Planar Chiral PHANOLs as Double Hydrogen Bonding Donor Organocatalysts: Synthesis and Catalysis

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Abstract: 4,12-Dihydroxy[2.2]paracyclophanediol (PHANOL; **1**), and its *para*-substituted derivatives **2, 5** and **7**, were found to catalyse Diels–Alder cycloadditions of α,β-unsaturated aldehydes or ketones with dienes and/or epoxide ring opening reactions with amines. The mode of catalysis by the PHANOLs is *via* double hydrogen bonding to the two sp^2 lone pairs of a carbonyl group or the two lone pairs of the epoxide. The order of activity of the PHANOLs for catalysis of the Diels–Alder reaction essentially correlates with the expected hydrogen-bond donor strength based on the degree of electron-withdrawing capability of the group(s) in the *para* position. In contrast, *ortho*-substituted PHANOLs **10**, **11** and **14** were not active as catalysts due to steric interference with the double hydrogen bonding mode. ^{1}H NMR and IR spectral data for the various PHANOLs are discussed in support of the proposed double hydrogen bond mode.

Keywords: Diels–Alder; double hydrogen bonding; epoxides; organic catalysis; [2.2]paracyclophane; PHANOL

Introduction

The use of hydrogen bonding to create and stabilise ground state architectures is ubiquitous in supramolecular chemistry.[1] Arguably, the ultimate example of the utility of hydrogen bonding to assemble extended structures is the case of the base-paired DNA double helix.[2] However, the *activation* of substrates by the formation of temporary hydrogen bonds (i.e., catalytically) between a hydrogen bond donor and a hydrogen bond acceptor – in particular, the *explicit* activation of a carbonyl group by a "designer" hydrogen bond donor – has been much less explored. Clearly, this approach has parallels with the activation of a carbonyl group by a Lewis acid and their relative merits have been excellently summarised in a recent review.[3] Progress in the field[3–14] has focused on the use of *multiple* hydrogen bonding for the obvious reason of increased activation and two distinct categories are emerging. In one category, the use of matched hydrogen bond donors and acceptors creates an activated assembly for further reaction. For example, Schreiner has employed a thiourea (25 mol % loading) to activate oxazolidinones (complex **I**, Figure 1) for Diels–Alder reactions.[4] Philp has shown that a diamidopyridine (100 mol %) activates maleimide (complex **II**, Figure 1) for 1,3-dipolar cycloadditions.[5] Göbel reported that amidinium ions (25–100 mol %) were capable of activating 1,2-diketones (complex **III**, Figure 1) for Diels–Alder reactions,[6] and a sulfonamide has been used to accelerate the addition of pyrrolidine to 2(5*H*)-furanone, presumably *via* complex **IV** (Figure 1).[7] A second category aims for a more generic solution by forming multiple hydrogen bonds to a single acceptor atom.[8] Specifically, the aim is to use a double hydrogen bond donor with the correct spatial orientation to be able to form two hydrogen bonds to the two sp^2 lone pairs of a carbonyl group (complex **V**, Figure 1). Such an arrangement was first demonstrated crystallographically by Hine, who showed that 1,8-biphenylenediol forms two strong hydrogen bonds to an electron-rich carbonyl group (complex **VI**, Figure 1).[9] In this adduct the two components are essentially co-planar, the two O–H···O bond lengths and angles are essentially identical at 2.545 (3) Å and 2.548 (3) Å, and 177 (3)° and 174 (3)°, respectively. The first X-ray crystallographic evidence for a 1:1 adduct with two intermolecular hydrogen bonds to a simple ketone was reported later by Saied (complex **VII**, Figure 1).[10] However, until recently there had been only one report of such double hydrogen bonding to a carbonyl group in order to promote catalysis.[11] Kelly showed that a derivative of biphenylenediol (40–50 mol %) could activate α,β-unsaturated aldehydes and ketones for Diels–Alder reactions, presumably *via* a complex of the type **V** (Figure 1)

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by analogy with Hine's work. Schreiner has also recently reported the use of thioureas for the catalysis of Diels–Alder reactions where such a double hydrogen bonding mode is proposed.[12] From an asymmetrical catalysis perspective the use of a double hydrogen bonding interaction to the oxygen of a carbonyl group as in complex **V** (Figure 1) is attractive since it removes the conformational ambiguities associated with the single point binding of traditional Lewis acid-activated carbonyls (complex **VIII**, Figure 1). The first two examples using chiral double hydrogen bonding catalysts were reported independently by our group[13] and Rawal's group.[14] Rawal et al. demonstrated excellent enantioselectivities and activities in the asymmetric hetero-Diels–Alder reaction between aldehydes and electron-rich dienes using TADDOLs as double hydrogen bonding catalysts. We chose to study the Diels–Alder reaction of α,β-unsaturated aldehydes and ketones with various dienes using planar chiral 4,12-dihydroxy[2.2]paracyclophanes (PHANOLs)[15] as double hydrogen bonding catalysts. Herein we report these studies in full. We also report on the ability of PHANOLs to activate epoxides to nucleophilic ring opening by double hydrogen bonding to the two lone pairs of an epoxide (complex **IX**, Figure 1).[16]

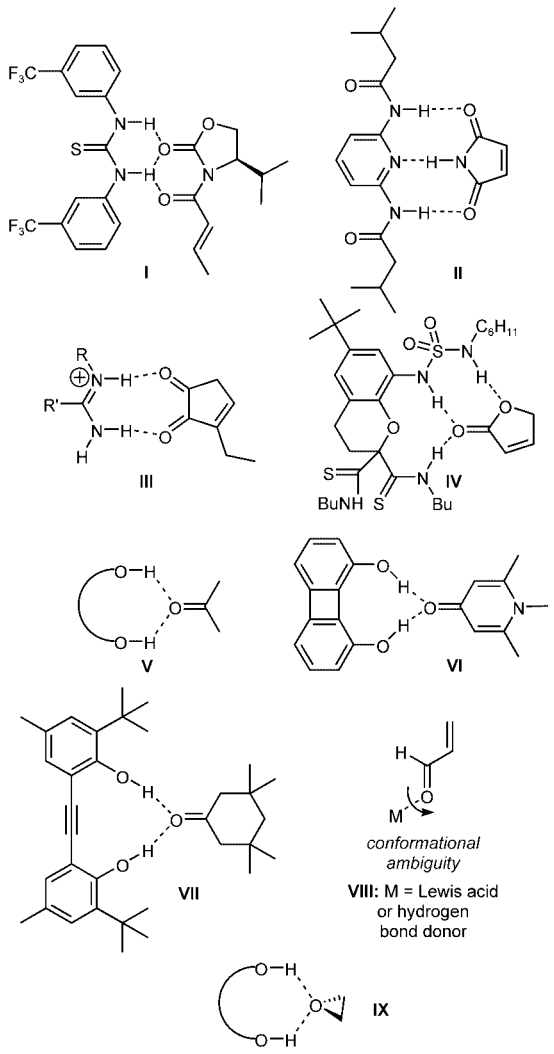


Figure 1. Hydrogen bonded complexes.

Results and Discussion

Catalyst Design

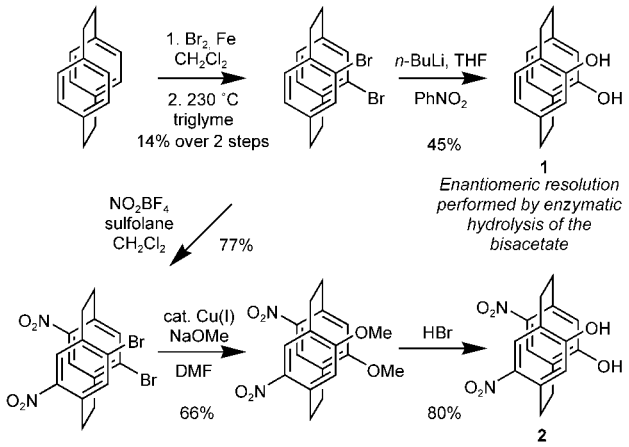
The selection of PHANOLs as potential double hydrogen bonding catalysts was driven by the inherent planar chirality of 4,12-disubstituted [2.2]paracyclophanes, and an estimated phenolic separation of *ca.* 4.1 Å based on in-house molecular modelling. This compares with a phenolic separation of *ca.* 4.0 Å in the biphenylenediol systems where X-ray crystallographic evidence for double hydrogen bonding has been secured.[9] Additionally, we considered it possible to introduce other substitutents variously at the *ortho* and *para* positions of the PHANOL to modulate activity, enantioselectivity and/or solubility as necessary (*vide infra*). The synthesis of the parent PHANOL, 4,12-dihydroxy[2.2]paracyclophane, as a racemate, had previously been reported by Cram in 1969[17] (although it was characterised as its dimethyl ether) and the above factors were deemed sufficient precedents to instigate our studies in this area.

It was considered that there are three major parameters that would influence the catalytic prowess of substituted PHANOLs: solubility, hydrogen bonding ability and "expression of chirality" around the binding site. The degree of hydrogen bonding – within a given series of PHANOLs – was expected to mirror pK_a values, and hence electron-withdrawing groups on the aromatic ring should increase their capability to be good hydrogen bond donors. *para*-Substituted ("rear-face" functionalised) PHANOLs should maximise this effect without perturbing the sterics of the binding site. *ortho*-Substitution ("front-face" functionalisation) would allow us to explore the steric effects and was expected to create a "chiral pocket". Substitution in either position should allow for the tuning of solubility. Accordingly, we targeted the synthesis of several PHANOLs with electron-withdrawing groups in the *para* position, and also *ortho*-alkyl substituted PHANOLS.

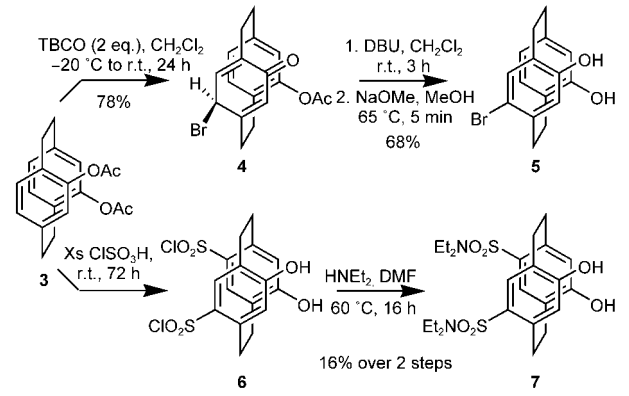
Synthesis

Both hands of enantiopure PHANOL **1**[15] and racemic 7,15-dinitroPHANOL **2**[13] are available through our previously published procedures (Scheme 1).

"Rear-face" functionalised (±)-7-Bromo-4,12-dihydroxy[2.2]paracyclophane **5** and (±)-4,12-dihydroxy-



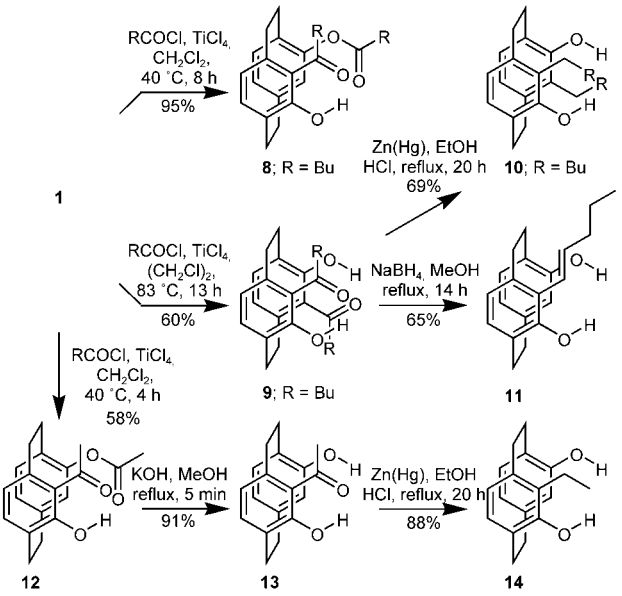
Scheme 1. Synthesis of PHANOLs **1** and **2**.



Scheme 2. Synthesis of PHANOLs **5** and **7**.

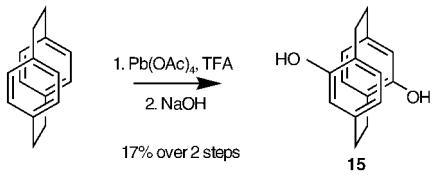
7,15-di(*N*,*N*-diethyl)sulfonyl[2.2]paracyclophane **7** were synthesised as follows (Scheme 2).

Attempted double aromatic electrophilic bromination of (±)-diacetate **3**[15] with wet tetrabromocyclohexadienone (TBCO) gave instead bromodienone **4** in good yield. This can be considered as a "trapped Wheland intermediate" where the loss of the evidently sterically shielded proton to a base is slow compared with competitive deacylation with H_2O acting as the nucleophile. To the best of our knowledge this is the first example of a 4-bromodienone where the other group in the 4-position is a hydrogen atom. The dienone could be rearomatised to the corresponding monobromoacetate by treatment with DBU, and subsequent acetate cleavage with methanolic NaOH delivered 7-bromoPHANOL **5**. Bissulfonamide **7** was prepared by double chlorosulfonation of diacetate **3** to give bissulfonyl chloride **6**, followed by heating with diethylamine in DMF solution. PHANOLs **5** and **7** were prepared as racemates, but the single enantiomers should be available by application of the above procedures to the bisacetates derived from either (*R*)- or (*S*)-PHANOL[15] separately.

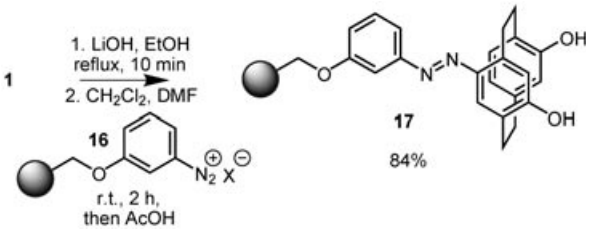


Scheme 3. Synthesis of PHANOLs **10, 11** and **14**.

Rozenberg has demonstrated the *ortho*-selective Fries rearrangement of *O*-acyl-4-hydroxy[2.2]paracyclophanes to give 5-acyl-4-hydroxy[2.2]paracyclophanes with $TiCl_4$, or by direct acylation of the phenol with the corresponding acid chloride also mediated by $TiCl_4$.[18] Treatment of PHANOL **1** with valeroyl chloride (a representative acyl grouping) and $TiCl_4$ in refluxing dichloromethane was found to give monoacyl ester **8**, presumably *via* double *O*-acylation and subsequent *ortho*-selective mono-Fries rearrangement (Scheme 3). Evidently, the desired second rearrangement is disfavoured by the transannular electron-withdrawing effect of the newly installed acyl grouping. The resulting hydroxyacyl motif in **8** may also act to chelate titanium: heightening the electron-withdrawing effect. Double acylation was achieved by direct treatment of PHANOL with valeroyl chloride and $TiCl_4$ in refluxing 1,2-dichloroethane to give diacylPHANOL **9**. With these procedures in hand a small library of potential double hydrogen bonding catalysts can be generated: Double Clemmensen reduction of diketone **9** provided "front-face" functionalised 4,12-dihydroxy-5,13-dipentyl[2.2]-paracyclophane **10**. Sodium borohydride reduction of diketone **9** gave monoolefin **11** as the major product, where a curious aromatic deacylation has also occurred.[19] 4,12-Dihydroxy-5-ethyl[2.2]paracyclophane **14** was synthesised *via* the application of mono-Fries rearrangement conditions to PHANOL **1** with acetyl chloride giving ketoester **12**. Ester hydrolysis to ketone **13** and subsequent Clemmensen reduction furnished **14**. 4,16-Dihydroxy[2.2]paracylophane **15**[17] was prepared by treatment of commercially available [2.2]paracylophane with lead tetraacetate in TFA[20] followed by basic hydrolysis (Scheme 4).[13] This compound represents a control PHANOL where the two hydroxy groups have



Scheme 4. Synthesis of PHANOL **15**.



Scheme 5. Synthesis of polymer-supported PHANOL **17**.

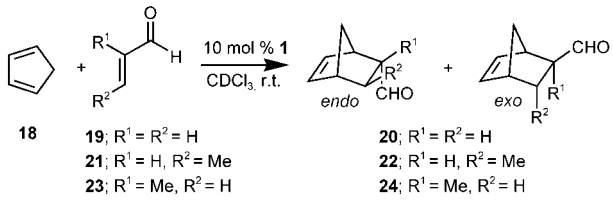
a pseudo-*para* relationship and should not be able to bind to carbonyl groups in a double hydrogen bonding mode.

A polymer-bound PHANOL **17** was also prepared by diazo coupling of an excess of the dilithio salt of PHANOL **1** with the solid-supported diazonium salt **16**, the latter recently reported by Brase et al. (Scheme 5).[21] The loading of the resulting dark-red resin **17** was calculated as 0.92 ± 0.9 mmol/g.

Diels–Alder Catalysis

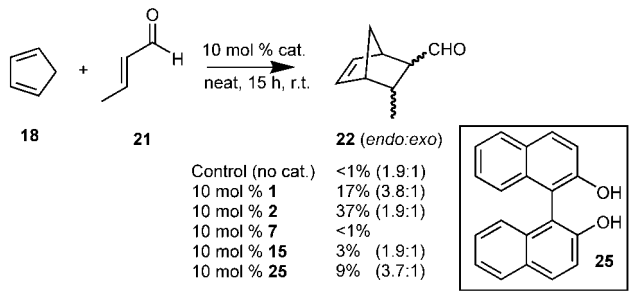
Initial catalyst testing utilised 10 mol % PHANOL **1** as a catalyst in the Diels–Alder reaction between a 1:1 mixture of cyclopentadiene **18** and acrolein **19** in chloroform solution at room temperature (Scheme 6). Compared to the control experiment where a 10% conversion to the desired cycloadduct **20** had occurred in 0.5 h without catalyst, it was found that the presence of 10 mol % PHANOL **1** resulted in a 20% conversion. The *endo*:*exo* ratio of **20** was found to increase from 4:1 in the control experiment to 5.5:1 in the presence of PHANOL **1**. Further Diels–Alder reactions were carried out under comparable conditions with crotonaldehyde **21** and methacrolein **23** as dienophiles in the Diels–Alder reactions with cyclopentadiene. The lower reactivity of these electrophiles, however, necessitated longer reaction times (70 h).[22] In both cases the extent of formation of the corresponding cycloadducts **22** and **24** was found to increase from 4% to 10% and 24% to 37%, respectively, compared to the control reaction in the presence of 10 mol % PHANOL. The *endo*:*exo* ratios of cycloadducts **22** and **24** were also found to increase from 2:1 to 3.5:1 and 1:6 to 1:5, respectively.

The above experiments demonstrate that catalytic quantities of PHANOL **1** are capable of modest acceleration of Diels–Alder reactions of α,β-unsaturated aldehydes with a representative diene (cyclopentadiene **18**). We propose that this occurs by double hydrogen bonding of PHANOL to the carbonyl group of the dienophile thus lowering the energy of the dienophile LUMO as per classical Lewis acids. The observation that the *endo*:*exo* ratios are enhanced is also consistent with this analysis. However, attempts to directly measure the extent of interaction of PHANOL **1** with a given carbonyl group were thwarted by its sparingly soluble nature in solvents such as dichloromethane, chloroform and hexane.[23] Thus in the experiments described above, PHANOL **1** was only partially solubilised in the reaction mixture. Further, it was found that dinitroPHANOL **2** was completely insoluble under these conditions and no significant increase in formation of cycloadduct **20** (11%, 0.5 h) was observed in its attempted use in the Diels–Alder reaction of cyclopentadiene **18** with acrolein **19**. Sulfonamide **7** was found to be sparingly soluble in chloroform, and when used at a nominal 10 mol % loading was found to give a 25% conversion to the cycloadduct **20** in the benchmark Diels–Alder reaction (7:1; *endo*:*exo*). Compared to the 20% conversion obtained with PHANOL **1**, this result is consistent with increased hydrogen bonding capability of the PHANOL **7** due to the strongly electron-withdrawing nature of the two *para*-sulfonamide substituents. However, the increase in conversion is only modest. This may be attributed to the relative insolubility of sulfonamide **7** (i.e., the true – *homogeneous* – catalyst loading may be much reduced than the nominal 10 mol % added). Alternatively, it may indicate that the sulfonamide groups are not fully conjugated to the aromatic ring where steric repulsion with either the benzylic position or the other sulfonamide moiety forces the groups to twist out of plane (i.e., steric inhibition of resonance).



Scheme 6. Diels–Alder reactions catalysed by PHANOL **1**.

It is evident that solubility issues are particularly important in this system. We were therefore pleased to find that all three of the *ortho*-alkyl PHANOLs **10**, **11** and **14** displayed complete solubility in chloroform at a 10 mol % loading. However, within the limits of experimental error it was found that they displayed no catalytic activity for the benchmark Diels–Alder reaction of cyclopentadiene **18** with acrolein **19** giving 13%, 11% and 10% conversions to cycloadduct **20**, respectively. We propose that these PHANOLs are unable to form double hydrogen bonds to a carbonyl group due to steric in-



Scheme 7. Diels–Alder reaction catalysed by PHANOLs.

terference by the *ortho*-alkyl substituent and therefore do not catalyse the reaction. This suggestion is supported by a comparison of IR and ^{1}H NMR data of various members of the PHANOL family (*vide infra*).

In light of the above results it was considered that successful catalysis of Diels–Alder reactions could instead be carried out in neat diene-dienophile mixtures. The reaction between neat cyclopentadiene **18** and crotonaldehyde **21** was chosen as the Diels–Alder reaction to study initially since the background rate of reaction is very slow at room temperature (<1%, 15 h) (Scheme 7). PHANOL **1** was indeed found to be soluble in this neat Diels–Alder reaction mixture, and dinitroPHANOL **2** displayed an improved solubility profile. The use of 10 mol % PHANOL **1** gave a 17% conversion (15 h) to the desired cycloadduct **22**, and the use of 10 mol % dinitroPHANOL **2** resulted in a 37% conversion in the same time period. PHANOL **7** proved to be insoluble in this reaction mixture, and therefore an increase in conversion was not observed. The use of 4,16-dihydroxy[2.2]paracyclophane **15**, which displayed good solubility in the reaction mixture, showed no significant increase in the quantity of cycloadduct **22** generated, reinforcing the argument that the catalytic effect of PHANOL and its derivatives is due to a double hydrogen bonding effect. Interestingly, we note that the use of BINOL **25** as a potential catalyst gave a 9% conversion to the desired cycloadduct, implying that the double hydrogen bonding mode is in operation here too.

The relative difference in reactivity between 4,16-dihydroxy-substituted PHANOL **15** and the 4,12-dihydroxy-substituted PHANOLs **1** and **2** is consistent with a double hydrogen bonding mode to the carbonyl group possible in **1** and **2** but not in **15**, and with the increased acidity (and hence hydrogen bonding ability) of dintroPHANOL **2** compared to PHANOL **1**. Further, in line with our proposal that carbonyl activation occurs *via* double hydrogen bonding to the carbonyl group, thus lowering the LUMO of the dienophile as per classical Lewis acids, the *endo:exo* ratio of the cycloadduct increased from 1.9:1 in the control experiment to 3.8:1 when employing catalytic quantities of **1**. However, despite the significant rate acceleration with **2** (>30-fold) as the catalyst, the *endo:exo* ratio in this case remained essentially unchanged compared to the control experiment.

Further Diels–Alder reactions are shown in Table 1. The use of either α,β-unsaturated aldehydes (entries 1–6) or ketone (entry 7) as dienophiles resulted in the increased formation of the respective cycloadducts in the presence of catalytic quantities of PHANOLs **1** or **2**, but PHANOL **1** apparently did not activate an α,β-unsaturated ester (entry 8). These results are consistent with those of Kelly who found that while α,β-unsaturated aldehydes and ketones could be activated by 1,8-biphenylenediol for Diels–Alder reactions, α,β-unsaturated esters were not.[11a] As seen for the Diels–Alder reaction of cyclopentadiene with acrolein (Table 1, entry 1) using PHANOL **1**, the *endo*:*exo* ratio of a given cycloadduct increases compared to the control reaction (Table 1, entries 2, 5, 6 and 7), but with dinitroPHANOL **2** the observed *endo*:*exo* ratios are somewhat less predictable.

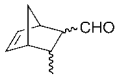
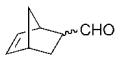
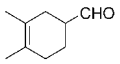
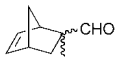
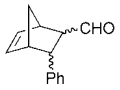
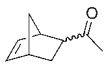
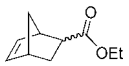
(*R*)-PHANOL[15] was examined with respect to its ability to catalyse the Diels–Alder reaction of crotonaldehdye **21** with cyclopentadiene **18** enantioselectively. However, after analysis of the resulting cycloadducts by diastereomeric imine formation with α-methylbenzylamine, the diastereomeric excesses, and hence the enantioselection in the Diels–Alder reaction were found to be minimal (<5%). It is reasonable to assume that the preferred conformation of a given PHANOL-bound α,β-unsaturated aldehyde or ketone is *s-trans* by analogy with complexes formed with Lewis acids (which generally bind *anti* to the double bond).[27] With this in mind, the minimal enantioselectivities observed are presumably a reflection of poor "expression of chirality" by the planar-chiral PHANOL backbone to the region of space where the dienophile is bound for reaction in the *s-trans* conformation. In marked contrast to α,β-unsaturated aldehydes, α,β-unsaturated esters are known to bind Lewis acids *syn* to the double bond so as to preserve the preferred *s-cis* geometry of the ester unit.[27] It follows that if PHANOL **1** can only make one hydrogen bond to the *syn* lone pair of the ester, then little activation will be observed.

Recycling of PHANOLs from a given Diels–Alder reaction was considered possible *via* basic work-up to sequester the catalyst as a salt in the aqueous phase, followed by re-acidification and extraction. Representative results of such recycling are shown in Table 2 for the Diels–Alder reaction of cyclopentadiene with crotonaldehdye using 10 mol % dinitroPHANOL **2**.

Inspection of the results in Table 2 shows that recycle is indeed possible and that catalytic activity holds-up from run to run although the mass of catalyst recovered diminishes. Pleasingly, ^{1}H NMR analysis of the recovered catalyst between runs showed no decomposition or contaminating impurities.

The use of solid-phase derivative **17** (Scheme 5) was explored as a catalyst for Diels–Alder reactions. Under

Table 1. Catalytic Diels–Alder reactions using PHANOLs **1** and **2**.

Entry[a]	Diene	Dienophile	Cycloadduct	Time	Control[b]	**1**[b]	**2**[b]
1[c]				15 h	<1 (1.9:1)	17 (3.8:1); *17*	37 (1.9:1); *37*
2[c]				10 min	35 (4.3:1)	79 (5.6:1); *2.3*	74 (6.2:1); *2.1*
3[c]				15 h	12	36; *3.0*	40; *3.3*
4[d]				15 h	3[e]	8[e]; *2.7*	13[e]; *4.3*
5[c]				15 h	34 (1:4.7)	74 (1:4.5); *2.2*	77 (1:6.5); *2.2*
6[c]				15 h	2 (1.1:1)	5 (1.8:1); *2.5*	7 (1.5:1); *3.5*
7[f]				10 min	26 (6.6:1)	72 (14:1); *2.8*	–
8				16 h	70[g]	73[g]; *1.0*	–

[a] All reactions carried out with 10 mol % catalyst and a 1:1 ratio of diene:dienophile at room temperature
[b] Percentage conversion as determined by integration of the relevant signals in the ^{1}H NMR spectrum ($CDCl_3$ solvent). The figures in parentheses give the *endo:exo* ratio respectively. The italicised figure after the semi-colon gives the acceleration factor.
[c] For characterization of this cycloadduct see Ref.[24]
[d] For characterization of this cycloadduct see Ref.[25]
[e] *endo* only.
[f] For characterization of this cycloadduct see Ref.[26]
[g] *endo:exo* ratio not determined.

Table 2. Recycling of dinitroPHANOL **2**.

Run[a]	Conversion[a]	Recovery [%]
1	50	100
2	58	90
3	45	81

[a] All reactions carried out with 10 mol% PHANOL **2** and a 1:1 ratio of cyclopentadiene:crotonaldehyde at room temperature for 96 h.
[b] Percentage conversion as determined by integration of the relevant signals in the ^{1}H NMR spectrum ($CDCl_3$ solvent).

neat conditions, it was found that an excess of diene (typically 10-fold) was required in order to swell the resin. The results are tabulated below (Table 3).

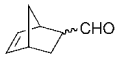
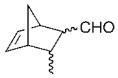
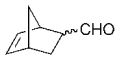
The results demonstrate that solid-supported PHANOL **17** is also capable of catalysing Diels–Alder reactions of α,β-unsaturated aldehydes with dienes, with a characteristic change in the *endo*:*exo* ratio. However, because of the need to swell the resin using excess diene the extent of the background Diels–Alder reactions increased.

Epoxide Ring-Opening Catalysis

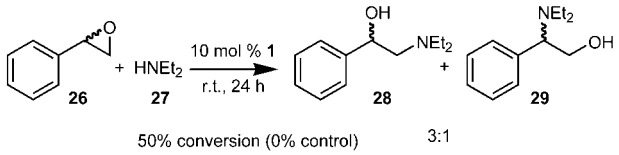
On the basis of Hine's report that biphenylenediol was significantly able to accelerate the nucleophilic ring-opening of phenyl glycidyl ether with diethylamine,[16b] we also investigated the ability of various PHANOLs to activate epoxides to nucleophilic attack by amines. Here, we postulate a model invoking double hydrogen bonding to the two lone pairs of the epoxides (Complex **IX**, Figure 1). Using an enantiopure catalyst raises the possibility of asymmetric *meso*-epoxide openings to give 1,2-amino alcohols as single enantiomers.

Initial experiments proved promising. The neat reaction of diethylamine **26** with (±)-styrene oxide **27** in

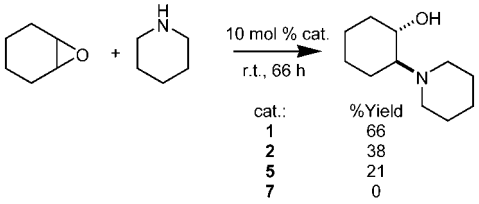
Table 3. Diels–Alder reactions with solid-phase catalyst **17**.

Entry[a]	Diene	Dienophile	Cycloadduct	Time	Control[b]	**17**[b]
1				10 min	48 (3.2:1)	73 (5.1:1); *1.5*
2				15 h	5 (1.7:1)	19 (3.8:1); *3.8*
3				18 h	3[c]	5[c]; *1.7*
5				18 h	48 (1:4.6)	73 (1:5.2); *1.5*

[a] All reactions carried out with 10 mol % solid-supported PHANOL **17** and a 10:1 ratio of diene:dienophile at room temperature for 96 h.
[b] Percentage conversion as determined by integration of the relevant signals in the ^{1}H NMR spectrum ($CDCl_3$ solvent). The figures in parentheses give the *endo:exo* ratio respectively. The italicised figure after the semi-colon gives the acceleration factor relative to the control experiment.
[c] *endo* only.



Scheme 8. Epoxide ring-opening catalysed by PHANOL **1**.



Scheme 9. Epoxide ring-opening catalysed by PHANOLs.

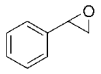
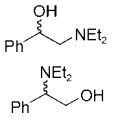
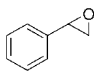
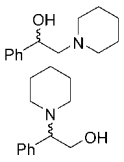
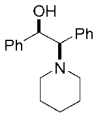
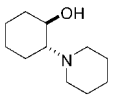
the presence of 10 mol % PHANOL **1** at room temperature for 24 h resulted in 50% conversion to the desired ring-opened products **28** and **29** (3:1) (Scheme 8). With no catalyst present no ring-opening was observed under the same conditions. Further, the use of phenol (10 mol %) as a potential monodentate activator of the epoxide resulted in less than 1% conversion to the ring-opened products. These experiments are consistent with activation of the epoxides by a double hydrogen bonding mode.

To further explore the ability of PHANOL **1** to catalyse epoxide ring openings with amines, we elected to screen some representative epoxides and amines. Styrene oxide, *cis*-stilbene oxide and cyclohexene oxide were selected as representative epoxides and diethylamine, piperidine and morpholine were selected as representative amines. The reactions were run neat with 10 mol % PHANOL **1** and 1.5 equivalents of amine (Table 4).

Inspection of the results immediately reveals that terminal epoxides are more reactive to ring opening than 1,2-disubstituted *meso*-epoxides. While diethylamine and piperidine both attack styrene oxide (Table 4, entries 1 and 2), only piperidine reacts with *cis*-stilbene oxide (Table 4, entry 3) and cyclohexene oxide (Table 4, entry 4). It is evident that morpholine is not sufficiently nucleophilic to attack any of the selected epoxides under these conditions, and no ring opening was observed in the control experiments either. These results can be readily rationalised on the basis of relative nucleophilicity where the order is piperidine > diethylamine > morpholine. An interesting feature of these PHANOL-catalysed reactions of styrene oxide is that the epoxide is preferentially attacked at the terminus of the epoxide. This suggests that the use of PHANOL for epoxide openings is analogous to activation by a relatively non-powerful Lewis acid and the lack of a strongly carbocationic centre in the transition state.[31] The success of opening cyclohexene oxide with piperidine as catalysed by PHANOL **1** where there is no background reaction without catalyst, proffered itself as an ideal test system for any enantioselectivity using enantiopure catalyst. Accordingly, the reaction was allowed to proceed to completion as catalysed by 10 mol % (*R*)-PHANOL. Chiral HPLC analysis of the product revealed it to be essentially a racemate, however.

The use of catalytic quantities of PHANOLs **2**, **5** and **7** was explored for the ring opening of cyclohexene oxide

Table 4. Ring opening of epoxides with amines catalysed by PHANOL **1**.

Run[a]	Epoxide	Amine	Product	Time	Control[b]	**1**[b]
1[c]		$HNEt_2$		24 h	0	50 (3.4:1)
2[c]				19 h	49 (14:1)	>95 (4:1)
3[d]				7 days	14	36
4[e]				32 h	0	50

[a] All reactions carried out neat with 10 mol % PHANOL **1** and a 1.5:1 ratio of amine:epoxide at room temperature.
[b] Percentage conversion as determined by integration of the relevant signals in the ^{1}H NMR spectrum ($CDCl_3$ solvent). The figures in parentheses give the ratio of "terminus" to "internal" attack, respectively;
[c] For characterization of this amino alcohol see Ref.[28]
[d] For characterization of this amino alcohol see Ref.[29]
[e] For characterization of this amino alcohol see Ref.[30]

with piperidine for comparison with PHANOL **1** (Scheme 9).

On the basis of potential hydrogen-bonding ability, it might be predicted that the "rear-face" functionalised PHANOLs **2**, **5** and **7** bearing electron-withdrawing groups should be better catalysts than PHANOL, and that PHANOLs with two electron-withdrawing groups (i.e., **2** and **7**) should be better catalysts than those with just one (i.e., **5**). In fact, the complete opposite of this is observed in the attempted ring opening of cyclohexene oxide with piperidine, where PHANOL **1** is more effective than bromoPHANOL **5** which is more effective than dinitroPHANOL **2** (it transpired that sulfonamide **7** was completely insoluble under these conditions and this fact accounts for the zero conversion observed). The results can be rationalised by noting that across the series **1** to **5** to **7**, the PHANOLs are expected to become more acidic. It seems reasonable to assume that piperidine is increasingly capable of deprotonating the PHANOLs of increasing acidity. This would increasingly reduce the amount of PHANOLs available for catalysis in line with the observed results.

IR and NMR Features of PHANOLs

The ^{1}H NMR chemical shifts and IR stretching frequencies for the OH group of various PHANOLs are collected in Table 5. For ^{1}H NMR data, it is well understood that hydrogen bonding leads to deshielding of a given proton that participates.[32] Similarly, hydrogen bonding is readily determined by inspection of the IR spectrum in the region of 3000+ wavenumbers.[32]

Table 5. NMR and IR spectral data for PHANOLs.

PHANOL	δ [ppm][a]	IR [cm^{-1}][b]
1	8.48[c]	3500–3100
2	10.83[c]	3500–3100
5	8.61 and 8.87[d]	3500–3100
7	8.66[e]	3500–3000
10	4.34[d]	3477
11	5.38 and 4.35[d]	3600–3100
14	5.84 and 5.38[d]	3600–3100

[a] Chemical shift of OH resonance(s) in the ^{1}H NMR spectrum.
[b] Wavenumber of OH stretch(es) in the IR spectrum.
[c] DMSO-d_6 solution.
[d] $CDCl_3$ solution.
[e] Acetone-d_6 solution.

Typically, a "strong" hydrogen bond is defined in which the total length is shorter than the sum of the Van der Waal's radii of the two substituents by at least 0.3 Å.[33] This works out to be 2.50 Å for an O-H···O system. Double-well ("weak") hydrogen bonds typically have O···O separations of 2.8 Å.[1] In this respect, where the PHANOLs are expected to have a phenolic O···O separation of *ca.* 4.0 Å (*vide supra*) it seems likely that

neither "strong" nor "weak" *intra*molecular hydrogen bonds between the phenolic groups can be formed. Therefore, the experimental data gathered in Table 5 can be used to indicate which PHANOLs are capable of *inter*molecular hydrogen bonding as required for catalysis. Moreover, these data also corroborate our proposal that the PHANOLs act as catalysts by double hydrogen bonding (*vide infra*).

The parent PHANOL **1** displays a sharp singlet with chemical shift of 8.48 ppm for the two OH protons in its ^{1}H NMR spectrum, and a broad stretching frequency at 3500–3100 cm^{-1} in the IR spectrum (Table 5, entry 1). On the basis of the analysis above, the characteristic broad signal in the IR spectrum requires that PHANOL **1** is participating in intermolecular hydrogen bonding. In comparison, dintroPHANOL **2** shows a singlet at 10.83 ppm in the ^{1}H NMR spectrum (Table 5, entry 2), indicating that it is a better hydrogen bond donor by virtue of the electron-withdrawing nitro groups – as witnessed by the experimental results for catalysis of Diels–Alder reactions (*vide supra*). The relative melting points of (±)-PHANOL **1** compared to dinitroPHANOL **2** of 229–231 °C and 280 °C (dec.), respectively, also testify to the increased hydrogen bonding ability of the latter. The monosubstituted bromide **5** shows two OH resonances in its NMR spectrum at 8.61 and 8.87 ppm (Table 5, entry 3) where presumably the higher chemical shift value represents the resonance for the phenol of the ring also bearing the *para*-bromine atom. PHANOL **7** shows a ^{1}H NMR resonance at 8.66 ppm (Table 5, entry 4). All these compounds also show broad IR signals showing intermolecular hydrogen bonding.

In direct contrast, di-*ortho*-alkylPHANOL **10** shows an extremely sharp OH stretch in its IR spectrum at 3477 cm^{-1} (Table 5, entry 5) unambiguously showing that it cannot make intermolecular hydrogen bonds. The ^{1}H NMR spectrum shows a resonance at 4.34 ppm – a much reduced magnitude of chemical shift compared to PHANOL **1** – entirely consistent with the above. The change in chemical shift from 8.48 ppm in PHANOL **1** to 4.34 ppm in PHANOL **10** is therefore diagnostic for a phenolic OH unable to participate in intermolecular hydrogen bonding in these systems. It also follows that if intermolecular hydrogen bonding cannot occur, then it should not be active for catalysis – as observed experimentally. Further, incremental evidence for the non-hydrogen bonding capability of **10** comes from the observed melting point of 135–140 °C (*cf.* PHANOL **1**: 229–231 °C) and from its improved solubility in non-polar solvents. We attribute the inability of PHANOL **10** to make intermolecular hydrogen-bonds simply to steric shielding by the *ortho*-alkyl groups.

In further contrast, monoalkylPHANOL **11**, shows two resonances in the ^{1}H NMR at 5.38 and 4.35 ppm, but shows a broad signal in its IR spectrum (Table 5, entry 6). The latter spectrum is consistent with the ability of PHANOL **11** to make intermolecular hydrogen bonds. Critically, however, the ^{1}H NMR chemical shift value of 4.35 ppm for PHANOL **11** by comparison to the value obtained for PHANOL **10** shows that at least one of the phenolic groups is unable to participate in intermolecular hydrogen bonding (assigned as the OH at the 4-position). The intermolecular hydrogen bonding is therefore due to the sterically unencumbered phenolic group resonating at 5.38 ppm in the NMR spectrum (presumably the broad band at 3600–3100 cm^{-1} in the IR spectrum is obscuring the expected sharp signal for the non-hydrogen bonded phenol in the IR spectrum at *ca.* 3475 cm^{-1}). Since PHANOL **11** is not active for catalysis, but is capable of making one intermolecular hydrogen bond, this clearly shows that PHANOLs **1**, **2**, **5** and **7** are catalysing reactions *via* a double hydrogen bonding mode. The results for monoalkylPHANOL **14** (Table 5, entry 7) are less clear-cut however. It is not an active catalyst, but it does display intermolecular hydrogen bonding as evidenced by the IR spectrum. Like PHANOL **11**, two resonances are observed in the ^{1}H NMR spectrum, but the chemical shifts are 5.84 and 5.38 ppm. This discrepancy may arise from the different steric shielding effects of a C_2-alkyl chain (**14**) versus a C_5-alkyl chain (**10**, **11**).

Conclusion

In conclusion, we have demonstrated catalysis of Diels–Alder and epoxide opening reactions *via* double hydrogen bonding interactions using catalysts based on the 4,12-dihydroxy[2.2]paracyclophane (PHANOL) framework. The double hydrogen bonding mode is supported by an analysis of ^{1}H NMR and IR data for the various PHANOLs. For Diels–Alder reactions the order of activity of a given PHANOL catalyst is in-line with increased electron-withdrawing groups at the *para*-positions. However, substitution at the *ortho*-position of a PHANOL sterically prevents double hydrogen bonding and kills catalysis. In contrast to Diels–Alder reaction catalysis, the more electron-deficient PHANOLs were found to display essentially the reverse order of activity for catalysis of epoxide opening with an amine. This was attributed to the increasing capability of the amine to deprotonate the increasingly acidic PHANOLs, reducing the amount of active catalyst. Attempts to use enantiopure catalyst (*R*)-PHANOL to effect asymmetric induction in either Diels–Alder reactions or epoxide openings failed, presumably due to poor "expression of chirality" by the planar chiral PHANOL at the reacting centre. Although the rate accelerations in the Diels–Alder reactions are in general modest, and could have been induced instead by, e.g., the application of pressure or heating, these results demonstrate that double hydrogen bonding to a carbonyl group can be achieved with a chiral catalyst and the potential for asymmetric (organo)catalysis is clear. Indeed, the recent work of Rawal[14] for the highly enantioselective catalysis of hetero-Diels–

Alder reactions *via* double hydrogen bonding with TADDOL shows the promise of this area, and this work should prove useful in further identifying enantioselective catalysts that operate *via* a multiple hydrogen bonding donor mode.[34]

Experimental Section

General

[2.2]Paracyclophane was purchased from Speciality Coating Systems. 4,12-Dihydroxy[2.2]paracyclophane (**1**),[17] 4,12-dihydroxy-7,15-dinitro[2.2]paracyclophane (**2**),[15] 4,12-diacetoxy-[2.2]paracyclophane (**3**),[17] 4,16-dihydroxy[2.2]paracyclophane (**15**)[15,19,22] and 2,4,4,6-tetrabromocyclohexa-2,5-dienone[35] were prepared according to published procedures. Acetyl chloride, valeryl chloride and titanium tetrachloride were distilled immediately before use. Cyclopentadiene was cracked from dicyclopentadiene (bath temperature 150 °C) immediately before use. CH_2Cl_2 was distilled from CaH_2. All other reagents and solvents were used as received. All reactions were performed under an atmosphere of nitrogen unless otherwise specified.

Analytical thin-layer chromatography (TLC) was carried out on silica gel $F_{254/366}$ 60 Å plates with visualisation using UV light (254 nm) or potassium permanganate as appropriate. Chromatography refers to flash column chromatography performed using BDH 33–70 μm grade silica gel using the method of Still.[36] Eluents are given in parentheses. Solvents for flash chromatography, i.e., EtOAc, Et_2O, petroleum ether, CH_2Cl_2, MeOH were ACS reagent grade or GPR grade and were used as received. Concentrated refers to concentrated under vacuum.

Melting points were recorded on a Reichart-Thermovar melting point apparatus and are uncorrected. Fourier transform infra-red (IR) spectra were recorded through Diffuse Reference Infra-red Fourier Transform Spectroscopy (DRIFTS) or a thin film on NaCl plates using a Mattson 500 FTIR spectrometer. Solid phase infra-red (IR) spectra were recorded using a Mattson Infinity Series FTIR spectrometer. ^{1}H NMR were recorded at 270 MHz on a JEOL GSX-270 spectrometer or at 300 MHz on a Bruker DRX spectrometer. ^{13}C NMR were recorded at 68 MHz and 75 MHz on a JEOL GSX-270 spectrometer or on a 300 MHz Bruker DRX spectrometer, respectively. NMR samples were run in the indicated solvents and were referenced internally. Low resolution mass spectroscopy (LR-MS) [EI and CI] and high resolution mass spectrometry (HR-MS) [EI] were recorded by the Imperial College Department of Chemistry Mass Spectroscopy Service. Elemental analyses were carried out by Mr. Stephen Bowyer at the University of North London.

13-Bromo-11-oxo-tricyclo[8.2.2.2^{4,7}]hexadeca-4(5),6,10(14),1(12)-pentaen-5-yl Acetate (4)

To a stirred solution of 2,4,4,6-tetrabromohexadieneone (3.15 g, 7.7 mmol) in CH_2Cl_2 (30 mL) at −20 °C was added a solution of diacetate **3** (1.00 g, 3.1 mmol) in CH_2Cl_2 (20 mL). The mixture was warmed to room temperature, stirred for 24 hours, concentrated and chromatographed (CH_2Cl_2) to give bromide **4** as a white solid; yield: 871 mg (78%); mp 150 °C (dec.); R_f = 0.25 (CH_2Cl_2); IR (thin film): ν = 3241, 2996, 2929, 1766, 1658, 1623 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz): δ = 2.10–2.21 (1H, m), 2.29 (3H, s), 2.61–2.67 (2H, m), 2.75–2.99 (3H, m), 3.14–3.25 (2H, m), 4.52 (1H, dd, J = 5.6, 0.9 Hz), 5.83 (1H, s), 6.07 (1H, d, J = 5.6 Hz), 6.44 (1H, d, J = 1.8 Hz), 6.64 (1H, dd, J = 8.0, 1.8 Hz), 6.95 (1H, d, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 68 MHz): δ = 21.1, 30.0, 31.0, 32.1, 32.8, 40.0, 126.8, 129.0, 129.9, 131.9, 133.6, 140.7, 142.2, 142.4, 150.7, 158.1, 168.6, 184.9; MS (EI): m/z = 362, 360, 320, 318, 282, 240, 200, 198, 162, 120; HR-MS (EI): m/z = 360.0357 (M)$^+$, 362.0335 (M)$^+$; calcd. for $C_{18}H_{17}O_3{}^{79}Br$: 360.0361, $C_{18}H_{17}O_3{}^{81}Br$: 362.0341.

7-Bromo-4,12-dihydroxy[2.2]paracyclophane (5)

To stirred solution of bromide **4** (950 mg, 2.7 mmol) in CH_2Cl_2 (23 mL) at 0 °C was added DBU in one portion (0.4 mL, 2.7 mmol). The resulting mixture was warmed to room temperature and stirred for 4 hours. The mixture was poured into aqueous HCl (30 mL, 2.5 M) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL), and the combined organics were washed with aqueous HCl (30 mL) and brine (30 mL), dried over $MgSO_4$, filtered, concentrated and chromatographed (1:99 MeOH:CH_2Cl_2) to give 12-acetoxy-7-bromo-4-hydroxy[2.2]paracyclophane as a white solid; yield: 650 mg (68%); mp 145–150 °C; R_f = 0.25 (1% MeOH in CH_2Cl_2); IR (DRIFTS, KBr): ν = 3600–3100, 2934, 1715 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz): δ = 2.32 (3H, s), 2.46–2.57 (1H, m), 2.65–2.77 (1H, m), 2.88–3.12 (4H, m), 3.22–3.39 (2H, m), 5.62 (1H, s), 5.94 (1H, s), 6.33 (1H, dd, J = 8.0, 1.8 Hz), 6.50 (1H, s), 6.80 (1H, d, J = 1.8 Hz), 7.08 (1H, d, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 68 MHz): δ = 21.6, 29.0, 30.7, 33.1, 34.0, 117.6, 121.2, 122.0, 128.5, 129.6, 130.6, 131.9, 138.8, 140.6, 141.7, 149.5, 153.8, 170.0; MS (EI): m/z = 362, 360, 320, 318, 282, 239, 200, 198, 162, 120; HR-MS (EI): m/z = 360.0364 (M)$^+$, 362.0344 (M)$^+$; calcd. for $C_{18}H_{17}{}^{79}BrO_3$: 360.0361, $C_{18}H_{17}{}^{81}BrO_3$: 362.0341.

To a stirred solution of 12-acetoxy-7-bromo-4-hydroxy[2.2]-paracyclophane (177 mg, 0.49 mmol) in MeOH (10 mL) was added powdered NaOH (500 mg, 8.9 mmol) in one portion. The resulting mixture was heated to reflux for 10 minutes, cooled to room temperature, poured into aqueous HCl (20 mL, 2.5 M) and extracted with EtOAc (3 × 10 mL). The organic layers were combined, washed consecutively with saturated aqueous sodium bicarbonate solution (2 × 20 mL) and brine (2 × 20 mL), dried over $MgSO_4$, filtered, concentrated and chromatographed (1:1 EtOAc:petroleum ether) to give **5** as a pale yellow oil; yield: 147 mg (95%); R_f = 0.50 (1:1 EtOAc:petroleum ether); IR (thin film): ν = 3600–3100, 2984, 2855 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz): δ = 2.31–2.53 (1H, m), 2.62–2.86 (4H, m), 2.95–3.04 (1H, m), 3.10–3.25 (2H, m), 5.99 (1H, dd, J = 7.7, 1.6 Hz), 6.15 (1H, d, J = 1.6 Hz), 6.26 (1H, s), 6.38 (1H, s), 6.84 (1H, d, J = 7.7 Hz), 8.61 (1H, s), 8.87 (1H, s); ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ = 29.3, 30.6, 33.8, 34.0, 115.8, 119.0, 119.8, 123.3, 124.4, 127.5, 131.5, 138.2, 140.6, 142.2, 155.7, 156.4.

4,12-Dihydroxy-7,15-di(*N*,*N*-diethyl)sulfonyl[2.2]paracyclophane (7)

Neat chlorosulfonic acid (8 mL, 120 mmol) was added cautiously to a vessel containing diacetate **3** (612 mg, 1.9 mmol). The resulting dark red mixture was stirred at room temperature for 3 days, and poured carefully onto ice (50 g). The mixture was further diluted with water (150 mL), extracted with EtOAc (3 × 100 mL), and the combined organics were washed with brine (2 × 50 mL), dried over $MgSO_4$, filtered and concentrated to give crude disulfonyl chloride **6** (>90% purity by ^{1}H NMR) as a black solid. DMF (10 mL) was added, followed by diethylamine (5 mL). The mixture was heated to 60 °C for 16 hours, allowed to cool to room temperature, diluted with water (30 mL), and extracted with EtOAc (3 × 20 mL). The combined organics were washed consecutively with aqueous HCl (2 × 20 mL) and brine (2 × 20 mL), dried over $MgSO_4$, filtered, concentrated and chromatographed (1:1 petroleum ether: EtOAc to 100% EtOAc) to give bissulfonamide **7** as an off-white powder; yield: 150 mg (16%); mp 240 °C (dec.); R_f = 0.45 (EtOAc); IR (DRIFTS): ν = 3600–3100, 2955, 2937, 1569, 1164 cm^{-1}; ^{1}H NMR (270 MHz, acetone-d_6): δ = 1.00 (12H, t, J = 7.6 Hz), 2.82–3.14 (4H, m), 3.10 (4H, q, J = 7.6 Hz), 3.12 (4H, q, J = 7.6 Hz), 3.15–3.28 (2H, m), 3.59 (2H, m), 6.51 (2H, s), 7.18 (2H, s), 8.66 (2H, s); ^{13}C NMR (68 MHz, acetone-d_6): δ = 13.8, 30.2, 33.2, 41.7, 120.8, 124.8, 129.6, 134.0, 141.5, 158.7; MS (EI): m/z = 510, 446, 349; HR-MS (EI): m/z = 510.1858 (M)$^+$; calcd. for $C_{24}H_{34}O_6N_2S_2$: 510.1861.

4-Hydroxy-5-pentanoyl[2.2]paracyclophan-12-yl Pentanoate (8)

To a stirred solution of PHANOL **1** (72 mg, 0.30 mmol) in dry CH_2Cl_2 (2 mL) was added a solution of $TiCl_4$ in CH_2Cl_2 (1.8 mL, 0.7 M, 1.26 mmol) and valeryl chloride (76 μL, 0.63 mmol) at 0 °C. The resulting dark red solution was heated to reflux, and maintained at this temperature for 8 hours. Water was added (2 mL), followed by aqueous HCl (2 mL, 2.5 M) and CH_2Cl_2 (4 mL), and the resultant mixture stirred for 0.5 hours. The organic layer was removed, and the aqueous layer was extracted with CH_2Cl_2 (5 mL). The combined organics were washed consecutively with water (1 × 10 mL) and brine (1 × 10 mL), dried over $MgSO_4$, filtered and concentrated to give **8** as a yellow oil; yield: 118 mg (95%); R_f = 0.32 (1:1 petroleum ether : CH_2Cl_2); IR (thin film): ν = 2931, 2861, 1757, 1612 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz): δ = 0.94 (3H, t, J = 7.4 Hz), 1.01 (3H, t, J = 7.5 Hz), 1.37 (2H, sextet, J = 7.5 Hz), 1.48 (2H, sextet, J = 7.4 Hz), 1.73 (4H, m), 2.47 (2H, dt, J = 4.7, 7.4 Hz), 2.53–2.60 (1H, m), 2.68–2.77 (1H, m), 2.91 (2H, t, J = 7.2 Hz), 3.02–3.17 (4H, m), 3.38–3.48 (2H, m), 6.18 (1H, d, J = 7.6 Hz), 6.51 (1H, dd, J = 7.9, 1.3 Hz), 6.53 (1H, d, J = 1.3 Hz), 6.58 (1H, d, J = 7.6 Hz), 6.66 (1H, d, J = 7.9 Hz), 13.10 (1H, s, Ar-O*H*); ^{13}C NMR ($CDCl_3$, 68 MHz): δ = 13.8, 14.0, 22.3, 22.6, 27.1, 28.1, 30.4, 31.0, 33.5, 34.2, 35.1, 43.3, 121.3, 123.5, 126.8, 128.6, 129.0, 129.4, 135.0, 139.6, 142.6, 142.7, 149.4, 162.1, 171.5, 207.5.

4,12-Dihydroxy-5,13-dipentanoyl[2.2]paracyclophane (9)

To a stirred solution of PHANOL **1** (200 mg, 0.83 mmol) in $(ClCH_2)_2$ (16 mL) at room temperature under nitrogen was added dropwise $TiCl_4$ (0.37 mL, 3.3 mmol), followed by valeryl chloride (1.0 mL, 8.8 mmol). The resulting cherry red mixture was heated to 85 °C for 13 hours, allowed to cool to room temperature and aqueous HCl (10 mL, 2.5 M) was added cautiously. After stirring for 15 minutes the organic layer was removed, and the aqueous layer extracted with CH_2Cl_2 (2 × 20 mL). The combined organics were washed consecutively with saturated aqueous sodium bicarbonate solution (2 × 30 mL) and brine (1 × 25 mL), dried over $MgSO_4$, filtered, concentrated and chromatographed (2:1 petroleum ether:CH_2Cl_2) to give diketone **9** as a yellow oil; yield: 200 mg (60%); R_f = 0.35 (1:1 petroleum ether:CH_2Cl_2); IR (thin film): ν = 2957, 2930, 2871, 1619, cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz): δ = 0.90 (6H, t, J = 7.3 Hz), 1.34 (4H, sextet, J = 7.3 Hz), 1.70 (4H, ddt, J = 6.5, 7.3, 8.9 Hz), 2.53 (2H, m), 2.80 (2H, ddd, J = 6.5, 8.9, 15.3 Hz), 2.99 (2H, ddd, J = 6.5, 8.9, 15.3 Hz), 3.07 (2H, m), 3.39 (2H, m), 3.61 (2H, m), 6.34 (2H, d, J = 7.6 Hz), 6.62 (2H, d, J = 7.6 Hz), 12.91 (2H, s); ^{13}C NMR ($CDCl_3$, 68 MHz): δ = 14.0, 22.2, 27.8, 30.3, 34.8, 43.2, 121.7, 125.8, 126.9, 138.8, 143.9, 162.2, 208.2; MS (EI): m/z = 408 (M)$^+$, 379, 295, 203; HR-MS (EI): m/z = 408.2320 (M)$^+$; calcd. for $C_{26}H_{32}O_4$: 408.2301; anal. calcd. for $C_{26}H_{32}O_4$: H 7.90, C 76.44; found: H 8.04, C 76.55.

4,12-Dihydroxy-5,13-dipentyl[2.2]paracyclophane (10)

Mossy zinc (9.21 g, 141 mmol) and mercuric chloride (1.14 g, 4.2 mmol) were combined in a round-bottomed flask, and water (25 mL) and HCl (3 mL, 12 M) were added. After stirring for 1 hour at room temperature, the aqueous layer was decanted and the amalgam washed thoroughly with water. A solution of diketone **9** (374 mg, 0.92 mmol) in EtOH (18 mL) was added to the amalgam along with HCl (3 mL, 10 M). The mixture was refluxed for 20 hours, with portions of HCl (4 × 1.5 mL, 12 M) added at regular intervals. Once all traces of yellow colour had disappeared (*ca.* 16 h) the mixture was cooled to room temperature and the aqueous layer extracted with EtOAc (3 × 25 mL). The organic layers were combined, washed with brine (2 × 20 mL), dried over $MgSO_4$, filtered, concentrated and recrystallised from petroleum ether:Et_2O (5:1), giving **10** as a white solid; yield: 242 mg (69%); mp 135–140 °C; IR (thin film): ν = 3477, 3109, 2923, 2856 cm^{-1}; ^{1}H NMR ($CDCl_3$; 270 MHz): δ = 0.83 (6H, t, J = 6.9 Hz), 1.23 (12H, m), 2.56–2.69 (4H, m), 2.73–2.84 (4H, m), 3.22–3.36 (4H, m), 4.34 (2H, s), 6.13 (2H, d, J = 7.8 Hz), 6.33 (2H, d, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$; 67.5 MHz): δ = 14.1, 22.7, 27.2, 28.7, 31.1, 31.8, 32.4, 124.2, 127.3, 128.3, 132.3, 139.3, 152.3.

(*E*)-4,12-Dihydroxy-5-pent-1-enyl[2.2]paracyclophane (11)

To a stirred solution of diketone **9** (100 mg, 0.25 mmol) in MeOH (5 mL), was added sodium borohydride (232 mg, 6.1 mmol) in one portion. The mixture was heated to reflux for 14 hours, cooled to room temperature, poured into aqueous HCl (30 mL, 2.5 M) and extracted with EtOAc (3 × 25 mL). The organic layers were combined, washed with saturated

aqueous sodium bicarbonate solution (1×25 mL) and brine (1×25 mL), dried over $MgSO_4$, filtered, concentrated and chromatographed (1:1 petroleum ether:CH_2Cl_2) to give alkene **11** as a pale yellow oil; yield: 50 mg (65%); $R_f = 0.25$ (CH_2Cl_2); IR (thin film): $\nu = 3600-3100$, 2958, 2931, 2870 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz): $\delta = 0.96$ (3H, t, $J =$ 7.4 Hz), 1.48 (2H, sextet, $J = 7.4$ Hz), 2.19 (2H, ddt, $J = 7.4$, 6.9, 1.3 Hz), 2.54–2.88 (3H, m), 2.94 (2H, m), 3.34 (3H, m), 4.35 (1H, s), 5.39 (1H, s), 5.66 (1H, dt, $J = 16.4$, 6.9 Hz), 6.14 (1H, d, $J = 7.7$ Hz), 6.15 (1H, dd, $J = 7.7$, 1.7 Hz), 6.19 (1H, d, $J = 1.7$ Hz), 6.33 (1H, d, $J = 7.7$ Hz), 6.49 (1H, d, $J = 7.7$ Hz), 6.65 (1H, dt, $J = 16.4$, 1.3 Hz); ^{13}C NMR ($CDCl_3$, 68 MHz): $\delta = 13.8$, 22.6, 29.2, 30.6, 31.6, 33.6, 35.6, 116.2, 124.2, 124.7, 124.9, 125.6, 126.1, 134.1, 135.2, 136.1, 140.0, 142.4, 151.3, 154.3; MS (CI, NH_4^+): $m/z = 356$, 339, 321, 307, 269, 189, 120.

4-Hydroxy-5-ethanoyl[2.2]paracyclophan-12-yl Acetate (12)

To a stirred solution of PHANOL **1** (200 mg, 0.83 mmol) in $(ClCH_2)_2$ (8.3 mL) at room temperature under nitrogen was added dropwise $TiCl_4$ (0.07 mL, 3.5 mmol), followed by acetyl chloride (137 mL, 2.1 mmol). The resulting cherry red mixture was heated to 40 °C for 4 hours, allowed to cool to room temperature, and HCl (4 mL, 2.5 M) was added cautiously. After stirring for 0.25 h the organic layer was removed, and the aqueous layer diluted with water (10 mL) and extracted with CH_2Cl_2 (2×5 mL). The organic layers were combined, washed consecutively with saturated aqueous sodium bicarbonate solution (10 mL) and brine (10 mL), dried over $MgSO_4$, filtered, concentrated and the crude material chromatographed (1:3 EtOAc:petroleum ether) to give ketoacetate **12** as a yellow solid; yield: 47 mg (58%); mp 175–180 °C; IR (thin film): $\nu = 2937$, 1753, 1609 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz): $\delta = 2.21$ (3H, s), 2.48–2.77 (2H, m), 2.63 (3H, s), 2.93–3.19 (4H, m), 3.40 (1H, m), 3.59 (1H, m), 6.15 (1H, d, $J = 8.0$ Hz), 6.47 (1H, dd, $J =$ 7.8, 1.8 Hz), 6.54 (1H, d, $J = 1.8$ Hz), 6.56 (1H, d, $J = 7.8$ Hz), 6.63 (1H, d, $J = 8.0$ Hz), 13.29 (1H, s); ^{13}C NMR ($CDCl_3$, 68 MHz): $\delta_C = 21.0$, 30.2, 30.6, 31.4, 33.5, 35.0, 120.9, 123.5, 126.9, 128.7, 129.0, 129.5, 135.0, 139.8, 142.8, 143.0, 149.3, 162.8, 166.9; MS (CI, NH_4^+): $m/z = 342$ $(M + NH_4)^+$, 324, 282.

4,12-Dihydroxy-5-ethanoyl[2.2]paracyclophane (13)

To a stirred solution of ketoacetate **12** (100 mg, 0.31 mmol) in MeOH (10 mL) was added powdered KOH (500 mg, 8.9 mmol). The resulting mixture was maintained at reflux for 5 minutes, cooled, acidified with HCl (10 mL, 2.5 M) and extracted with EtOAc (2×25 mL). The organic layers were combined, washed with saturated aqueous sodium bicarbonate solution (1×25 mL) and brine (1×25 mL), dried over $MgSO_4$, filtered and concentrated to give hydroxyketone **13** as a white solid; yield: 80 mg (91%); IR (DRIFTS): $\nu = 3500-3100$, 2929, 2852 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz): $\delta = 2.47-2.75$ (2H, m), 2.69 (3H, s), 2.87–3.11 (3H, m), 3.34–3.49 (2H, m), 3.60–3.72 (1H, m), 6.13 (1H, d, $J = 7.6$ Hz), 6.17 (1H, d, $J =$ 1.6 Hz), 6.24 (1H, dd, $J = 7.7$, 1.6 Hz), 6.50 (1H, d, $J = 7.6$ Hz), 6.61 (1H, d, $J = 7.7$ Hz), 13.23 (1H, s); ^{13}C NMR ($CDCl_3$, 68 MHz): $\delta = 30.3$, 30.4, 31.4, 33.6, 34.6, 117.5, 120.8, 123.6, 124.3, 127.2, 128.1, 135.5, 139.8, 143.0, 144.3, 155.2, 162.6, 206.4; MS (CI, NH_4^+): $m/z = 282$ $(M)^+$, 161, 120; HR-MS (EI): $m/z = 282.1266$ $(M)^+$; calcd. for $C_{18}H_{18}O_3$: 282.1256.

4,12-Dihydroxy-5-ethyl[2.2]paracyclophane (14)

Water (10 mL) and HCl (1 mL, 12 M) were added to a solid mixture of mossy zinc (3.58 g, 59 mmol) and mercuric chloride (432 mg, 1.6 mmol). After stirring for 1 hour at room temperature, the aqueous layer was decanted and the amalgam washed thoroughly with water. A solution of ketone **13** (100 mg, 0.42 mmol) in EtOH (6 mL) was added to the amalgam along with HCl (1 mL, 12 M). The mixture was refluxed at 78 °C for 20 hours, with portions of HCl (4×0.5 mL) added over regular intervals. Once all traces of yellow colour had disappeared the mixture was cooled to room temperature, diluted with water, and the aqueous layer extracted with EtOAc (3×25 mL). The combined organics were washed with brine (2×20 mL), dried over $MgSO_4$, filtered, concentrated and chromatographed (4:1 petroleum ether:EtOAc) giving ethylPHANOL **14** as a white solid; yield: 100 mg (88%); mp 148–149 °C; IR (DRIFTS) $\nu = 3600-3100$ cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz): $\delta = 0.95$ (3H, t, $J = 7.4$ Hz), 2.60–2.89 (5H, m), 2.95 (2H, m), 3.20–3.43 (3H, m), 5.38 (1H, br s), 5.84 (1H, br s), 6.12 (1H, dd, $J = 7.6$, 1.4 Hz), 6.21 (1H, d, $J = 7.8$ Hz), 6.27 (1H, d, $J = 1.4$ Hz), 6.32 (1H, d, $J = 7.8$ Hz), 6.47 (1H, d, $J =$ 7.6 Hz); ^{13}C NMR ($CDCl_3$, 68 MHz): $\delta = 16.1$, 20.5, 28.8, 30.5, 32.1, 33.8, 116.0, 124.6, 125.2, 126.1, 127.2, 131.2, 132.3, 135.1, 139.8, 141.6, 151.3, 154.7; MS (CI, NH_4^+): $m/z = 269$ $(M + H)^+$, 148, 120.

Solid-Supported PHANOL 17

To a stirred solution of PHANOL **1** (1.54 g, 6.43 mmol) in EtOH (60 mL) was added finely ground lithium hydroxide monohydrate (540 mg, 12.86 mmol). The suspension was homogenised through sonication and heated to reflux for 5 minutes. The EtOH was removed under vacuum to give the dilithio salt of PHANOL (yield: 1.58 g, 97%) as a dark brown solid, which was used immediately without further purification.

To a nitrogen-agitated suspension of resin **16**[23] (0.70 mmol, loading 1.4 mmol/g) in CH_2Cl_2 (5 mL) at room temperature was added the dilithio salt in DMF (8 mL). The suspension was maintained under nitrogen for 2 hours, diluted with MeOH, filtered and washed with a solution of AcOH in CH_2Cl_2 (3×5 mL, 20%). The mother liquor was concentrated, diluted with water (20 mL), extracted with ethyl acetate ($2 \times$ 20 mL), the organic layers combined, washed consecutively with saturated aqueous sodium bicarbonate solution ($2 \times$ 20 mL) and brine (20 mL), dried over $MgSO_4$, filtered and evaporated to give diol **1** (1.24 g, 5.2 mmol recovery). The remaining resin was washed consecutively with CH_2Cl_2, DMF and MeOH, then dried under vacuum to give **17** (yield: 1.260 g, 0.92 mmol/g based on mass gain and recovered diol **1**) as a dark red resin. IR (solid phase): $\nu = 3444$, 3024, 2924, 1724, 1585, 1493, 1451, 1330, 1226, 1147 cm^{-1}.

General Procedure for the Diels–Alder Reaction Catalysed by PHANOLs

The appropriate PHANOL (0.1 equiv., 0.042 mmol, 10 mol %) was loaded into one of two identical reaction tubes. The appropriate dieneophile (1 equiv.) and diene (1 equiv.) were added sequentially to each tube, and the resulting reaction mixtures were stirred for the appropriate length of time before being diluted with $CDCl_3$ (0.7 mL). This resulted in the PHANOL catalysts precipitating, thereby "quenching" the reaction and simultaneously solubilising the Diels–Alder products and any remaining unreacted dienophile and diene (and cyclopentadiene dimer). The mixture was then directly analysed by ^{1}H NMR. The results are shown in Table 1. The percentage conversions were determined by integrating selected resonances for the desired cycloadducts and unreacted dienophile. Entry 1 (CpH + crotonaldehyde): *endo* adduct,[24] δ_H (C$\underline{H}$O) = 9.35 ppm, *exo* adduct, δ_H (C$\underline{H}$O) = 9.77 ppm, unreacted crotonaldehyde, δ_H (C$\underline{H}$O) = 9.48 ppm [contains *ca.* 2.5% *Z*-olefin, δ_H (C$\underline{H}$O) = 10.12 ppm]. Entry 2 (CpH + acrolein): *endo* adduct,[24] δ_H (C$\underline{H}$O) = 9.39 ppm, *exo* adduct, δ_H (C$\underline{H}$O) = 9.77 ppm, unreacted acrolein, δ_H (C$\underline{H}$O) = 9.55 ppm. Entry 3 (2,3-dimethyl-1,3-butadiene + acrolein): cycloadduct,[24] δ_H (C$\underline{H}$O) = 9.65 ppm, unreacted acrolein, δ_H (C$\underline{H}$O) = 9.55 ppm. Entry 4 (cyclohexa-1,3-diene + acrolein): cycloadduct (*endo* only),[25] δ_H (C$\underline{H}$O) = 9.44 ppm, unreacted acrolein, δ_H (C$\underline{H}$O) = 9.55 ppm. Entry 5 (CpH + methacrolein): *endo* adduct, δ_H (C$\underline{H}$O) = 9.39 ppm, *exo* adduct,[24] δ_H (C$\underline{H}$O) = 9.68 ppm, unreacted methacrolein, δ_H (C$\underline{H}$O) = 9.54 ppm. Entry 6 (CpH + cinnamaldehyde): *endo* adduct,[24] δ_H (C$\underline{H}$O) = 9.59 ppm, *exo* adduct, δ_H (C$\underline{H}$O) = 9.90 ppm, unreacted cinnamaldehyde, δ_H (C$\underline{H}$O) = 9.70 ppm. Entry 7 (CpH + methyl vinyl ketone): *endo* adduct,[26] δ_H (COC$\underline{H}_3$) = 2.12 ppm, *exo* adduct,[26] δ_H (COC$\underline{H}_3$) = 2.20 ppm, unreacted methyl vinyl ketone, δ_H (COC$\underline{H}_3$) = 2.28 ppm.

General Procedure for the Nucleophilic Ring Opening with Amines Catalysed by PHANOLs

The appropriate PHANOL (0.1 equiv., 0.042 mmol) was loaded into one of two identical reaction tubes. The appropriate epoxide (1 equiv.) and nucleophile (1.5 equiv.) were added sequentially to each tube. The resulting reaction mixtures were stirred for the appropriate length of time before being diluted with $CDCl_3$ (0.7 mL) and analysed by ^{1}H NMR. The results are shown in Table 4 and Scheme 9.

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