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Chiral Tricarbonyl(η^6-cyclobutabenzene)chromium Complexes. Diastereoselective Synthesis and Use in Asymmetric Cycloaddition Reactions.

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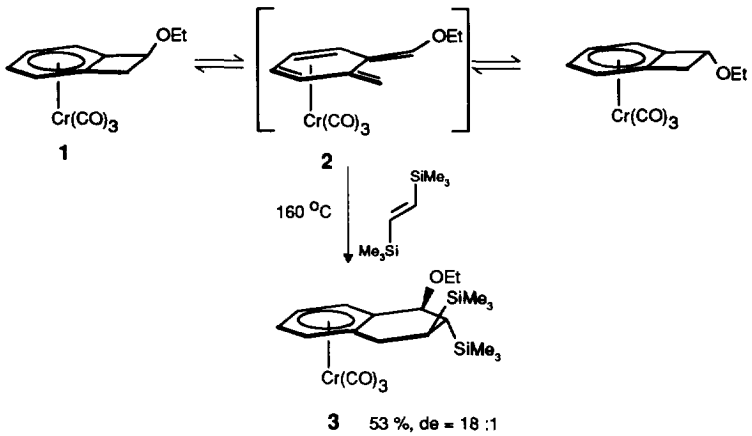
Abstract: The intermolecular Diels-Alder reaction of a nonracemic planar chiral (*ortho*-quinodimethane)$Cr(CO)_3$ intermediate **6** with dienophiles gave, after decomplexation, chiral nonracemic tetralins **23-25**. Access to **6** was obtained *via* enzyme catalyzed acetate hydrolysis of 1-acetoxycyclobutabenzene (**13**), derivatization of the highly enantioenriched 1-hydroxycyclobutabenzene (S-(+)-**8**) as the tetrahydropyranyl ether **20** diastereoselective complexation to $Cr(CO)_3$ followed by hydrolysis and charge accelerated electrocyclic ring opening of the anion of (1-hydroxycyclobutabenzene)$Cr(CO)_3$ ((1S,6aR)-(-)-**4**). Copyright © 1996 Elsevier Science Ltd

The asymmetric intermolecular Diels-Alder reaction of *ortho*-quinodimethanes[1] with dienophiles gives access to chiral nonracemic tetralins. Chiral auxiliaries attached to the dienophiles have been used very successfully in this reaction and products of high diastereomeric purity have been obtained[2]. The alternative approach in which a chiral auxiliary is tethered to the diene has been less thoroughly investigated. Moreover, in the few cases reported[3], the level of asymmetric induction falls far short of that obtained with chiral dienophiles. We here consider a new approach in which the planar chirality of a metal complexed *ortho*-quinodimethane is used to direct a dienophile selectively to one face of the diene.

At first we focused on the thermal ring opening of [(1-EtO-cyclobutabenzene)$Cr(CO)_3$] (**1**) and on the trapping of the intermediate *o*-quinodimethane complex (**2**) with *trans*-bis(trimethylsilyl)ethene. The stereochemistry of the major product (**3**) was that expected from a highly selective cycloaddition to the *exo*-face of the Cr-bound *o*-quinodimethane intermediate **2** (Scheme 1).[4]

While this confirmed the validity of our hypothesis it was also obvious that this was not a practical route to substituted tetralins. The high temperature required for the ring opening to the *o*-quinodimethane complex intermediate (160 °C) together with the reactivity of the chromium center at this temperature severely limits the scope of this procedure. Reactions which generate the *o*-quinodimethane complex intermediate under mild conditions would hold much higher synthetic promise. It is well established that resonance donor substituents at the benzylic center accelerate electrocyclic ring opening of cyclobutabenzenes.[1a,5] We were particularly attracted by reports from *Choy et al.* who found that the anion of 1-hydroxycyclobutabenzene undergoes ring opening below 0 °C.[6]

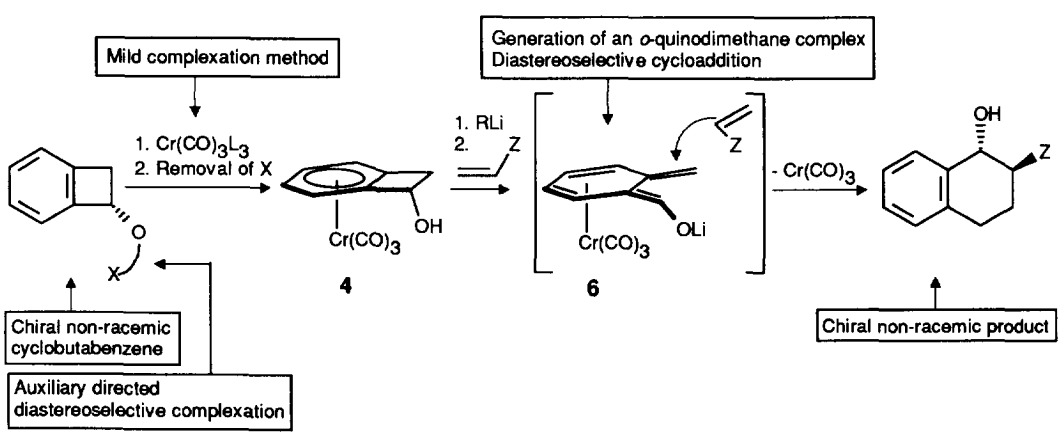
Scheme 1



We and, in parallel and independent work, *Butenschön and coworkers*, found that this anion accelerated ring opening can be successfully applied to the $Cr(CO)_3$ complexed cyclobutabenzenes.[7,8] Deprotonation of [(1-hydroxycyclobutabenzene)($Cr(CO)_3$)] (**4**) or treatment of [(1-acetoxycyclobutabenzene)($Cr(CO)_3$)] (**5**) with n-BuLi gave the intermediate complex **6** which reacted with a number of dienophiles with excellent diastereoselectivity furnishing *exo*-tetralol complexes.[7b] Decomplexation under mild conditions yielded stereoselectively substituted tetralols. It is evident that the merit of this method depends on its success to yield non racemic products. This is the subject of this article.

The reaction sequence presents a number of interesting synthetic and mechanistic problems. It notably involves the first generation of a chiral non-racemic *ortho*-quinodimethane complex intermediate and its use in cycloaddition reactions. An outline of our approach is shown in Scheme 2. The individual steps are described in the following sections.

Scheme 2

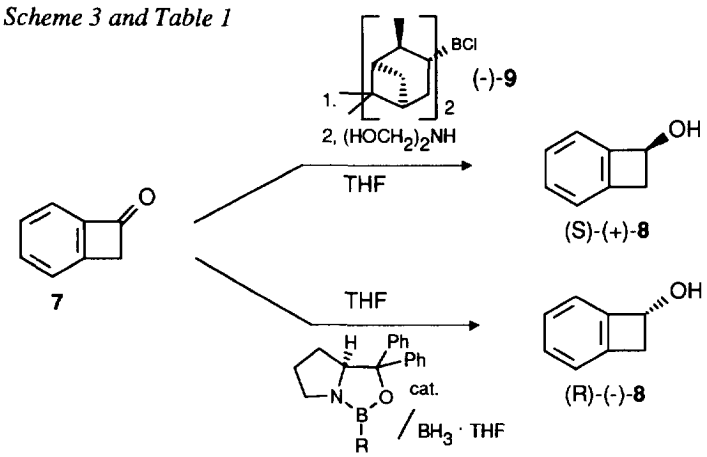


APPROACHES TO ENANTIOMERICALLY ENRICHED 1-HYDROXYCYCLOBUTABENZENE (8)

Racemic 1-hydroxycyclobutabenzene (*rac*-**8**) can be resolved into its enantiomers *via* reaction with phthalic anhydride and fractional crystallization with brucine.[9] Looking for alternative routes of access, we first investigated the asymmetric reduction of 1-oxocyclobutabenzene (**7**). This route looked particularly attractive because ketone **7** is readily obtained by preparative flash vapor pyrolysis of *o*-toluic acid chloride.[10]

Two reducing systems, chlorodiisopinocamphenylborane (**9**)[11] and the two oxazaborolidines **10a**[12] and **10b**[13], were selected for their demonstrated efficiency in the asymmetric reduction of 1-indanone and 1-tetralone. The results of the the asymmetric reduction of **7** are listed in Table 1. The literature emphasizes that enantioselectivity in the reactions of oxazaborolidines is very sensitive to traces of aminoalcohol and alkylboronic acid, and we therefore carried out control experiments using **10a** and **10b** with 1-tetralone (**11**) (Table 1, entries 6 and 7).

Scheme 3 and Table 1



R=Me: (S)-**10a**
R=Bu: (S)-**10b**

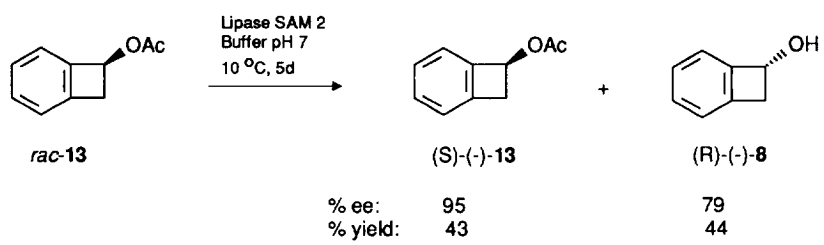
Entry	Substrate	Reducing Agent	T [°C]	t [h]	Product	Yield [%]	ee [%]
1	**7**	(-)-**9**	-25	20	(S)-**8**	73	68
2	**7**	(-)-**9**	-50	22	(S)-**8**	63	67
3	**7**	(S)-**10a**, 0.1 eq.	23	0.5	(R)-**8**	96	66
4	**7**	(S)-**10a**, 0.1 eq.	-10	0.5	(R)-**8**	93	58
5	**7**	(S)-**10b**, 0.2 eq.	23	8	(R)-**8**	90	44
6	**11**	(S)-**10a**, 0.1 eq.	-10	0.5	(R)-**12**	96	93
7	**11**	(S)-**10b**, 0.2 eq.	23	8	(R)-**12**	95	96

Asymmetric reduction of ketone **7** proceeded with only moderate enantioselectivity. The results show that the chiral reducing agents tested do not differentiate sufficiently between the enantiotopic faces of this very constrained aromatic ketone to be of use in synthesis. The β-hydroxysulfoximine catalyzed asymmetric hydro-

genation method developed by *Bolm et al.*, when applied to **7**, afforded close to racemic **8** (4% ee).[14] We next tried enantioselective reduction using baker's yeast.[15,16] The reaction proceeded efficiently and was faster than that of acetophenone but it gave (S)-**8** with only 52 % ee. Samples removed at intervals showed that asymmetric induction varied little during the course of the reaction and we therefore decided not to pursue this approach and turned to enzymatic resolution methods.[15,17]

Enantioselective enzyme catalyzed acetate transfer[18] from vinyl acetate to alcohol **8** in t-butyl methyl ether with the lipase *Pseudomonas sp* gave (R)-**13** and (S)-**8**. After 33 h at 23 °C, the two products were isolated with yields of 47 and 43% respectively and enantiomeric excess of 68 and 73 %. The reverse reaction with the same lipase was more successful. Enantioselective acetate hydrolysis[19] of 1-acetoxycyclobutabenzene (**13**) in a phosphate buffer solution proceeded with an enantiomeric ratio E of about 35 and thus provided a practical route to highly enantiomerically enriched material. The best control on a scale of up to 50 mmol of **13** was achieved by lowering the temperature to 10 °C and using the procedure described by *Schneider et al.*[19c] The reaction medium was maintained at pH 7 by continuous addition of 1M NaOH with an autoburette. By going to a conversion of ca. 54 %, this procedure routinely provided (S)-**13** in quantities of several g (43% yield) and with an ee of 95%. The alcohol **8** was obtained under these conditions with an ee of 79%. Higher enriched samples were obtained by allowing the reaction to go to 63% conversion to give (S)-**13** in 34% yield and >99.5% ee (Scheme 4).

Scheme 4



The absolute configuration of the enantiomers of **8** and **13** was at first assigned tentatively on the basis of literature precedent of asymmetric induction of reactions with closely related compounds.[11-19] The assignment was confirmed for enantiomerically pure (S)-(+)-**8** *via* an X-ray structural analysis of the ester **14**[20] formed by its reaction with (-)-camphanic acid chloride (Scheme 5, Fig.1).[21]

Scheme 5

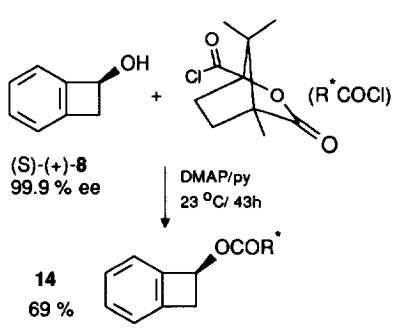
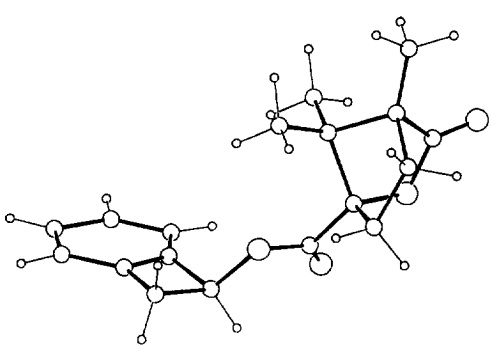


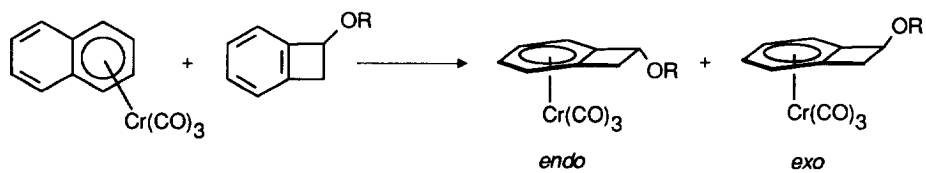
Figure 1: Structure of ***14***



DIASTEREOSELECTIVE COMPLEXATION

The next step required a highly diastereoselective complexation to either the *endo* or the *exo*-face of **8** or a derivative thereof. Bulky benzylic alkyl groups in cycloalkabenzenes guide the $Cr(CO)_3$ group to the arene face *exo* to the substituent.[22] Conversely, benzylic OR and NR_2 groups, presumably *via* temporary coordination of the incoming chromium tricarbonyl group, guide the metal into the *endo*-face of the arene.[23] Mild reaction conditions improve diastereoselectivity in arene exchange reactions, and they are essential with **8** and its ether derivatives because racemisation associated with reversible ring opening is facile at temperatures above 80 °C. Both 1-indanol and 1-tetralol react with the efficient $Cr(CO)_3$ transfer reagent [(naphthalene) $Cr(CO)_3$][24] to give the *endo* isomer exclusively.[25,26] 1-Methoxyindane also reacts analogously.[25] It was reasonable to assume that 1-hydroxy cyclobutabenzene (**8**) would react likewise. This expectation was not fulfilled, however. Our results are shown in Scheme 6 and Table 2.

Scheme 6 and Table 2

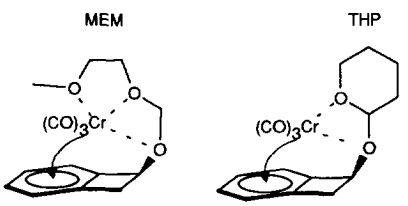


Entry	R, Arene (equiv.)	Solvent	T [°C]	t [h]	Product (*endo*/*exo* ratio)	Yield [%]
1	H, **8** (3)	THF	23	96	**4** (1 : 1)	35
2	H, **8** (3)	Et_2O	34	106	**4** (9 : 1)	35
3	H, **8** (3)	Et_2O	50	11	**4** (10 : 1)	25
4	Ac, **13** (2)	THF	70	9	**5** (1 : 1)	70[7b]
5	Me **15** (2)	Et_2O/THF	70	22	**16** (1.2 : 1)	54
6	Et, **17** (2)	Et_2O/THF	70	22	**1** (1.5 : 1)	70[4]
7	MEM,**18** (2)	THF	23	116	**19** (0.8 : 1)	40
8	MEM,**18** (2)	Et_2O	70	44	**19** (4.3 : 1)	58
9	THP, **20** (3)	THF	70	4	**21** (1 : 1)[a]	76
10	THP, **20** (3)	Et_2O	70	12	**21** (33 : 1)[b]	61

[a] The ratio of the two diastereomeric *exo*-complexes was 1.8 : 1; that of the *endo*-complexes was 1.2 : 1 (see text). [b] *Exo*-complexes: 1 : 1; *endo*-complexes: 2.4 : 1.

Alcohol **8** gave only low yields of complex **4**. Major impediments were a slow reaction accompanied by decomposition resulting in a difficult product isolation. Higher temperatures led to rapid degradation of **8**. Moreover, attempts to separate the two diastereoisomers by chromatographic methods (column, rotating disc, HPLC) were not successful. Surprisingly, *endo* and *exo* diastereoisomers formed in equal proportion when THF was used as solvent (entry 1). Low diastereoselectivity was also observed in the complexation of the acetate **13** and the ethers **15** and **17** (entries 4-6) with the difference that *endo*- and *exo*-diastereoisomers of the

resulting complexes **1**, **5**, and **16** were readily separated by column chromatography. The results suggest that the rigidity of the 1-OR-cyclobutabenzenes prevents efficient complexation of the benzylic oxygen to the incoming Cr-complex fragment or places it in a position which is not favorable for the formation of the arene complex. THF competes successfully for the Cr coordination sites and this results in low diastereoselectivities of $Cr(CO)_3$ tranfer. Support for this interpretation stems from the observation that diastereoselectivity of the complexation of **8** is much higher in the less coordinating solvent diethylether but at the price of a lower yield and longer reaction time. As expected, the formation of the *endo*-isomer of complex **4** is now largely favored (entries 2 and 3). In this context it was noted that *endo*-**4** is considerably more stable than the *exo*-diastereoisomer. Pure *endo*-**4** was obtained by treating the acetate complex *endo*-**5** with 2 eq. of BuLi at -78 °C followed by reaction with sat. NH_4Cl solution. Following the same procedure, the transformation of *exo*-**5** into *exo*-**4** afforded an oil. While crystals formed at -30 °C from toluene/hexane solution, they readily turned oily with partial degradation on isolation. Faced with low yields and/or low diastereoselectivities and separation problems we decided to modify **8** by temporarily increasing the complexing ability of the cyclobutabenzene side-chain. The derivatives selected were the 2-methoxyethoxymethyl ether (MEM) **18** and the THP ether **20**. Again, significant diastereoselection was restricted to the reactions carried out in ether, whereas in THF equal or close to equal amounts of the diastereoisomers were formed (entries 7 - 10). In ether, the less flexible, THP-protected alcohol **20** gave an acceptable yield (61%) of almost pure *endo*-complex (*endo*-**21**. The presence of an additional chiral center in **21** results, after complexation, in the formation of four diastereoisomers. HPLC - analysis (silica, 254 nm, hexane/diisopropyl ether 4:1 + 1% ethanol, 3ml/min) shows two peaks for the *endo*-diastereoisomers (19.5 min and 21 min) and one peak for one of the *exo*-diastereoisomers (10.5 min). The peak of the second *exo*-diastereoisomer overlaps with that of [(naphthalene)$Cr(CO)_3$] (9.2 min). The ratio of the two *endo*-products was thus readily determined by HPLC whereas that of the *exo*-products was determined from the ^{1}H-NMR spectrum after column chromatographic separation from *endo*-**21**.

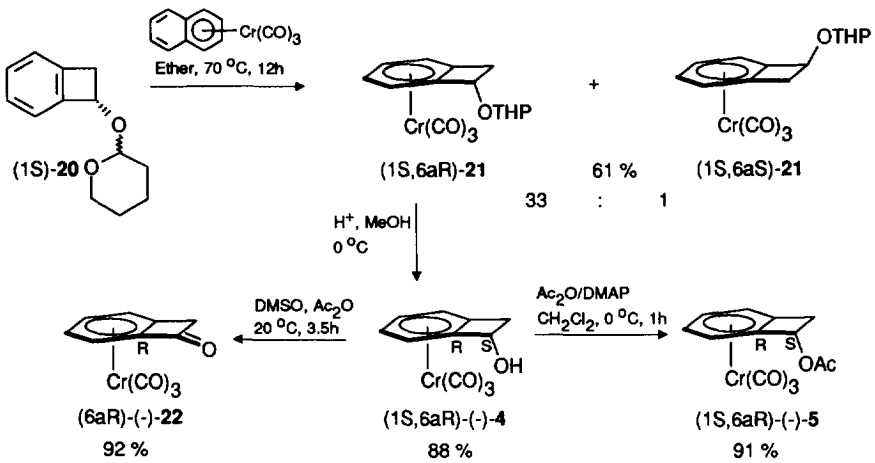


The highly diastereoselective complexation of the THP derivative was used in the synthesis of the complex (6aR)-*endo*-**21**. Hydrolysis and recrystallization gave enantiopure (1S,6aR)-(-)-**4** in good yield. Acetylation of **4** afforded the corresponding acetate (1S,6aR)-(-)-**5** and mild oxidation gave the ketone (6aR)-(-)-(**22**)[27] (Scheme 7).

GENERATION OF AN ENANTIOMERICALLY PURE *O*-QUINODIMETHANE COMPLEX AND DIASTEREOSELECTIVE CYCLOADDITION REACTIONS

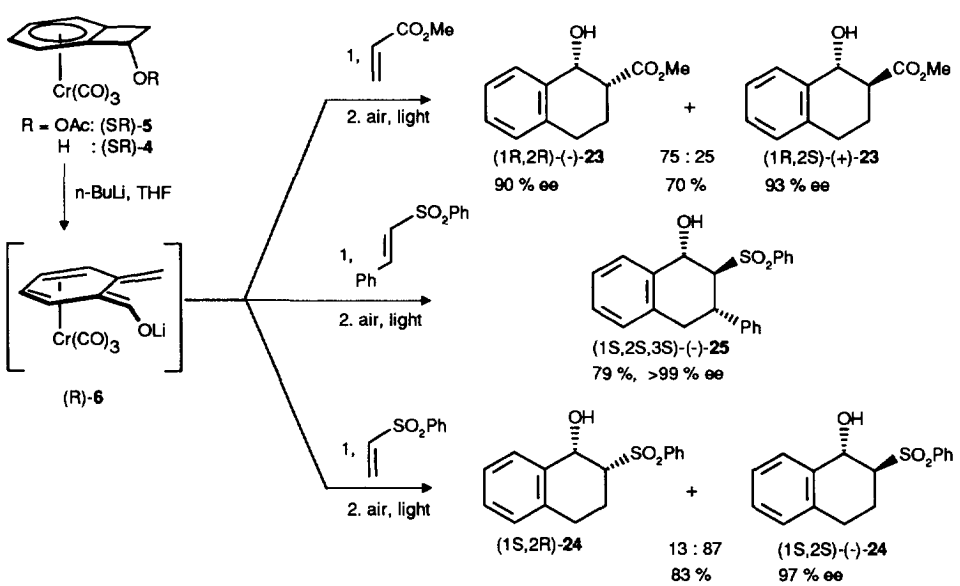
The generation of the racemic *o*-quinodimethane $Cr(CO)_3$ complex intermediate *rac*-**6** and the scope and limitations of its cycloaddition reactions were described in a previous full paper.[7b] The same procedure was applied to the enantiopure complexes (1S,6aR)-(-)-**4** and (1S,6aR)-(-)-**5**. Treatment of a THF solution of (-)-**4** with 1.05 eq. of n-BuLi, or of (-)-**5** with 2.1 eq. n-BuLi at -78 °C, followed by slow warm up to 0 °C and decomplexation gave the tetralols **23** - **25** in the yields, ratios and enantiomeric purities shown in Scheme 8.

Scheme 7



These results and previously established relative stereochemistry in the $Cr(CO)_3$ complexes of the tetralol products resulting from the reaction with methyl acrylate are in accord with an approach of the dienophile to the *o*-quinodimethane face opposite to the metal.[7] Vinyl sulfones react with good to excellent *exo*-selectivity while methyl acrylate reacts preferentially *via* an *endo* transition state to give a 3 : 1 mixture of the two diastereomers (1R,2R)-**23** and (1R,2S)-**23**. The results rule out the alternative sequence *via* a η^6 to η^4 slippage of the *o*-quinodimethane, coordination of the dienophile to the metal followed by cycloaddition of the two metal bound ligands. We can not, however, exclude a stepwise sequence of Michael addition/aldol reaction.

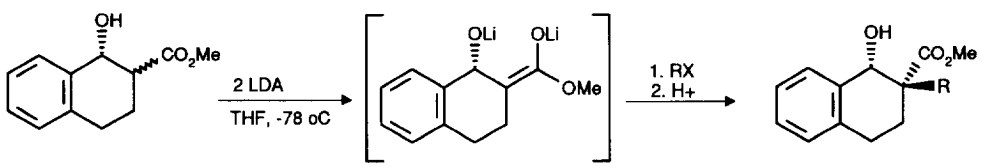
Scheme 8



DIASTEREOSELECTIVE ALKYLATION OF TETRALOL 23

The $Cr(CO)_3$ fragment efficiently controls the stereochemistry at C(1) in the cycloaddition reaction of the *o*-quinodimethane complex intermediate **6**. The approach of the dienophile is exclusively to the diene face opposite to the metal. With methyl acrylate, face selectivity of the dienophile is much less satisfactory. The *endo*-Diels-Alder product dominates but with a selectivity of only 3 : 1. Regardless of this ratio, earlier work by *Frater* [28] and by *Seebach*[29] on cyclic and acyclic β-hydroxy esters demonstrate the possibility of using the hydroxy function at the stereogenic center C(1) to control the stereochemistry of the adjacent center *via* alkylation of the ester enolate.

Scheme 9



(1R, 2RS)-**23** **26**

R = Et: (1S,2R)-(-)-**27** 68 %, 90 % ee
allyl: (1S,2S)-(-)-**28** 72 %, 88 % ee
benzyl: (1S,2S)-(-)-**29** 64 %, 88 % ee

This procedure can be readily applied to tetralol **23**. The dianion **26** was generated as shown in Scheme 9 and treated with C-electrophiles. The alkylated, allylated and benzylated products **27** - **29** were obtained as single diastereomers and were assigned structures as shown based on literature precedent of alkylation of enolates of β-hydroxy esters.[28,29] The high enantiomeric purity was maintained, confirming that no racemisation at C(1) had taken place during this procedure.

CONCLUSION

The study presented in this article touches on a number of aspects of the use of arene complexes in asymmetric synthesis. Significant advances have been made recently in the area of asymmetric preparation of planar chiral arene complexes.[30] Diastereoselective complexation of a chiral arene remains one of the most successful methods but has the disadvantage of a very narrow scope of arenes that can be used. The present work demonstrates the importance of pre-coordination of a chiral arene substituent to the Cr intermediate to guide the metal into one diastereoface selectively. It also shows that planar chirality is a very efficient element in the control of diastereoface selection in the Diels-Alder reaction. Demonstrated here for asymmetric intermolecular cycloaddition reactions of an *in situ* generated o-quinodimethane, this concept should be applicable to a wide range of cycloaddition reactions.[31]

Acknowledgements. Financial support of this work by the Swiss National Science Foundation (grant No 20-39'118.93) is gratefully acknowledged. We express our gratitude to C. Bolm and M. Felder for kindly carrying out the catalytic reduction of **7** (ref 14). We thank P. Romanens for technical assistance and J. P. Saulnier, A. Pinto and D. Clément for NMR and MS measurements.

EXPERIMENTAL

1. General

All manipulations involving organometallics were carried out under an atmosphere of purified nitrogen or argon and using an inert gas/vacuum double manifold and standard Schlenk techniques. $Cr(CO)_6$ (Strem Chemicals). [(Naphthalene)$Cr(CO)_3$] was obtained in 75% yield (10g scale) using *Hudecek and Toma's* procedure (decalin/ethyl formate).[32] 1-Acetoxycyclobutabenzene (**13**)[33], 1-hydroxycyclobutabenzene (**8**)[33], 1-ethoxycyclobutabenzene (**15**)[34], 1-oxocyclobutabenzene (**7**)[10] and 1-phenyl-2-(phenylsulfonyl)ethene[35] were obtained by literature methods. Methyl acrylate was passed through neutral Alox before use. Phenyl vinyl sulfone was recrystallized prior to use. Tetrahydrofuran and ether were distilled from sodium-benzophenone ketyl immediately prior to use. Hexamethylphosphortriamide (HMPA) (Fluka) was stirred with CaH_2 (15h at 60 °C) then distilled (10 mm Hg, N_2). Ethyl iodide, allyl bromide, and benzyl bromide (Fluka) were distilled from P_2O_5 under N_2. Diisopropylamine was freshly distilled from KOH under N_2. Benzene-d_6 (Glaser): vac. transfer from CaH_2. n-BuLi (Fluka) was titrated. Lipase from pseudomonas (SAM-2) was obtained from Fluka. Analytical and preparative TLC: Merck silica gel 60 F_{254} plates. Semipreparative HPLC: Kontron chromatograph using a 10x250 mm silica column. Flash column chromatography: silica gel 60, (Merck). M.p.: Büchi 510, not corrected. IR: Mattson Polaris or Perkin-Elmer 1650 FT-IR, NaCl solution cells. ^1H, ^{19}F, and ^{13}C-NMR: Bruker 400 MHz or Varian-XL-200 spectrometer. MS: Varian CH 4 or SM 1, 70 eV, rel. intensities in parenthesis. High res. MS: VG analytical 7070E. . Elemental analyses: by H. Eder, Service de Microchimie, Institut de Chimie Pharmaceutique, Université de Genève.

2. Approaches to enantioenriched 1-hydroxycyclobutabenzene (8).

*2.1. Reduction of 1-Oxocyclobutabenzene (7) with chlorodiisopinocamphenlborane (Ipc_2BCl, (-)-**9**).*[11] A THF (1ml) solution of 1-oxocyclobutabenzene (**7**) (0.236 g, 2 mmol) was added dropwise to a cold (-25 °C) THF solution of borane (-)-**9** (0.772 g, 2.4 mmol in 9 ml THF). The reaction was stirred at this temperature and its progress was followed by TLC. After 20 h, volatiles were removed in vacuum to give an oil which was taken up in ether (13 ml) and treated with diethanolamine (0.4626 g, 4.4 mmol). After 2h, the white precipitate formed was removed by filtration, the solution concentrated and the crude product purified by flash chromatography on silica gel (eluent hexane/Et_2O 4:1). Recrystallization from hexane gave **8** (0.175 g, 73 %) and ^{19}F-NMR analysis of its derivative with (S)-(+)-MTPA-Cl showed a diastereomeric excess of 68 %. The major isomer was (S)-(+)-**8** (see text).

*2.2. Asymmetric Reduction of 7 with oxazaborolidines (S)-**10a** et (S)-**10b**.* The oxazaborolidines (S)-**10a**[12] et (S)-**10b**[13] were prepared according to the literature methods from (S)-(-)-diphenylhydroxy methylpyrrolidine (Fluka) and trimethylboroxine or butylboronic acid.

*a) With 0.1 eq. of (S)-**10a**.* To a stirred mixture of 1-oxocyclobutabenzene (**7**) (0.118 g, 1 mmol) et (S)-**10a** (0.625 ml of a 0.16 M toluene solution, 0.1 mmol) in THF (2.5 mmol) was added BH_3·THF (0.6 ml of a 1.0 M THF solution, 0.6 mmol). The addition was carried out at 23 °C over a period of 30 min by using a syringe pump. After stirring a further 30 min, the reaction was quenched by addition of MeOH (0.5 ml). Flash chromatography yielded the alcohol **8** in 96 % yield. Derivatization with (S)-(+)-MTPA-Cl gave a product shown by ^{19}F-NMR spectroscopy to have 66 % diastereomeric excess. The major enantiomer formed in the reduction was R-(-)-**8** (see text).

*b) With 0.2 eq. of (S)-**10b*** To a stirred mixture of 1-oxocyclobutabenzene (**7**) (0.118 g, 1 mmol) et (S)-**10b** (0.4 ml of a 0.5 M toluene solution, 0.2 mmol) in THF (2.5 mmol) was added BH_3·THF (0.6 ml of a 1.0 M THF solution, 0,6 mmol). The addition was carried out at 23 °C over a period of 8h by using a syringe pump to give R-(-)-**8** in 90 % yield and 44 % ee.

2.3. Enzymatic Resolution. A 3-neck flask equipped with a magnetic stirring bar, an auto burette (aq. NaOH, 1M), and a pH-electrode linked to a pH-meter was charged with 1-acetoxycyclobutabenzene (*rac*-**13**) (6 g, 37 mmol) and a phosphate buffer (74 ml, 0.1 M, pH = 7). Pseudomonas lipase sp (564 mg) was added and the mixture was stirred for 112 h. Throughout this time the temperature was maintained at 10 °C and the pH at 7.0 (addition of 20.9 ml of 1M NaOH). The mixture was extracted with ether, the combined organic phases washed with water and then dried over $MgSO_4$. Filtration, solvent removal and flash-chromatography (hexane/Et_2O 4:1) yielded (S)-1-acetoxycyclobutabenzene ((S)-**13**) (2.562 g, 43 %, 95 % ee by ^{1}H-NMR (Eu(HFC)$_3$)) and (R)-1-hydroxycyclobutabenzene (R-**8**)(1.958 g, 44 %, 79 % ee). Enantiomerically pure samples were obtained by letting the resolution run longer (see text). (S)-(-)-**13**: $[\alpha]_D^{20}$ = - 69 ($CHCl_3$, c = 1.13). (S)-(+)-**8**: $[\alpha]_D^{20}$ = + 83 ($CHCl_3$, c = 1.47).

3. Diastereoselective Complexation

*3.1. (endo-1-Hydroxycyclobutabenzene)Cr(CO)$_3$ (**4**). a) Via complexation of rac-**8**.* A flame dried glass vessel (5 ml) with a sealed on Teflon tap was charged with [(naphthalene)Cr(CO)$_3$] (132 mg, 0.5 mmol), 1-hydroxycyclobutabenzene (180 mg, 1.5 mmol), a magnetic stirring bar, and ether (2.5 ml). The mixture was degassed *via* 3 freeze/pump/thaw cycles and then stirred in the dark at 34 °C for 106 h. After cooling to ambient temperature, the mixture was filtered over celite and then reduced to dryness by an oil pump vacuum. The product, after passage through a short column of silicagel (hexane/Et_2O 1:1) was isolated (44 mg, 35%) and shown by ^{1}H-NMR to consist of a 9 : 1 mixture of *rac-endo*-**4** and *rac-exo*-**4**.

*b) Via hydrolysis of endo-**21**.* To a solution of the diastereomeric mixture of (1S,1'R,6aR)-/(1S,1'S,6aR)-*endo*-**21** (2.4:1) (777.3 mg, 2.28 mmol) in methanol (14 ml) at 0 °C was added *p*-toluenesulfonic acid monohydrate (43.4 mg, 0.228 mmol). After stirring for 2 days at 0 °C, the reaction was taken to dryness and the residue purified by chromatography (hexane/Et_2O 1:1) to give complex (1S,6aR)-**4** (512 mg, 88 %). Recrystallization from hexane/ether gave 73 % of product as yellow crystals of >99 % enantiomeric purity (^{1}H-NMR, Eu(HFC)$_3$, after conversion to the acetate **5**). (1S,6aR)-(-)-**4**: $[\alpha]_D^{20}$ = - 46 ($CHCl_3$, c = 1.1).

*3.2. endo- and exo-1-Acetoxycyclobutabenzene Cr(CO)$_3$ (**5**). a) Via complexation of (S)-**13** and separation of the diastereoisomers.* Complexes (1S,6aS)-**5** and (1S,6aR)-**5** were obtained from (S)-(-)-**13** (94.4 % enantiomeric purity) and [(naphthalene)Cr(CO)$_3$] (7.5 mmol scale) as a 1 : 1 mixture of diastereoisomers in 70 % yield according to the published procedure[7b]. Following separation and recrystallization, the complexes (S,S)-(+)-**5** and (S,R)-(-)-**5** were of > 98 % enantiomeric purity as determined by ^{1}H-NMR spectroscopy with the chiral shift reagent Eu(HFC)$_3$. (1S,6aS)-(+)-**5**: $[\alpha]_D^{20}$ = + 83 ($CHCl_3$, c = 1.14), (1S,6aR)-(-)-**5**: $[\alpha]_D^{20}$ = - 288 ($CHCl_3$, c = 1.1).

b) Via acylation of (1S,6aR)-(-)-**4**. A degassed solution (CH_2Cl_2, 13 ml) of complex (1S,6aR)-**4** (541 mg, 2.11 mmol) was treated at 0 °C with acetic anhydride (0.219 ml, 2.32 mmol) and DMAP (258 mg, 2.11 mmol). After stirring at this temperature for 1 h, volatiles were removed in vacuum and the residue purified by chromatography on silica gel (hexane/ether 4:1, then 1:1). Recrystallization yielded (S,R)-(-)-**5** (571 mg, 91 %) in >95 % enantiomeric purity.

3.3. endo- and exo-1-Methoxycyclobutabenzene $Cr(CO)_3$ (16). A flame dried thick wall glass vessel (5 ml) with a sealed on Teflon tap was charged with [(naphthalene)$Cr(CO)_3$] (264 mg, 1 mmol), 1-methoxycyclobutabenzene[9](**15**) (273 mg, 2 mmol), a magnetic stirring bar, and ether (7.8 ml). The mixture was degassed *via* 3 freeze/pump/thaw cycles, then THF (0.25 ml) was added and the mixture was stirred in the dark at 73 °C for 22 h. After cooling to ambient temperature, the mixture was filtered over celite. The crude product was analyzed by HPLC. Chromatography on silicagel (hexane/ Et_2O 9:1, then 4:1) eluted successively [(naphthalene)$Cr(CO)_3$] (25 mg, 10 %), *exo*-**16** (66 mg, 24 %) and *endo*-**16** (81 mg, 30%). Complexes **16** were recrystallized from ether/hexane at -78 °C.

(endo-1-Methoxcyclobutabenzene)$Cr(CO)_3$ (endo-16). M.P.: 133-135 °C. IR ($CHCl_3$): 1968*s*, 1894*s*. ^{1}H-NMR (C_6D_6, 400 MHz): 4.81 (*d*, 1H, J = 6 Hz, H_{arom}), 4.44-4.49 (*m*, 2H, H-C(1) and H_{arom}), 4.06-4.09 (*m*, 2H, H_{arom}), 3.08 (*s*, 3H, OMe), 2.79 (*dd*, 1H, J = 2, 14 Hz, H_{endo}-C(2)), 2.54 (*dd*, 1H, J = 5, 14 Hz, H_{exo}-C(2)). HR-MS: calc. for $C_{12}H_{10}O_4Cr$ (M^+): 269.9984; found: 269.9983.

(exo-1-Methoxcyclobutabenzene)$Cr(CO)_3$ (exo-16). M.P.: 65-67 °C. IR ($CHCl_3$): 1975*s*, 1900*s*. ^{1}H-NMR (C_6D_6, 400 MHz): 4.98 (*d*, 1H, J = 6 Hz, H_{arom}), 4.55-4.58 (*m*, 2H, H-C(1) and H_{arom}), 4.29 (*t*, 1H, J = 6 Hz, H_{arom}), 4.11 (*t*, 1H, J = 6 Hz, H_{arom}), 2.95 (*s*, 3H, OMe), 2.93 (*dd*, 1H, J = 4, 14 Hz, H_{endo}-C(2)), 2.54 (*bd*, 1H, J = 14 Hz, H_{exo}-C(2)). Anal. calc. for $C_{12}H_{10}O_4Cr$: C 53.34, H 3.73; found: C 53.24, H 3.69.

3.4. endo- and exo-1-(2-Methoxyethoxymethyl)oxycyclobutabenzene $Cr(CO)_3$ (19). a) Preparation of 1-(2-methoxyethoxymethyl)oxycyclobutabenzene (18). To a solution of 1-hydroxycyclobutabenzene (**8**) (1.5 g, 12.5 mmol) in CH_2Cl_2 (15 ml) were added successively MEM-Cl (2.6 ml, 18.75 mmol) and N-ethyldiisopropylamine (3.2 ml, 18.69 mmol). After 2 h stirring at ambient temperature, water (25 ml) was added. The organic phase was separated and the aq. phase extracted repeatedly with ether. The combined organic phases were washed with brine, then dried over $MgSO_4$. After filtration and solvent removal, the crude oil was purified by chromatography (hexane/ether 4:1) to give ether **18** (2.38 g, 91 %).

1-(2-methoxyethoxymethyl)oxycyclobutabenzene (18). IR ($CHCl_3$): 3025*m*, 2925*m*, 1456*m*, 1356*w*, 1125*m*, 1100*s*. ^{1}H-NMR ($CDCl_3$, 200 MHz): 7.10-7.30 (*m*, 4H, H_{arom}), 5.21 (*dd*, 1H, J = 2, 5 Hz, H-C(1)), 4.95 (*d*, 1H, J = 11.5 Hz,-OCH_2O-), 4.91 (*d*, 1H, J = 11.5 Hz, -OCH_2O-), 3.76-3.81 (*m*, 2H, -OCH_2-C), 3.56-3.62 (*m*, 2H, -OCH_2-C), 3.50 (*dd*, 1H, J = 5, 14 Hz, H-C(2)), 3.41 (*s*, 3H, OMe), 3.16 (*dd*, 1H, J = 2, 14 Hz, H-C(2)). MS: 133 (7), 119 (6), 103 (26), 89 (39), 77 (17), 59 (100), 45 (51).

b) Complexation. A flame dried, thick wall glass vessel (25 ml) with a sealed on Teflon tap was charged with [(naphthalene)$Cr(CO)_3$] (267 mg, 1 mmol), 1-(MEM)oxycyclobutabenzene(**18**) (451 mg, 2.16 mmol), a magnetic stirring bar, and ether (7.8 ml). The mixture was degassed *via* 3 freeze/pump/thaw cycles and then stirred in the dark at 70 °C for 44 h. After cooling to ambient temperature, the mixture was filtered over celite and then reduced to dryness by an oil pump vacuum. A sample of the crude product was analyzed by HPLC (254 nm, hexane/*i*-Pr_2O 4:1 + 1% EtOH, 7 ml/min) and showed a *endo/exo* ratio of 4.6 : 1. Column chromatography of the crude product first eluted [(naphthalene)$Cr(CO)_3$] (hexane/ether 4:1), then *exo*-**19** (hexane/ether 1:1, 38.5 mg, 11 %), and finally *endo*-**19** (ether, 164 mg, 47 %). Analytically pure samples of *endo*- and *exo*-**19** were obtained by recrystallization from hexane/ether.

(endo-1-(2-Methoxyethoxymethyl)oxycyclobutabenzene)$Cr(CO)_3$ (endo-19). M.P.: 92-93 °C. IR ($CHCl_3$): 2925*w*, 2825*w*, 1975*s*, 1900*s*, 1137*w*, 1100*w*, 663*m*, 625*m*. ^{1}H-NMR (C_6D_6, 400 MHz): 5.14 (*d*, 1H, J = 6 Hz, H_{arom}), 4.66 (*d*, 1H, J = 7 Hz, -OCH_2O-), 4.57 (*d*, 1H, J = 7 Hz, -OCH_2O-), 4.56 (*dd*, 1H, J = 2, 5.5 Hz, H-C(1)), 4.47 (*d*, 1H, J = 6 Hz, H_{arom}). 4.43 (*t*, 1H, J = 6 Hz, H_{arom}), 4.09 (*t*, 1H, J = 6 Hz, H_{arom}), 3.72-3.78 (*m*, 1H, -OCH_2-C), 3.59-3.66 (*m*, 1H, -OCH_2-C), 3.33-3.39 (*m*, 2H, -C-CH_2-O-), 3.17 (*s*,

3H, -OMe), 2.97 (*dd*, 1H, *J* = 2, 14 Hz, H_{endo}-C(2)), 2.69 (*dd*, 1H, *J* = 5.5, 14 Hz, H_{exo}-C(2)). MS: 344 (3), 260 (4.3), 239 (1.8), 230 (14.9), 126 (17.4), 103 (8.2), 96 (26.3), 89 (4.4), 59 (21), 52 (100), 45 (24.4). Anal. calc. for $C_{15}H_{16}O_6Cr$: C 52.33, H 4.68; found: C 52.30, H 4.70.

(exo-1-(2-Methoxyethoxymethyl)oxycyclobutabenzene)Cr(CO)$_3$ (exo-19). M.P.: 55-56 °C. IR ($CHCl_3$): 2937*w*, 2825*w*, 2362*w*, 2345*w*, 1968*s*, 1894*s*, 1131*w*, 1094*w*, 663*m*, 625*m*. ^{1}H-NMR (C_6D_6, 400 MHz): 5.41 (*d*, 1H, *J* = 6 Hz, H_{arom}), 4.94 (*dd*, 1H, *J* = 2, 4.5 Hz, H-C(1)), 4.57 (*d*, 1H, *J* = 6 Hz, H_{arom}), 4.55 (*d*, 1H, *J* = 6.5 Hz, -OCH_2O-), 4.48 (*d*, 1H, *J* = 6.5 Hz, -OCH_2O-), 4.32 (*t*, 1H, *J* = 6 Hz, H_{arom}), 4.19 (t, 1H, *J* = 6 Hz, H_{arom}), 3.51-3.56 (*m*, 1H, -C-CH_2-O-), 3.37-3.42 (*m*, 1H, -C-CH_2-O-), 3.25-3.28 (*m*, 2H, -C-CH_2-O-), 3.13 (*s*, 3H, -OMe), 3.09 (*dd*, 1H, *J* = 4.5, 14 Hz, H_{endo}-C(2)), 2.76 (*dd*, 1H, *J* = 2, 14 Hz, H_{exo}-C(2)). MS: 344 (2.5), 260 (2.1), 239 (1.3), 230 (11), 126 (14), 103 (9.1), 96 (23.3), 89 (8.8), 59 (35.2), 52 (100), 45 (23.6). Anal. calc. for $C_{15}H_{16}O_6Cr$: C 52.33, H 4.68; found: C 52.35, H 4.71.

3.5. endo- and exo-1-(Tetrahydropyranyloxy)cyclobutabenzene Cr(CO)$_3$ (21). a) Preparation of 1-(tetrahydropyranyloxy)cyclobutabenzene (**20**). A mixture of 1-hydroxycyclobutabenzene (**8**) (1.0 g, 8.3 mmol), 3,4-dihydro-2H-pyran (1.74 g, 20.75 mmol), and a cat. amount of p-TsOH monohydrate in CH_2Cl_2 (30 ml) was stirred at ambient temperature. The progress of the reaction was followed by TLC. After 5h, ether (80 ml) was added and the organic phase washed successively with aq. sat $NaHCO_3$, water, and brine. Drying over $MgSO_4$ and solvent removal yielded a crude product which was purified by chromatography (hexane/ether). Product **20** (1.519 g, 90 %) was isolated as a ca.1:1 mixture of diastereomers. The same procedure was used for the reaction with (S)-**8** (93 % ee, 12 mmol scale) to afford (S,S)-/(S,R)-**20** in 94 % yield.

1-(Tetrahydropyranyloxy)cyclobutabenzene (20). IR ($CHCl_3$): 3034*m*, 3007*m*, 2946*s*, 2853*m*, 2402*w*, 1685*w*, 1541*w*, 1456*m*, 1339*m*, 1226*s*, 1210*m*, 1202*s*, 1125*s*, 1075*s*, 1039*s*. ^{1}H-NMR ($CDCl_3$, 400 Mhz): diastereoisomer A: 7.12-7.28 (*m*, 4H, H_{arom}), 5.29 (*dd*, 1H, *J* = 2, 4.5 Hz, H-C(1)), 4.98 (*bt*, 1H, *J* = 4 Hz, H-C_{ketal}), 3.93-4.03 (*m*, 1H,-OCH_2), 3.53-3.65 (*m*, 1H,-OCH_2), 3.56 (*dd*, 1H, *J* = 4.5, 14 Hz, H-C(2), 3.22 (*dd*, 1H, *J* = 2, 14 Hz, H-C(2)), 1.54-1.67 (m, 6H, -CH_2-). Diastereoisomer B: 7.12-7.28 (*m*, 4H, H_{arom}), 5.23 (*dd*, 1H, *J* = 2, 4.5 Hz, H-C(1)), 4.85 (*bt*, 1H, *J* = 4 Hz, H-C_{ketal}), 3.93-4.03 (*m*, 1H,-OCH_2), 3.53-3.65 (*m*, 1H,-OCH_2), 3.53 (*dd*, 1H, *J* = 4.5, 14 Hz, H-C(2), 3.16 (*dd*, 1H, *J* = 2,14 Hz, H-C(2)), 1.54-1.67 (m, 6H, -CH_2-). MS: 161 (0.1), 120 (5.5), 119 (4.8), 104 (2.7), 103 (25.2), 102 (5.8), 92 (1.2), 91 (7.1), 90 (1.9), 89 (2.8), 86 (6.2), 85 (100), 77 (13), 67 (19.5), 57 (28.2) 55 (12.1).

b) Complexation. A flame dried thick wall glass vessel (80 ml) with a sealed on Teflon tap was charged with [(naphthalene)$Cr(CO)_3$] (2.714 g, 10.3 mmol), 1-(THPoxy)cyclobutabenzene (**20**) (6.291 g, 30.8 mmol), a magnetic stirring bar, and ether (40 ml). The mixture was degassed via 3 freeze/pump/thaw cycles and then stirred in the dark at 70 °C for 12 h. After cooling to ambient temperature, the mixture was filtered over celite and then solvent was removed by vacuum. Column chromatography allowed recovery of excess **20**, and yielded the *endo*-**21** diastereomers (1.968 g, 56 %) and a fraction containing the *exo*-**21** diastereomers together with some recovered [(naphthalene)$Cr(CO)_3$].

Analogous conditions were used for the reaction with (S,S)-/(S,R)-**20** (93 % ee, 1S). The yield of complex **21** obtained was 61 % with a 33: 1 (94 % de) selectivity for (R,S,R)-/(R,S,S)-*endo*-**21** (analysis see text).

(endo-1-(tetrahydropyranyloxy)cyclobutabenzene)Cr(CO)$_3$ (endo-21). IR ($CHCl_3$): 2948*m*, 1971*s*, 1896*s*, 1428*w*, 1394*w*, 1333*w*, 1206*m*, 1131*m*, 1076*w*, 1036*m*. ^{1}H-NMR (C_6D_6, 400 MHz): selected resonances of diastereoisomer A: 4.78 (*dd*, 1H, *J* = 2, 5.5 Hz, H-C(1)), 3.01 (*dd*, 1H, *J* = 2, 14 Hz, H_{endo}-C(2)), 2.75 (*dd*, 1H, *J* = 5.5, 14 Hz, H_{exo}-C(2)). Selected resonances of diastereoisomer B: 4.58 (*dd*, 1H, *J* = 2.5, 5.5 Hz, H-C(1)), 2.93 (*dd*, 1H, *J* = 2.5, 14 Hz, H_{endo}-C(2)), 2.67 (*dd*, 1H, *J* = 5.5, 14 Hz, H_{exo}-C(2)). MS: 340

(8), 308 (1), 284 (6), 256 (18), 239 (2.6), 228 (1.4), 211 (1.9), 152 (41), 122 (10), 103 (11), 85 (24), 77 (12), 67 (9.7), 57 (13), 52 (100). Anal. calc. for $C_{16}H_{16}O_5Cr$): C 56.47, H 4.74; found: C 56.58, H 4.90.

3.6. Preparation of ((6aR)-(-)-1-oxocyclobutabenzene)Cr(CO)$_3$ (22). Acetic anhydride (1.3 ml) was added to a solution of (1S,6aR)-**4** (> 99 % ee) (64 mg, 0.25 mmol) in DMSO (2 ml) and the reaction was stirred for 3.5 h. Extraction with ether, washing of the organic phase with aq. $NaHCO_3$, water and brine, drying over $MgSO_4$ afforded after filtration and solvent evaporation crude complex **22**. Chromatography (hexane/ether 4:1) yielded pure (-)-**22** (58.3 mg, 92 %).

((6aR)-1-oxocyclobutabenzene)Cr(CO)$_3$ (6aR)-(-)-22). $[\alpha]_D^{20}$ = - 12.8, ($CHCl_3$, c = 0.36). IR ($CHCl_3$): 3684*w*, 3618*w*, 3022*s*, 2400*s*, 1990*s*, 1925*s*, 1775*w*, 1521*s*, 1424*s*, 1230*s*, 1202*s*, 1042*m*, 928*m*, 798*s*, 716*s*, 625*w*, 489*s*. ^{1}H-NMR (C_6D_6, 200 MHz): 4.79 (*d*, 1H, *J* = 6.5 Hz, H_{arom}), 4.42 (2 x *d*, *J* = 3, 3.5 Hz, H_{arom}), 3.8 (*ddd*, 1H, *J* = 3, 3.5, 6.5 Hz, H_{arom}), 3.34 (*d*, 1H, *J* = 16.5 Hz, -CH_2-), 3.04 (d, 1H, *J* = 16.5 Hz, -CH_2-). ^{13}C-NMR (C_6D_6, 50 MHz): 231.0, 183.0, 118.7, 105.8, 94.7, 81.1, 88.0, 86.4, 52.9. MS: 254 (3), 226 (1), 170 (7), 142 (25), 90 (10), 52 (100). Anal. calc. for $CrC_{11}H_6O_3$: C 51.98, H 2.38; found: C 52.19, H 2.51.

4. Cycloaddition Reactions

4.1. (1R,2R)- and (1R,2S)-1-hydroxy-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid methyl ester (23).[36] The cycloaddition reaction was carried out with (1S,6aR)-**5** (> 98 % ee) (259 mg, 0.868 mmol) following previously published procedures.[7b] Chromatography yielded a 3:1 mixture of the diastereoisomers (1R,2R)-(-)-**23** and (1R,2S)-(+)-**23** (125 mg, 70 %). The enantiomeric purities of the products were determined by ^{19}F-NMR spectroscopy after derivatization with S-(+)-MTPA-Cl. (1R,2R)-(-)-**23**: 90 % ee, $[\alpha]_D^{20}$ = -36 ($CHCl_3$, c = 1.26).[36a] (1R,2S)-(+)-**23**: 93 % ee, $[\alpha]_D^{20}$ = + 106 (EtOH, c = 1.94).[36a]

4.2. (1S,2R)- and (1S,2S)-2-benzenesulfonyl-1,2,3,4-tetrahydronaphthalen-1-ol (24). The cycloaddition reaction was carried out with (1S,6aR)-**4** (> 99 % ee) (128. mg, 0.5 mmol) following previously published procedures.[7b] Chromatography yielded a 1:7 mixture of the diastereoisomers (1S,2R)-**24** and (1S,2S)-**24** (118.8 mg, 83 %). The enantiomeric purity of (1S,2S)-(-)-**24** was determined by ^{19}F-NMR spectroscopy after derivatization with S-(+)-MTPA-Cl to be > 97 %. The optical rotation was measured on a sample of > 99 % ee obtained after recrystallization from hexane/EtOH. (1S,2S)-(-)-**24**: $[\alpha]_D^{20}$ = -79.5 ($CHCl_3$, c = 1.9)

4.3. (1S, 2S, 3S)-2-benzenesulfonyl-3-phenyl-1,2,3,4-tetrahydronaphthalen-1-ol (25). The cycloaddition reaction was carried out with (1S,6aR)-**4** (> 99 % ee) (128. mg, 0.5 mmol) following previously published procedures.[7b] Chromatography yielded a single diastereoisomer: (1S,2S,3S)-**25** (144.3 mg, 79 %). The enantiomeric purity was determined by ^{19}F-NMR spectroscopy after derivatization with S-(+)-MTPA-Cl to be >99 %. (1S,2S,3S)-**25**: $[\alpha]_D^{20}$ = -59 ($CHCl_3$, c = 1.2)

5. Alkylation, allylation, benzylation of the enolate 26.

5.1. Ethyl iodide : (1S,2R)-cis-1-hydroxy-2-ethyl-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid methyl ester (27). The enolate **26** was generated from a 3:1 mixture of (1R,2R)-**23** et (1R,2S)-**23** (182.7 mg, 0.89 mmol) and reacted with ethyl iodide as described previously.[7b] Workup and purification afforded (1S,2R)-**27** (141.8 mg, 68 %) and HPLC and ^{1}H-NMR spectroscopy of the crude product indicated that a single diastereomer was formed. The enantiomeric excess was determined to be 90% by ^{19}F-NMR analysis after derivatization with S-(+)-MTPA-Cl. (1S,2R)-**27**: $[\alpha]_D^{20}$ = - 6.3 ($CHCl_3$, c = 4.4)

5.2. Allyl bromide: (1S,2S)-cis-2-allyl-1-hydroxy-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid methyl ester (28). The enolate **26** was generated from a 3:1 mixture of (1R,2R)-**23** et (1R,2S)-**23** (126.9 mg, 0.616 mmol) and reacted with allyl bromide as described previously.[7b] Workup and purification afforded (1S,2S)-**28** (108.6 mg, 72 %) and HPLC and ^{1}H-NMR of the crude product indicated that a single diastereomer was formed. The enantiomeric excess was determined to be 88% by ^{19}F-NMR analysis after derivatization with S-(+)-MTPA-Cl. (1S,2S)-**28**: $[\alpha]_D^{20}$ = - 32 ($CHCl_3$, c = 1.8).

5.3. Benzyl bromide: (1S,2S)-cis-2-benzyl-1-hydroxy-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid methyl ester (29). The enolate **26** was generated from a 3:1 mixture of (1R,2R)-**23** et (1R,2S)-**23** (153.7 mg, 0.746 mmol) and reacted with benzyl bromide as described previously.[7b] Workup and purification afforded (1S,2S)-**29** (141.3 mg, 64 %). The enantiomeric excess was determined to be 88% by ^{19}F-NMR analysis after derivatization with S-(+)-MTPA-Cl. Crystallization from hexane (71 % yield) afforded a product of >99 % ee. (1S,2S)-**29**: $[\alpha]_D^{20}$ = - 56.5 ($CHCl_3$, c = 1.2).

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