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Catalytic Asymmetric Induction Part 2. Chiral Tricarbonyl (η6 arene) Chromium (0) Complexes as Enantioselective Catalysts[1]

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Abstract: A chiral metallocyclic Lewis acid based catalyst system derived from norephedrine is reported. A key stereodirective element emanates from a tricarbonyl chromium (0) group complexed to the aryl ring. The catalysts mediate the addition of dialkyl zinc species to a variety of aldehydes with high enantioselectivity.

Introduction:

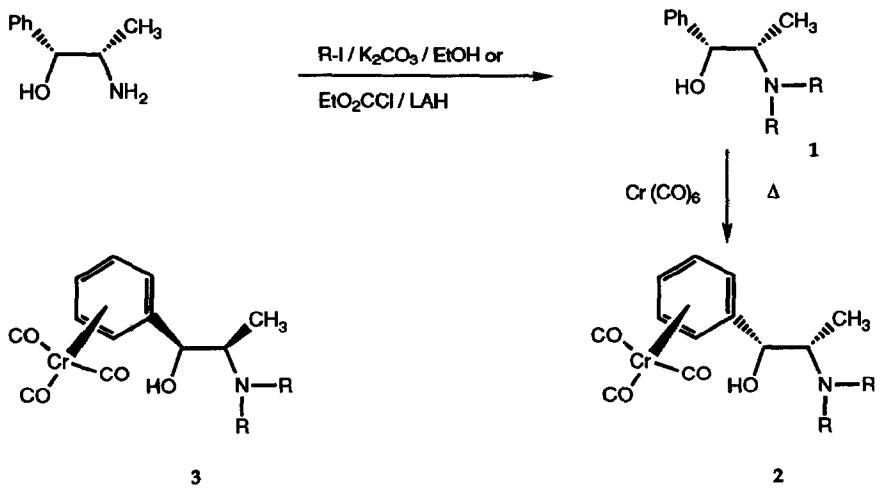
The chemistry of η6 arene chromium tricarbonyl complexes is both rich and varied, and their synthetic utility has been demonstrated by a number of research groups over the last few years.[2] By virtue of the steric bulk that the chromium carbonyl group offers complexed to one face of an arene, enantiocontrol in asymmetric processes involving organo arene chromium tricarbonyl complexes where the active chiral transition state involved is in close proximity to the chromium tricarbonyl group is usually extremely high.[3] This effect has been utilized recently in enantioselective alkylations,[4] allylborations,[5] aldol reactions[6] and cycloadditions.[7] Another benefit is that by virtue of its electron withdrawing capacity (from an arene ring), the chromium tricarbonyl tripod posseses a dipole moment,[8] which may be exploited by encouraging attractive interactions between it and a substrate in a transition state assembly. Such stereodirective and attractive capacity had yet to be harnessed in the form of a catalytic system, and was the goal of this investigation.[9]

Discussion:

The development of chiral controller ligands for use in catalytic enantioselective processes has been widespread over the past few years, reflecting the general importance of such facility.[10] It was desired to develop a novel family of chiral controller ligands which (i) could be synthesized from readily available precursors, and (ii) could utilize the stereodirective and dipole attractive effects inherent to arene chromium tricarbonyl complexes. The tricarbonyl arene chromium (0) moiety has a number of distinct advantages associated with it, and would seem particularly well suited to incorporation into a chiral catalyst : In addition to the obvious benefits associated with having such a large steric bulk in a transition state, the metal carbonyl tripod could also participate in a transition state assembly with attractive dipole based interactions between the tricarbonyl arene chromium (0) group and any appendage(s) involved in the reacting species and / or ligand which have (or can temporarily develop) an appreciable dipole moment.[5,7,8] Based on the above rationale, and in order to quickly investigate this potentially rich field, distinct catalyst types were designed, and their effectiveness in catalytic enantioselective additions to aldehydes investigated. (1R, 2S) Norephedrine was chosen as the initial ligand system, the rationale being that a transition state assembly as depicted in Figure 1 would function as anticipated, as a highly enantioselective catalyst system for the addition of dialkyl zincs to aldehydes. Accordingly, (1R, 2S) norephedrine was bis

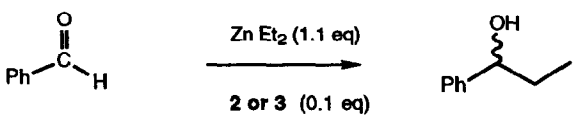
alkylated to give N,N dialkyl precursors **1** using a variety of alkyl iodides (Scheme 1). The bis alkylated norephedrines were then subjected to tricarbonyl arene chromium (0) complexation, which was best achieved using chromium hexacarbonyl, to give catalyst precursors **2** in quantitative yield.[11] Correspondingly, the catalyst precursors derived from (1S, 2R) norephedrine, **3**, were also prepared. Deprotonation of **2/3**, (R=alkyl) using diethyl zinc in hexane (or toluene) gave the corresponding zinc alkoxides, which proved to be highly selective catalysts for the addition of diethyl zinc to aldehydes (Scheme 2).

Scheme 1. Formation of tricarbonyl arene chromium (0) catalyst precursors from norephedrines.



The relationship between the N,N dialkyl substituent (R) and the observed e.e. in the catalytic enantioselective addition of diethyl zinc to benzaldehyde was examined first. The results are summarised in Table 1.

Scheme 2. Enantioselective alkylation of benzaldehyde.



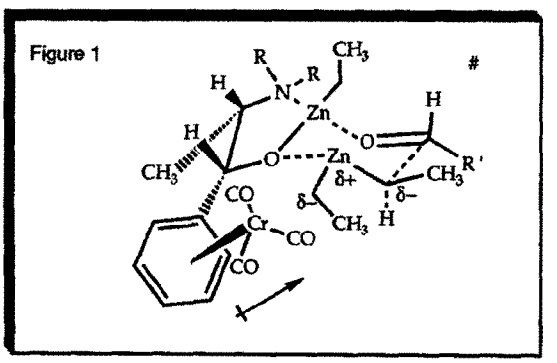
Our initial catalyst was the N,N dimethyl catalyst derived from **2**, (R= Me) and using 10 mole % obtained a 99% yield of (R)- 1-phenyl propanol, in 86% e.e. (entry 1).[1] The control reaction using the same catalyst but devoid of the tricarbonyl (η6 arene) chromium (0) group gave the product carbinol in similarly high yield, but with diminished enantioexcess (entry 2). Switching to a cyclopiperidyl catalyst **3**, (R=-$(CH_2)_5$-), (S)- 1-phenyl propanol was obtained in excellent yield and high e.e. (entry 3). The control reaction again confirmed the positive effects of the tricarbonyl (η6 arene) chromium (0) group (entry 4), but the most selective catalysts of all were realized in **2, 3** R=Bu. The (1R, 2S) derived catalyst gave the (R) product carbinol and the (1S, 2R) gave the (S) carbinol in >99% e.e. in both cases (entries 5, 7). The control reactions (entries 6, 8) showed

the catalyst template itself to be effective (in agreement with the results of Soai),[12] but the added benefit of the tricarbonyl (η6 arene) chromium (0) group had transformed the catalyst into a genuinely versatile system.

Table 1. Formation of 1- phenyl propanol using norephedrine based catalysts **2** and **3**

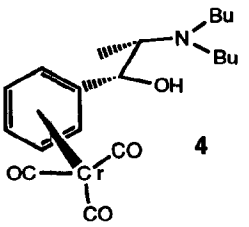
	Catalyst			Product	
Entry	Ligand	R group	%yield	% e.e.	config.
1	**2**	Me	99	86	R
2	**2**, uncomplexed	Me	99	67	R
3	**3**	-(CH2)5-	99	96	S
4	**3**, uncomplexed	-(CH2)5-	99	90	S
5	**2**	Bu	99	99	R
6	**2**, uncomplexed	Bu	99	94	R
7	**3**	Bu	99	99	S
8	**3**, uncomplexed	Bu	99	94	S

The origin of the extremely high selectivity observed in these reactions can be attributed to a possible transition state assembly, as shown in Figure 1. The chiral zinc metallocycle coordinates the incoming aldehyde in such a way as the R' group is shielded from the N,N dialkyl groups. An incoming equivalent of dialkyl zinc (diethyl zinc illustrated) coordinates to the oxygen of the metallocycle, and in doing so becomes polarized, and as such is activated for addition to the aldehyde. This coordinated alkyl zinc is stabilized by attractive dipole-dipole interactions with the chromium tricarbonyl group, and the stabilization itself helps establish a six membered



chair transition state for the addition, allowing intramolecular delivery of the alkyl group in a controlled manner. In this way, the (1R, 2S) derived catalysts give as predicted the (R) enantiomeric carbinols, and the (1S, 2R) catalysts give the (S) carbinols. The transition state proposed accounts for the fact that aryl aldehydes give slightly higher enantioexcess than alkyl aldehydes (see Table 2) since the bulk of the R' group will dictate the degree to which the aldehyde will coordinate as shown, with the R' group preferentially equatorial in the envisioned six membered chair. In support of this attractive interaction ordered transition state theory, is the fact that an impure mixture (ca. 3:1) of precursor **2**, **(R= Bu)** and **1**, **(R=Bu)** gave on treatment with 1 eq.

of diethyl zinc, a catalyst system which still delivered diethyl zinc to benzaldehyde (0°C/ hexanes / 12h) in 99% e.e. using 15 mol % of the catalyst. The enhanced reactivity of the tricarbonyl arene chromium (0) based catalysts can therefore be explained by increased transition state activation, and as expected, it is found that crude **2, (R=Bu)** (containing up to 20%of **2, (R=Bu)** can be used with little or no loss in e.e. for the reactions reported herein. An alternative transition state assembly could be invoked in which the chromium tricarbonyl group provides steric buttressing only, and as such directs the incoming dialkyl zinc species to the upper face of the metallocycle. Selective coordination of the aldehyde, again on the upper face of the metallocycle would then account for the observed stereocontrol in the alkylation process. Such a transition state would however involve a half chair conformation.[13] The N,N dibutyl catalysts (viz. **4, 5**) were selected for



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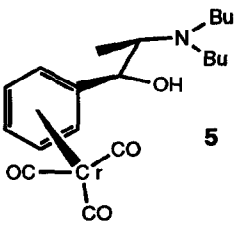

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further study. A natural extension of this highly enantioselective process was to explore the potential of using a range of alkyl zinc species as alkyl donors in order to effect the corresponding 1,2 alkyl addition to a number of aldehydes, as depicted in Scheme 3. It was important that such a strategy offer high enantioselectivity, in order that a process that is truly complimentary to the enantioselective reduction of (the derived) ketones be realized. Since both diethyl and dimethyl zinc are commercially available, and a variety of dialkyl zinc reagents are available by synthesis, the strategy is potentially versatile.[14] The results of this study are presented in Table 2, which documents our results using three different alkyl zincs and a variety of alkyl and aryl aldehydes. Nearly total selectivity was achieved in the addition of diethyl zinc to the napthaldehydes, with only traces of the other enantiomer detectable by chiral H.P.LC. analysis (entries 1&2). The results using other aromatic (entries 3,4) and aliphatic (entries 5, 7) aldehydes were also very good, using 10 mole % of the catalyst.[15] Alkyl addition proceeded smoothly and with high enantioexcess using dimethyl zinc with benzaldehyde (entry 8), and a control reaction using a catalyst devoid of the chromium tricarbonyl group again confirmed the utility behind the catalyst design (entry 9). Dimethyl zinc addition to other aromatic aldehydes proceeded with good e.e., but using dihydrocinnamaldehyde, the e.e. fell to 81% (entry 12). A similar result was obtained with the tert butyl dimethyl silyl ether of 7-hydroxy heptanal (entry 14),[16] so control reactions were run using

Scheme 3. Enantioselective additions of alkyl zincs to various aldehydes

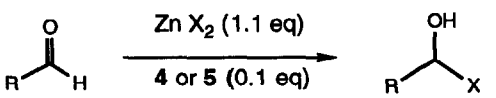


Table 2. Enantioselective alkylation of aldehydes using zinc alkoxides of **4 / 5**

Entry	Catalyst	Alkyl Zinc X	Aldehyde R	%yield	%e.e.
1	5	Et	1-napthyl	98%	>99%
2	4	Et	2-napthyl	99%	>99%
3	5	Et	p-anisyl	99%	94%
4	4	Et	9-phenanthryl	97%	93%
5	5	Et	dihydrocinnamyl	89%	92%
6	5(uncomplexed)	Et	dihydrocinnamyl	90%	38%
7	5	Et	aldehyde **6**	88%	85%
8	5	Me	phenyl	85%	92%
9	4(uncomplexed)	Me	phenyl	90%	81%
10	5	Me	1-napthyl	95%	92%
11	5	Me	2-napthyl	90%	94%
12	5	Me	dihydrocinnamyl	87%	81%
13	5(uncomplexed)	Me	dihydrocinnamyl	89%	39%
14	4	Me	7-hydroxyheptanal(TBDPS ether)	82%	85%
15	4(uncomplexed)	Me	7-hydroxyheptanal(TBDPS ether)	60%	19%
16	5	Me	4-benzyloxy butanal	86%	72%
17	4	Me	5-hexyn-1-al	95%	64%
18	5	Bu	phenyl	75%	91%
19	5	Bu	2-napthyl	95%	93%

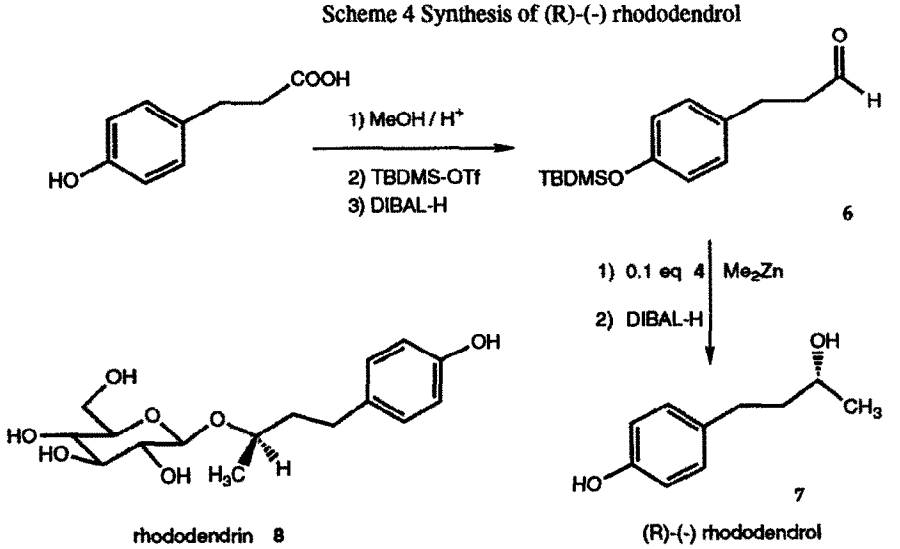
uncomplexed catalysts (entries 13 & 15 respectively). After repeated runs and careful analysis, the maximum e.e. obtained for the methyl addition to dihydrocinammaldehyde using non complexed catalyst was less than 40%. In the case of the hydroxyheptanal, the maximum e.e. was even lower still. Addition of di n-butyl zinc to aromatic aldehydes proceeded in good e.e. (entries 18 and 19), and in all cases examined, the chemical yields of product carbinols were excellent, and the catalysts were recovered in near quantitative yield on work up, suitable for reuse. *The results served to reinforce the idea of the use of the arene chromium tricarbonyl catalysts, since reasonable e.e.'s were attainable, and were routinely reproducible using aldehyde substrates which typically give low selectivity in dialkyl zinc addition reactions.*[15]

A number of studies were carried out in order to determine the effects of solvents on the rate and e.e. of the reactions. Within the limits of experimental error, it was observed that the reactions studied herein gave identical results when conducted either in a mixture of hexane: toluene or toluene alone. Results were slightly inferior using neat hexane as solvent. However, using methylene chloride, though the e.e. did not change, the reaction rates were slowed significantly. Interestingly, using methylene chloride as the solvent with ultrasound sonication of the reaction vessel, the rate of reaction was speeded up significantly, but the added heating effect caused by the sonication led to a slight drop in e.e. such that for entry 14 in Table 2, the maximum e.e. obtained using this method was 61%, *but complete reaction was achieved in only 2h.*[17] No improvement in e.e. was noticed by conducting the reactions at lower temperatures, this only serving to retard the rates of reaction, such that they became sluggish at -10°C, and stunted at -20°C. No reaction occurred at -40°C even

after several days. Optimum conditions were determined to be between 0 and +5°C, since warming to room temperature was shown to have a marginally detrimental effect on overall %e.e.. In accord with the observation of others, the ratio of dialkyl zinc to aldehyde had a marked effect on the rate of the reactions, but not the e.e. or chemical yields.[18] It was found best to use a catalyst: dialkyl zinc: aldehyde ratio of 0.1: 4: 1, giving consistently the fastest conversion to product, and consistently high e.e..

Finally, in order to demonstrate the synthetic utility of the enantioselective alkylation procedure, a synthesis of (R)-(-) rhododendrol **7**, the aglycone of the hepatoprotecive agent rhododendrin (**8**) isolated from *Taxus baccata* was executed (Scheme 4).[19] Aldehyde **6** was prepared from the commercially available *p*-hydroxy 3-phenyl propanoic acid. The required enantioselective methylation was performed using the methyl zinc alkoxide of catalyst **4** giving the desired (R) enantiomeric carbinol in 85% e.e.. Mild silyloxy deprotection of the carbinol was accomplished using DIBAL-H [20] to give (R)-(-) rododendrol **7**, in 98% yield. In a similar manner, using catalyst **5**, (S)-(+) rhododendrol, a constituent of *Rhododendron maximum* was synthesized in 95% overall yield and in 85 % e.e..[21]

Scheme 4 Synthesis of (R)-(-) rhododendrol



Conclusion:

A new family of enantioselective catalysts has been developed, which mediate the addition of dialkyl zincs to aldehydes with good to excellent enantioselectivity. The catalysts operate on the basis of secondary attractive interactions in the transition state assembly, achieved by incorporation of a tricarbonyl (η6 arene) chromium (0) complex. The catalysts are versatile and mediate highly selective additions, which in a variety of cases give the most selective alkylations yet reported using dialkyl zincs.[10] Since the catalysts are available from the chiral pool, and formation of the precursors is a trivial operation, application of the described methodology to the enantioselective synthesis of pharmaceuticals and agrochemicals is a viable possibility. The basic design features incorporated into the described catalyst systems offer potential for future development and extension in a wide variety of catalyst and controller systems, and is the subject of ongoing effort in this group.

Acknowledgement

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EXPERIMENTAL SECTION

General procedures

All oxygen and moisture sensitive reactions described herein were performed in glassware which had been oven dried (140°C / 12h) and flame dried prior to use. Reactions were conducted under an atmosphere of nitrogen, using pre-dried septa. The tips of cannulae were flame dried under a stream of dry nitrogen gas prior to use. Butyl ether, THF and diethyl ether were distilled immediately prior to use from sodium / benzophenone ketyl. Methylene chloride was distilled from P_2O_5. All other reagents and solvents were purified according to standard convention. Hexacarbonyl chromium and dimethyl zinc were obtained from Strem chemicals. Diethyl zinc was purchased from the Aldrich chemical company. Dibutyl zinc was prepared in accordance with literature reports.[14] Silica gel chromatography was perfomed on 70-240 mesh according to the method of Still.[21] Analytical t.l.c. was perfomed on glass backed 250μ plates visualizing with anisaldehyde and phosphomolybdic acid. ^1H spectra were recorded at 300 MHz and ^{13}C spectra at 75 MHz, both on a Bruker AM 300 instrument. Mass spectra were recorded on a Hewlett Packard 59-85B GC / MS system. Chiral HPLC was conducted using an Isco 2350 isocratic pump coupled to an Isco V^4 detector set at 254 nM. Data were analyzed on a Hewlett Packard 3396 series II integrator. Enantiomer separations were conducted using Diacel Chiralcel analytical columns (4.6 x 250 mm). In all cases, racemic samples of the product carbinols to be analysed (prepared by the addition of Grignard reagents to the requisite aldehydes) were run on the HPLC *prior to and following* injection of the enantiomerically enriched samples. Microanalyses were performed at Atlantic Microlab, Norcross, GA. Stereochemistry indicated for the product alcohols is assigned on the basis of comparison of optical rotation data of known compounds. For new compounds the assignments are therefore necessarily tentative. [In agreement with the work of others,[12] the catalysts derived from (1R, 2S) norephedrine (**2**) consistently mediated enantioselective alkylations of aldehydes to give (R) product carbinols both in the arene complexed and uncomplexed series, and the (1S, 2R) norephdrine derived catalysts (**3**) gave (S) product carbinols].

Preparation of catalyst precursors **2, 3**

The following procedure was found to be optimium, and is suitable for the preparation of all the catalyst precursors described in this manuscript: Preparation of catalyst (1R, 2S) **2**, (R= butyl) [= **4**]: (1R,2S) N,N dibutyl norephedrine (0.480 g, 1.83 mmol),[12] and hexacarbonyl chromium (1.21 g, 5.49 mmol) were placed in a flame dried round bottomed flask fitted with a reflux condenser. The contents were evacuated and purged with argon three times. A 7.5 : 2.5 mixture of deoxygenated di-n-butyl ether: THF (25 ml) was cannulated into the flask, and the resulting mixture was heated to reflux under argon for 12 h. The mixture was cooled to -40°C, warmed to room temperature, filtered through a fritted funnel, thence through a plug of 60 H silica gel. The washings were subjected to dry flash chromatography (1:1 ether:hexanes eluent), to yield the complex **2** R= butyl (=**4**) (0.728 g, 99.8%) as a deep yellow oil; $[\alpha]_D$ +42.9 (c 4.04, benzene); (Found: C, 60.18; H, 7.30; N, 3.49. $C_{20}H_{29}NO_3Cr$ requires C, 60.14; H, 7.32; N, 3.5 %); R_f 0.45 (1:1 hexane : ether); υ_{max} (neat)/ cm^{-1} 3445, 3093, 2959, 2931, 2861, 1975, 1884, 1870, 1455, 667 and 632; δ_H (300 MHz; $CDCl_3$) 5.20-5.50 (5H, m), 4.15 (1H, s), 3.70 (1H,br s), 2.90 (1H, q, *J* 6.65 Hz), 2.30 (4H, t, *J* 7.60 Hz), 1.20-1.40 (8H, m), 1.10

(3H, d, *J* 6.84 Hz) and 0.88 (6H, 2 x t, *J* 7.0 Hz) ; δ_C (75 MHz; $CDCl_3$) δ 233.1, 115.5, 92.58, 92.3, 91.97, 91.89, 89.7, 72.2, 60. 85, 50.58, 30.57, 20.4, 14.0 and 10.06; m/z (EI) 400 (M^+, 12 %), 382 (8), 264 (11), 246 (11) and 156 (100).

2, R= methyl

prepared from **1**, R=methyl[12] as a deep yellow oil; $[\alpha]_D$ +16.1 (c 4.0, EtOH); R_f0.40 (1:1 hexane : ether); δ_H (300 MHz; $CDCl_3$) 5.1-5.7 (5H, m), 4.5 (1H, s), 2.4 (1H, m), 2.30 (6H, s) and 0.9 (3H, d, *J* 6.46 Hz); δ_C (75 MHz; $CDCl_3$) δ 233.1, 114.8, 92.8, 92.7, 91.76, 90.8, 90.2, 71.3, 65.5, 42.7 and 9.3.

2, R=-$(CH_2)_5$-

prepared from **1**, R=-$(CH_2)_5$-[12] as a deep yellow oil; $[\alpha]_D$ +47.8 (c 5.5, EtOH); R_f0.950 (1:1 hexane : ether); δ_H (300 MHz; $CDCl_3$) 5.20-5.50 (5H, m), 4.3 (1H, d, *J* 4.87 Hz), 3.80 (1H,br s), 2.5-2.6 (5H, m), 1.4-1.5 (6H, m), and 0.90 (3H, d *J* 6.7 Hz) ; δ_C (75 MHz; $CDCl_3$) δ 233.1, 115.0, 92.67, 92.58, 91.80, 91.3, 89.9, 71.3, 65.0, 51.3, 26.3, 24.3 and 9.9.

Enantioselective addition of alkyl zincs to aldehydes using catalysts **4** and **5**:

The following experimental procedure is typical: (R)-(+) 1-(9-phenanthryl)propan-1-ol. Phenanthrene-9-carboxaldehyde (0.064 g, 0.31 mmol) and catalyst **4** (0.012 g, 0.031 mmol) were placed in a flame dried flask which was fitted with a septum, then purged with nitrogen. Dry toluene (10ml) was cannulated into the flask and the solution cooled to 0°C with stirring. Diethyl zinc (0.47 ml, 0.47 mmol 1M, hexanes) was added down the walls of the flask over 15 min. The reaction was stirred for 12h at 0°C, quenched by the addition of saturated aqueous ammonium chloride solution (10 ml), and then extracted into ether (3 x 20 ml). The ethereal extracts were dried ($MgSO_4$), filtered, then the solvent was removed *in vacuo*, and the crude product carbinol was purified by flash chromatography (9:1 hexanes: ethyl acetate eluents) to give pure (R)-(+) 1-(9-phenanthryl)propan-1-ol (0.071 g, 97%) as a colourless solid m.p. 87-88°C $[\alpha]_D$ +53.57 (c 1.95, $CHCl_3$); (Found: C, 86.24; H, 6.87. $C_{17}H_{16}O$ requires C, 86.44; H, 6.78 %); R_f0.60 (1:1 hexane : ether); υ_{max} (nujol) / cm^{-1} 3290, 3198, 2931, 2854, 1462, 1377, 737 and 723; δ_H (300 MHz; $CDCl_3$) 8.75 (1H, d, *J* 7.67 Hz), 8.65 (1H, d, *J* 7.88 Hz), 8.1 (1H, d, *J* 8.78 Hz), 7.9 (2H,m), 7.57-7.67 (4H, m), 5.4 (1H, q, *J* 7.5, 4.6 Hz), 2.0 (2H, m), 1.58 (1H, br s) and 1.00 (3H, t, *J* 7.4 Hz) ; δ_C (75 MHz; $CDCl_3$) δ 128.7, 126.7, 126.6, 126.2, 123.9, 123.7, 123.4, 122.47, 72.8, 30.8 and 10.6; HPLC conditions: Chiralcel OD column, flow rate 1ml / min, 10% isopropanol 90% hexane eluent, major enantiomer 14.8 min, minor 17.2 min.

(S)-1-(1-napthyl)propan-1-ol

R_f0.60 (1:1 hexane : ether); δ_H (300 MHz; $CDCl_3$) 8.1 (1H, *d*, J 8.3 Hz), 7.88 (1H, *d*, J 7.09 Hz), 7.78 (1H, d, *J* 8.22 Hz), 7.64 (1H, d, *J* 6.84 Hz), 7.45-7.54 (3H, m), 5.4 (1H,q, *J* 5.0, 7.46 Hz), 2.0 (3H, m) and 1.00 (3H, t, *J* 7.3 Hz) ; δ_C (75 MHz; $CDCl_3$) δ 140, 134, 130, 128.9, 127.9, 125.9, 125.5, 123.2, 122.9, 72.6, 31.1 and 10.57; HPLC conditions: Chiralcel OD column, flow rate 1ml / min, 10% isopropanol 90% hexane eluent, major enantiomer 7.9 min, minor 13.4 min.

(R)-1-(2-napthyl)propan-1-ol

m. p. 35-37°C; R_f0.40 (1:1 hexane : ether); δ_H (300 MHz; $CDCl_3$) 7.8 (4H, m), 7.4 (3H, m), 4.74 (1H,t, *J* 6.5 Hz), 2.05 (1H, br s), 1.80 (2H, m) and 0.92 (3H, t, *J* 7.4 Hz) ; δ_C (75 MHz; $CDCl_3$) δ 141, 133.2, 132.9, 128.2, 127.9, 127.7, 126.1, 125.7, 124.7, 124.1, 76.1, 31.7 and 10.2; HPLC conditions: Chiralcel OD column, flow rate 1ml / min, 10% isopropanol 90% hexane eluent, major enantiomer 28.8 min, minor 26.4 min.

(R)-1-(phenyl)pentan-3-ol

R_f0.45 (1:1 hexane : ether); δ_H (300 MHz; $CDCl_3$) 7.36-6.97 (5H, m), 3.56 (1H,m), 2.7 (2H, m), 1.7 (2H, m), 1.5 (3H, m) and 0.94 (3H, t, *J* 7.4 Hz) ; δ_C (75 MHz; $CDCl_3$) δ 142.2, 128.4, 125.7, 72.6, 38,59, 32.08, 30.3 and 9.86; HPLC conditions: Chiralcel OD column, flow rate 1ml / min, 5% isopropanol 95% hexane eluent, major enantiomer 8.8 min, minor 12.2 min.

(S)-1-(*p*-anisyl)propan-1-ol

R_f0.55 (1:1 hexane : ether); δ_H (300 MHz; $CDCl_3$) 7.2 (2H, d, *J* 8.9 Hz), 6.8 (2H, d, *J* 8.9 Hz), 4.5 (1H, t, *J* 6.7 Hz), 3.78 (3H, s), 2.13 (1H, br s), 1.67-1.87 (2H, m) and 0.87 (3H, t, *J* 7.4 Hz) ; δ_C (75 MHz; $CDCl_3$) δ 158.9, 136.7, 127.2, 113.6, 75.6, 55.2, 31.7 and 10.2; HPLC conditions: Chiralcel OD column, flow rate 1ml / min, 10% isopropanol 90% hexane eluent, major enantiomer 7.71 min, minor 6.90 min.

(S)-1-(4-tertbutyl dimethylsilyloxy phenyl)pentan-3-ol

$[\alpha]_D$ +11.9 (c 0.05, $CHCl_3$); (Found: C, 69.33; H, 10.25. $C_{17}H_{30}SiO_2$ requires C, 69.33; H, 10.27 %); R_f0.55 (1:1 hexane : ether); υ_{max} (neat)/ cm^{-1} 3353, 2959, 2931, 2861, 1609, 1511, 1258, 920, 843 and 780; δ_H (300 MHz; $CDCl_3$) 7.04 (2H, d, *J* 8.43 Hz), 6.75 (2H, d, *J* 8.43 Hz), 3.5 (1H, m), 2.6-2.7 (2H,m), 1.4-1.8 (4H, m), 0.91-0.97 (15H, m) and 0.18 (6H, s) ; δ_C (75 MHz; $CDCl_3$) δ 153.5, 134.8, 129.2, 119.9, 72.7, 38.76, 31.2, 30.3, 25.7, 19.8, 9.8 and –4.40; Deprotected for HPLC analysis: HPLC conditions: Chiralcel OD column, flow rate 1ml / min, 10% isopropanol 90% hexane eluent, major enantiomer 14.2 min, minor 12.6 min.

(S)-1-(phenyl)ethanol

R_f0.40 (1:1 hexane : ether); δ_H (300 MHz; $CDCl_3$) 7.4-7.15 (5H, m), 4.75 (1H, q, *J* 6.47 Hz), 3.17 (1H,br s) and 1.3 (3H, d, *J* 6.58 Hz) ; δ_C (75 MHz; $CDCl_3$) δ 145.8, 128.2, 127.1, 125.3, 69.96 and 24.97; HPLC conditions: Chiralcel OD column, flow rate 1ml / min, 2.5% isopropanol 97.5% hexane eluent, major enantiomer 15.8 min, minor 13.2 min.

(S)-1-(1-napthyl)ethanol

m. p. 70-71°C; $[\alpha]_D$ -60.23 (c 0.44, EtOH); R_f0.55 (1:1 hexane : ether); δ_H (300 MHz; $CDCl_3$) 8.1 (1H, d, *J* 9.15 Hz), 7.87 (1H, d, *J* 7.30 Hz), 7.76 (1H, d, *J* 8.16 Hz), 7.66 (1H, d, *J* 7.08 Hz), 7.2-7.5 (3H, m), 5.6 (1H, q, *J* 6.45, 12.9 Hz), 1.96 (1H, br s) and 1.65 (3H, d, *J* 6.4 Hz) ; δ_C (75 MHz; $CDCl_3$) δ 141.3, 133.8, 130.2, 128.9, 127.9, 126.0, 125.5, 123.1, 121.99, 67.1 and 24.4; HPLC conditions: Chiralcel OD column, flow rate 1ml / min, 6% isopropanol 94% hexane eluent, major enantiomer 13.9 min, minor 22.2 min.

(S)-1-(2-napthyl)ethanol

m. p. 71°C; $[\alpha]_D$ -20.9 (c 1.22, EtOH); R_f0.50 (1:1 hexane : ether); δ_H (300 MHz; $CDCl_3$) 7.8 (4H, m), 7.4 (3H, m), 5.0 (1H,q, *J* 6.5 Hz), 1.89 (1H, br s) and 1.58 (3H, d *J* 6.45 Hz) ; δ_C (75 MHz; $CDCl_3$) δ 143,

133.3, 133, 128.3, 127.9, 127.7, 126.2, 125.8, 123.8, 70.5 and 25.2; HPLC conditions: Chiralcel OJ column, flow rate 1ml / min, 6% isopropanol 94% hexane eluent, major enantiomer 16.5 min, minor 21.3 min.

(S)-4-(phenyl)butan-2-ol
$[\alpha]_D$ +13.03 (c 4.85, $CHCl_3$); R_f0.51 (1:1 hexane : ether); δ_H (300 MHz; $CDCl_3$) 7.14-7.3 (5H, m), 3.8 (1H, m), 2.7 (2H,m), 1.75 (2H, m), 1.7 (1H, br s) and 1.2 (3H, d, *J* 2.4 Hz) ; δ_C (75 MHz; $CDCl_3$) δ 142.0, 128.4, 125.8, 67.4, 40.8, 32.1 and 23.58; HPLC conditions: Chiralcel OD column, flow rate 1ml / min, 5% isopropanol 95% hexane eluent, major enantiomer 10.6 min, minor 15.3 min.

(R)-8-hydroxy octan-2-ol-8-tertbutyl diphenylsilyl ether
$[\alpha]_D$ +14.1 (c 13.7, $CHCl_3$); (Found: C, 74.83; H, 9.46. $C_{24}H_{36}SiO_2$ requires C, 74.95; H, 9.43 %); R_f0.55 (1:1 hexane : ethyl acetate); δ_H (300 MHz; $CDCl_3$) 7.68 (m, 4H), 7.41 (m, 6H), 3.79 (m, 1H), 3.66 (t, 2H, *J* 6.4 Hz), 1.56 (m, 2H), 1.41-1.31 (m, 9H), 1.19 (d, 3H, *J* 5.6 Hz) and 1.05 (s, 9H); δ_C (75 MHz; $CDCl_3$) 135.5, 134.1, 129.4, 127.5, 68.1, 63.9, 39.2, 32.5, 29.3, 26.8, 25.71, 25.70, 23.4 and 19.2; HPLC conditions: Chiralcel OD column, flow rate 1ml / min, 0.5% isopropanol 99.5% hexane eluent, major enantiomer 17.6 min, minor 19.6 min.

(S)-5-hydroxy pentan-2-ol benzyl ether
$[\alpha]_D$ +3.2 (c 3.5, $CHCl_3$); R_f0.41 (1:1 hexane : ethyl acetate); δ_H (300 MHz; $CDCl_3$) 7.32 (m, 5H), 4.52 9s, 2H), 3.80 (m, 1H), 3.51 (t, 2H, *J* 6.0 Hz), 2.42 (br s, 1H), 1.75- 1.51 (m, 4H) and 1.19 (d, 3H, *J* 6.2 Hz); δ_C (75 MHz; $CDCl_3$) 138.1, 128.4, 127.7, 73.0, 70.5, 67.7, 36.6, 26.3 and 23.4; HPLC conditions: Chiralcel OD column, flow rate 1ml / min, 1.5% isopropanol 98.5 % hexane eluent, major enantiomer 24.3 min, minor 22.6 min.

(R)-6-heptyn-2-ol
$[\alpha]_D$ +14.2 (c 4.7, $CHCl_3$); R_f0.42 (1:1 hexane : ethyl acetate); δ_H (300 MHz; $CDCl_3$) 3.81, (m, 1H), 2.21 (m, 2H), 1.95 (t, 1H, *J* 2.7 Hz), 1.67-1.53 (m, 5H) and 1.19 (d, 3H, *J* 6.2 Hz); δ_C (75 MHz; $CDCl_3$) 84.3, 68.5, 67.6, 38.1, 24.6, 23.6 and 18.3; Converted to 7-hydroxy -2-octyne-1-ol-(2-tert butyl diphenyl silyl ether) for HPLC analysis, using conventional protocol: HPLC conditions: Chiralcel OD column, flow rate 1ml / min, 1.0 % isopropanol 99.0 % hexane eluent, major enantiomer 19.0 min, minor 16.7 min.

(S)-1-(Phenyl)pentan-1-ol
R_f0.60 (1:1 hexane : ether); δ_H (300 MHz; $CDCl_3$) 7.22-7.36 (5H, m), 4.6 (1H, t, *J* 7.36 Hz), 2.08 (1H, br s), 1.7-1.8 (2H, m), 1.22-1.38 (4H, m) and 0.87 (3H, t, *J* 7.0 Hz); δ_C (75 MHz; $CDCl_3$) δ 144.96, 128.38, 127.4, 125.9, 74.6, 38.8, 28, 22.6 and 14; HPLC conditions: Chiralcel OD column, flow rate 1ml / min, 1% isopropanol 99% hexane eluent, major enantiomer 19.6 min, minor 17.8 min.

(R)-1-(2-napthyl)pentan-1-ol
m. p. 46-48°C; $[\alpha]_D$ +32.1 (c 1.74, $CHCl_3$); R_f0.6 (1:1 hexane : ether); δ_H (300 MHz; $CDCl_3$) 7.7-7.8 (3H, m), 7.7 (1H, s), 7.4-7.5 (3H, m), 4.8 (1H, t, *J* 6.5 Hz), 1.7-1.9 (3H, m), 1.2-1.44 (4H, m) and 0.9 (3H, t, *J* 6.87 Hz); δ_C (75 MHz; $CDCl_3$) δ 142.3, 132.3, 132.2, 128.2, 127.9, 127.7, 126.1, 125.8, 124.6 and 124.1;

HPLC conditions: Chiralcel OD column, flow rate 1ml / min, 4% isopropanol 96% hexane eluent, major enantiomer 24.5 min, minor 18.0 min.

tert butyl dimethylsilyloxy (R) rhododendrol

Silyloxy aldehyde **6** (0.156g, 0.59 mmol)[23] and catalyst **4** (0.0235g, 0.059 mmol) were placed in a flame dried flask which was fitted with a septum, then purged with nitrogen. Dry toluene (10ml) was cannulated into the flask and the solution cooled to 0°C with stirring. Dimethyl zinc (0.325 ml, 0.65 mmol 2M, hexanes) was added down the walls of the flask over 15 min. The reaction was stirred for 12h at 0°C, quenched by the addition of saturated aqueous ammonium chloride solution (45 ml), then extracted into ether (3 x 30 ml). The ethereal extracts were dried ($MgSO_4$), filtered, then the solvent was removed *in vacuo*, and the crude product carbinol was purified by flash chromatography (8:2 hexanes: ethyl acetate eluents) to give pure tert butyl dimethylsilyloxy rhododendrol (0.0991 g, 60%) as a colourless oil .$[\alpha]_D$ -5.96 (c 2.7, $CHCl_3$); (Found: C, 68.5; H, 10.10. $C_{16}H_{28}SiO_2$ requires C, 68.57; H, 9.99 %); R_f0.50 (1:1 hexane : ether); υ_{max} (neat)/ cm^{-1} 3360, 2959, 2931, 1511, 1258, 920, 836 and 780; δ_H (300 MHz; $CDCl_3$) 7.03 (2H, d, *J* 8.41 Hz), 6.79 (2H, d, *J* 8.41 Hz), 3.8 (1H, m) 2.65 (2H, m), 1.75 (2H, m), 1.65 (1H, br s), 1.2 (3H, d, *J* 6.19 Hz), 0.97 (9H, s) and 0.18 (6H, s); δ_C (75 MHz; $CDCl_3$) δ 153.5, 134.6, 129.2, 120, 67.6, 41.1, 31.4, 25.7, 23.6, 18.2 and –4.4; HPLC conditions: Chiralcel OJ column, flow rate 1ml / min, 0.25% isopropanol 99.75% hexane eluent, major enantiomer 14.0 min, minor 16.8 min.

(R)-(-) rhododendrol

tert Butyl dimethylsilyloxy rhododendrol (0.015 g, 0.055 mmol) was dissolved in dry toluene (5 ml) and stirred for 5 min at 23°C, thence diisobutyl aluminium hydride (0.19 ml, 0.275 mmol, 1.46M, toluene) was added over 1 min, and the solution stirred for a further 2h. Saturated aqueous ammonium chloride solution (10 ml) was added, and the mixture was then extracted into ether (3 x 30 ml), dried ($MgSO_4$), filtered and condensed *in vacuo*. The resulting residual solid was recrystallised from benzene to yield pure R-(-) rhododendrol (0.009 g, 98%) as a colourless solid, m.p.80°C (lit.,[19] m.p. 80-81°C) spectroscopically identical with reported data.[19, 21] HPLC conditions: Chiralcel OD column, flow rate 1ml / min, 10% isopropanol 90% hexane eluent, major enantiomer 16.2 min, minor 17.9 min. The e.e. of the crude rhododendrol from the enantioselective addition was shown to be 85% e.e. A second recrystallisation from benzene increased the apparent e.e. to at least 88%.

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