 (d, 2H, *J* = 8.3 Hz), 10.04 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 115.9, 118.2, 123.3, 125.5, 126.8, 127.1, 127.2, 127.5, 128.8, 130.6, 132.0, 135.6, 139.6, 139.7, 141.7, 153.5, (6 C not located). EI-MS *m/z* (%): 692 [M^+ + 2] (17), 691 [M^+ + 1] (57), 690 [M^+] (100), 672 (8), 614 (20), 615 (11), 446 (13), 346 (15), 345 (25).

Coupling of (*S*)-8 with 3,5-di-*t*-butylphenyl Grignard reagent — Synthesis of (*S*)-11

Synthesis of 3,5-di-t-butylbromobenzene (17).

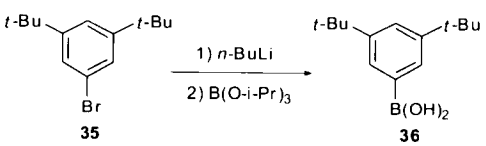


34 **35** 54%

A 25 mL RB flask with stir bar was charged with pulverized $CuBr_2$ (544 mg, 2.43 mmol) and 5 mL freshly distilled CH_3CN. NO gas was bubbled through the mixture for 10 min. The reaction mixture was then cooled to –30 °C, while maintaining NO gas bubbling. A solution of 500 mg of the *tert*-butylated aniline **34** (2.43 mmol) in 1.5 mL CH_3CN was added over 5 min. After stirring 5 additional minutes, the cold bath was removed, NO gas flow was

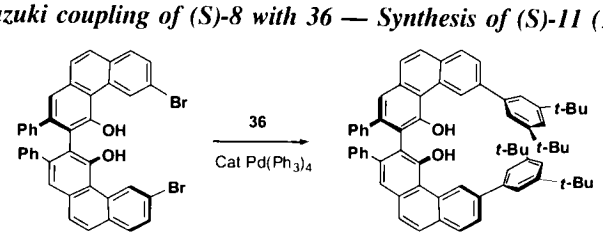
reduced to a trickle, and the solution stirred at RT for 1 h 10 min. The reaction was partitioned between 50 mL H_2O and 100 mL ether. The murky green organic layer was then washed with brine, dried over $MgSO_4$, filtered, and adsorbed onto a small amount of SiO_2. Purification by SiO_2 chromatography (hexane) afforded 355 mg of a clear, colourless oil, which crystallized on sitting at RT (54% yield). R_f = 0.40 (hexane). ^{1}H NMR (500 MHz, CD_3CN) δ: 1.09 (s, 18H), 7.13 (s, 2H), 7.19 (s, 1H). The aryl protons showed the same chemical shift in $CDCl_3$. EI-MS *m/z* (%): 271 (3), 270 [M^+] (24, ^{81}Br), 269 (3), 268 [M^+] (24, ^{79}Br), 256 (15), 255 (99), 254 (10), 253 (100).

Synthesis of boronic acid 36 (18)



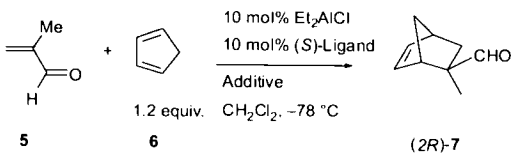
A 25 mL RB flask with stir bar was charged with 320 mg of aryl bromide **35** (1.19 mmol) and then covered with Ar. THF (5 mL) was added and after dissolution the flask was cooled to –78 °C, whereupon 0.48 mL of a 2.5 mol/L solution of *n*-BuLi in hexanes (1.2 mmol) was added dropwise. After stirring at –78 °C for 1 h, a solution of 0.68 mL triisopropyl borate in THF (1 mL, 2.9 mmol) was added all at once by syringe to give a clear solution. The cold bath was removed and while warming to RT the solution became cloudy. After stirring 1 h the mixture was poured into a vigorously stirred mixture of 10% aq HCl (30 mL) and ether (40 mL) and stirred a few minutes. Both the aqueous and organic layers were clear and colourless. The organic layer was removed, washed with 30 mL H_2O, dried over $MgSO_4$, and filtered. Rotary evaporation of the solvent yielded **36** as a white solid, which was used in the next step without purification. ^{1}H NMR analysis (500 MHz, $CDCl_3$) of the aryl region suggested a mixture of two compounds; major: δ 7.52 (s, 2H), 8.06 (s, 1H); minor: δ 7.63 (s, 2H), 7.94 (s, 1H). In addition there was a pronounced singlet at δ 4.54, which is attributed to the BOH of the desired product.

Suzuki coupling of (S)-8 with 36 — Synthesis of (S)-11 (14)



Ethanol, aq Na_2CO_3 (2 mol/L), and benzene were sparged (>10 min) with inert gas (Ar or N_2) prior to use. Optically pure (*S*)-**8** (66 mg, 75.9 µmol, based on MW 872.6, containing two equiv. of EtOAc) was dissolved in a minimum of CH_2Cl_2 in a 25 mL RB flask, the solvent was removed by rotory evaporator, and then the ethyl acetate was removed on high vacuum. To the flask was added $Pd(PPh_3)_4$ (6 mg, 5.2 µmol) and the solids were covered with Ar. Benzene (4 mL) and aq Na_2CO_3 (2 mL 2 mol/L) was added. To the vigorously stirred mixture was added a solution of crude boronic acid **36** (89 mg, ~304 µmol, based on 80% purity) in EtOH (2 mL). The mixture was refluxed for 14 h and then stirred at RT for 11 h. The reaction mixture was partitioned between 50 mL ether and 25 mL brine containing a pipette tip of HCl. The organic layer was dried over $MgSO_4$, filtered, and adsorbed onto a small amount of SiO_2. Purification by chromatography on silica gel (hexane–EtOAc, 9:1) afforded 70.0 mg of (*S*)-**11** as a clear, colourless solid film (100% yield). $[\alpha]_D$ 565° (*c* 1.0, THF). R_f = 0.42 (hexane–EtOAc, 9:1). Chiral HPLC retention time: 5.7 min. IR (neat film, NaCl, cm^{-1}): 3486 (m, sharp), 2962 (s, sharp), 2863 (w), 1594 (m, sharp). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.35 (s, 36H), 6.55 (s, 2H), 6.69 (d, 4H, *J* = 7.2 Hz), 6.94 (t, 4H, *J* = 7. 5 Hz), 7.04 (t, 2H, *J* = 6.6 Hz), 7.37 (s, 2H), 7.56 (s, 4 H), 7.43 (s, 2H), 7.64 (d, 2H, *J* = 8.7 Hz), 7.81 (d, 2H, *J* = 8.8 Hz), 7.85 (d, 2H, *J* = 7.7 Hz), 7.96 (d, 2H, *J* = 8.1 Hz), 9.95 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 31.6, 115.8, 118.4, 121.4, 122.3, 123.4, 126.2, 126.9, 127.6, 127.7, 128.8, 128.9, 129.1, 130.6, 131.8, 135.6, 139.8, 141.2, 141.3, 141.8, 151.2, 153.7 (2 C not located). EI-MS *m/z* (%): 916 [M^+ + 1] (30), 915 [M^+] (42), 710 (69), 709 (87), 576 (63), 575 (82), 574 (86), 481 (26), 259 (50), 183 (33), 57 (100).

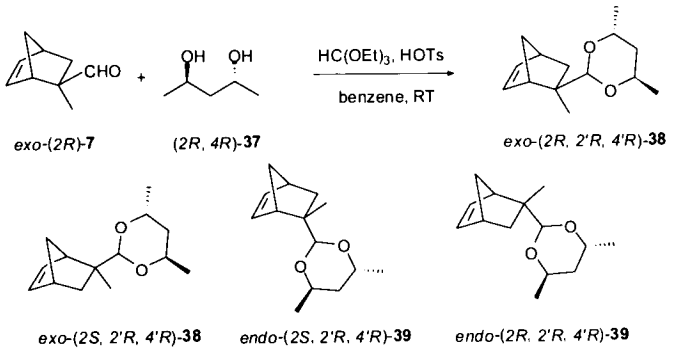
Diels–Alder reaction of methacrolein and cyclopentadiene



A sample of the desired ligand (45–75 mg) was added to a 5 mL RB flask containing a stirbar and the flask was flushed with Argon. Methylene chloride (1 to 2 mL) was added by syringe followed by 1 equiv. Et_2AlCl (1 mol/L solution in hexane), which turned the solution a deep blood-red color. After stirring at RT for 0.5 h the flask was cooled to –78 °C. Methacrolein (10 equiv. relative to ligand) was then added by syringe. After stirring at –78 °C for 0.5–0.75 h, 12–14 equiv. of cyclopentadiene was added. If an additive was used, it was added 15 min before the cyclopentadiene was added. After 0.5 h at –78 °C, the reaction was quenched by the addition of 1 mL brine. The mixture was then partitioned between 20 mL CH_2Cl_2 and 10 mL H_2O and stirred vigorously. The organic layer was dried over $MgSO_4$, filtered, and then taken to near dryness on the rotory evaporator. The yield of the exo product **7** was determined on this concd CH_2Cl_2 solution by ^{1}H NMR using the ligand as an internal standard. The product was separated from the ligand by bulb-to-bulb distillation under high vacuum into a –78 °C trap prior to the measurement of the exo–endo ratio and the ee%, which were each determined by one of the two methods indicated below. Catalyst formation for ligands **10** and **11** were much slower as indicated by ^{1}H NMR. For these ligands, catalyst formation required heating at 55 °C for 24 h. ^{1}H NMR for *exo*-**7** (500 MHz, $CDCl_3$) δ: 0.76 (d 1H, *J* = 11.9 Hz), 1.00 (s, 3H), 1.38 (s, 2H), 2.23 (dd, 1H, J = 11.9, 3.5 Hz), 2.80 (s, 1H), 2.87 (s, 1H), 6.06 (dd, 1H, J = 5.2, 2.9 Hz), 6.25 (dd, 1H, J = 5.1 Hz, 2.9 Hz), 9.62 (s, 1H).

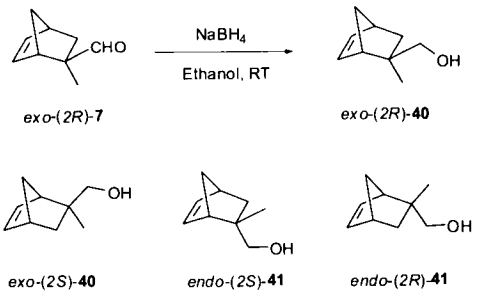
This data matches that previously reported for this compound (19).

Analysis of exo-adduct 7 by conversion to chiral acetals



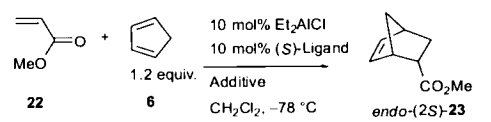
This method was originally developed by Yamamoto (20). A pipette tip of product **7** (~20 mg) was mixed with 25–30 mg (2*R*,4*R*)-(−)-pentanediol, 40 mL triethyl orthoformate, a small crystal of TsOH·H_2O, and 1 to 2 mL benzene and stirred overnight. The de% of the exo product (and hence ee% of the exo product) and the exo–endo ratio were determined by GC on an Alltech Econocap capillary column (cat. #19646, ser. # 2475–9): 0.32 mm i.d., 0.25 mm film thickness, and 30 m in length. Column temperature was 50 °C for 2 min and then ramped up at 4 °C per min. Under these conditions, the following retention times were observed: (2*R*,2′*R*,4′*R*)-**38** (23.15 min); (2*S*,2′*R*,4′*R*)-**38** (23.25 min), **39** (21.98 and 22.93 min, not assigned). It was previously established that (*S*)-VAPOL is selective for (2*R*,2′*R*,4′*R*)-**38** (4*a*). Spectral data for (2*R*,2′*R*,4′*R*)-**38**: IR (neat, cm^{-1}): 3139 (w), 3059 (m), 2979 (s), 2932 (s), 2878 (s), 2700 (w), 1572 (w), 1451 (s), 1398 (m), 1376 (s), 1333 (s), 1289 (m), 1241 (s), 1181 (m), 1158 (s), 1135 (s), 1093 (m), 1081 (m), 1007 (s), 972 (m), 906 (m), 839 (m), 721 (s). ^{1}HNMR ($CDCl_3$) δ: 0.76 (d, 1H, J = 12.0 Hz), 0.86 (s, 3H), 1.19 (d, 3H, J = 6.2 Hz), 1.29–1.31 (m, 2H), 1.34 (d, 3H, J = 7.1 Hz), 1.60 (d, 1H, J = 8.4 Hz), 1.74–1.82 (m, 2H), 2.66 (s, 1H), 3.90–3.94 (m, 1H), 4.27–4.66 (m, 1H), 4.66 (s, 1H), 6.01–6.11 (m, 2H). ^{13}C NMR (CDC_3) δ: 17.25, 18.77, 21.96, 36.87, 37.10, 43.07, 45.45, 47.15, 48.06, 67.68, 67.74, 99.48, 135.54, 137.15. MS *m*/*z* (%): 222 [M^+] (4), 157 (22), 115 (78), 69 (100). HRMS *m*/*z*: calcd. for $C_{14}H_{22}O_2$: 222.1620; found: 222.1662. Anal. calcd. for $C_{14}H_{22}O_2$: C 75.63, H 9.97; found: C 75.88, H 10.26. Spectral data for (2*S*,2′*R*,4′*R*)-**38** (prepared from (*R*)-VAPOL): ^{1}H NMR ($CDCl_3$) δ: 0.74 (dd, 1H, J = 2.7, 12.0 Hz), 0.86 (s, 3H), 1.20 (d, 3H, J = 6.2 Hz), 1.28–1.33 (m, 2H), 1.36 (d, 3H, J = 7.0 Hz), 1.58–1.85 (m, 3H), 2.75 (bs, 2H), 3.89–3.96 (m, 1H), 4.30–4.35 (m, 1H), 4.70 (s, 1H). ^{13}C NMR ($CDCl_3$) δ: 17.26, 18.57, 21.93, 36.83, 37.35, 43.25, 45.48, 47.41, 47.94, 67.43, 67.98, 99.43, 135.74, 137.10. IR (neat, cm^{-1}): 3060 (w), 2972 (s), 2941 (s), 2877 (m), 1449 (m), 1398 (w), 1375 (m), 1333 (m), 1288 (w), 1241 (w), 1217 (w), 1158 (s), 1135 (s), 1102 (w), 1081 (w), 1059 (s), 1024 (m), 1003 (s), 982 (w), 722 (s). MS *m*/*z* (%): 222 [M^+] (18), 157 (70), 115 (100), 69 (13). HRMS calcd. for $C_{14}H_{22}O_2$ *m*/*z*: 222.1620; found: 222.1617. Anal calcd. for $C_{14}H_{22}O_2$: C 75.63, H 9.97; found: C 75.85, H 10.12.

Analysis of exo-adduct 7 by reduction to alcohol 40



The aldehyde **7** (71.7 mg) distilled from the reaction described above was dissolved in 1.2 mL of ethanol and treated with $NaBH_4$ (24 mg). After 1 h the reaction was quenched by the slow addition of water. The reaction mixture was partitioned between 10 mL of H_2O and 10 mL of ethanol. The aqueous phase was extracted with ether (2 × 5 mL) and the combined organic layer was washed with 15 mL of brine and dried over $MgSO_4$. Removal of solvent left 77 mg of crude product, which was purified by chromatography on silica gel with a 5:1 mixture of hexanes – ethyl acetate to give 61 mg of **40** as a white solid. The de% of the exo product (and hence ee% of the exo product) and the exo–endo ratio were determined by GC on an Astec B-MB capillary column (Beta-cyclodextrin Dimethyl, *t*-Butyl, ser. # 9606–29) of 0.25 mm i.d. and 30 m in length. Column temperature was isothermal at 140 °C. Under these conditions, the following retention times were observed: (2*R*)-**40** (6.12 min); (2*S*)-**40** (6.01 min); **41** (5.67 and 5.41 min, not assigned).

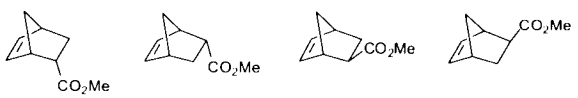
Diels–Alder reaction of methacrolein and cyclopentadiene



A sample of the desired ligand (45 mg) was added to a 5 mL RB flask containing a stir bar and the flask was then flushed with argon. Methylene chloride (1 to 2 mL) was added by syringe followed by 1 equiv. Et_2AlCl (1 mol/L solution in hexane), which turned the solution a deep blood-red color. After stirring at RT for 0.5 h, the flask was cooled to −78 °C. Methyl acrylate (10 equiv. relative to ligand) was then added by syringe. After stirring 0.5–0.75 h at −78 °C, 12–14 equiv. of cyclopentadiene was added. If an addtive was used it was added 15 min before methyl acrylate. After 24 h at −78 °C the reaction was quenched by the addition of 1 mL brine. The mixture was then partitioned between 20 mL of CH_2Cl_2 and 10 mL of H_2O and stirred vigorously. The organic layer was dried over $MgSO_4$, filtered, and then taken to near dryness on a rotatory evaporator. The yield of *endo*-**23** was determined on this concentrated CH_2Cl_2 solution by ^{1}H NMR using the ligand as an internal standard. The product was separated from the ligand by bulb-to-bulb distillation under high vacuum into a −78 °C trap prior to the measurement of the exo–endo ratio and the ee%, which were

both determined by the method indicated below. Catalyst formation for ligands **10** and **11** were much slower as indicated by ^{1}H NMR. For these ligands, catalyst formation required heating at 55 °C for 24. Spectral data for *endo*-**23**: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.28 (d, 1H), 1.40–1.45 (m, 2H), 1.88–1.96 (m, 1H), 2.92–2.99 (m, 2H), 3.21 (s, 1H), 3.63 (s, 3H), 5.94 (dd, 1H, J = 5.6, 2.8 Hz), 6.20 (dd, 1H, J = 5.6, 3.0 Hz).

Analysis of endo-adduct 23 by GC



endo-(2*S*)-**23** *endo*-(2*R*)-**23** *exo*-(2*R*)-**42** *exo*-(2*S*)-**42**

The methyl ester **23** distilled from the reaction described above was directly assayed for endo–exo selectivity and for enantioselectivity by chiral GC on a J & W Cyclodex-B capillary column (part #1122532, ser. #5094942) of 0.25 mm i.d., 0.25 mm film thickness, and 30 m in length, and with column temperature 90 °C (isothermal). The oven was baked at 200 °C a few minutes before each run, which improved GC peak resolution. Under these conditions, the following retention times were observed: (2*S*)-**23** (16.43 min), (2*R*)-**23** (15.90 min), **42** (12.79 and 12.98 min, not assigned). It was previously shown that (*S*)-VAPOL gives selectively the *endo*-(2*S*) isomer of **23** (4).

Acknowledgment

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