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On the origins of enantioselectivity in oxazaborolidine mediated carbonyl reductions

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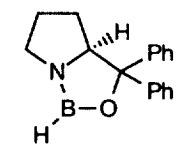
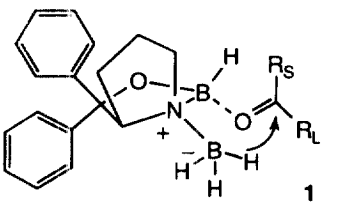
Abstract: A series of tricyclic oxazaborolidine catalysts have been prepared from readily available (*S*)-indoline-2-carboxylic acid. In each case, an arene chromium(0) carbonyl group was introduced on one face of the catalyst. Results obtained in the borane mediated reduction of ketones highlight the stereodirective importance of the α,α-appendages in the catalyst architecture. © 1997 Published by Elsevier Science Ltd

Introduction:

Since its introduction in 1987, the α,α-diphenyl-2-pyrrolidinemethanol derived oxazaborolidine [CBS] catalyst, has become one of the most popular systems for the catalytic enantioselective reduction of prochiral ketones.[1] One of the proposed transition state assemblies for the borane induced reduction of generic ketones is depicted in **1**. Enantioselectivity is a function of the preference for the larger of two ketone appendages (R_L) to adopt an orientation *anti* to the bulky upper hemisphere of the catalyst assembly, thereby inducing intramolecular delivery of hydride to one enantiotopic face of the ketone. While this catalyst and its close analogs typically provide extremely high enantiocontrol for the reduction of many ketones, a primary limitation revolves around the requirement that the ketone appendages R_S and R_L differ appreciably (steric A values) in order for maximum (coordinative) discrimination.[2] For this reason, numerous research groups continue to investigate modified analogs of the CBS catalysts, in the hope of overcoming this limitation.[3] One of the reports from the laboratories of Martens documents indoline-2-carboxylic acid derived oxazaborolidines **2**, where it was envisioned that the fused aryl ring may impart additional steric demand on incoming substrates.[4] Though the level of control (**2**, R=Ph) was found to be essentially unchanged when compared to the original proline derived CBS catalyst, we became interested in the possibility of introducing arene transition metal carbonyl appendages to the aryl ring in order to increase discrimination further, and, based on earlier reports from this laboratory, decided to investigate the corresponding tricarbonyl arene chromium (0) complexes.[5–11]



"CBS" catalyst



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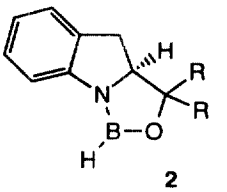

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Tricarbonyl (η^6-arene) chromium complexes are routinely formed by thermolyzing the desired arene with chromium hexacarbonyl, or its equivalent. Since the tricarbonyl chromium tripod coordinates discretely above or below the plane of the arene, it can therefore serve as a powerful stereodirective entity, and numerous groups have been active in the field of asymmetric induction using chiral chromium tricarbonyl complexes.[12] An additional benefit of using tricarbonyl (η^6-arene) chromium

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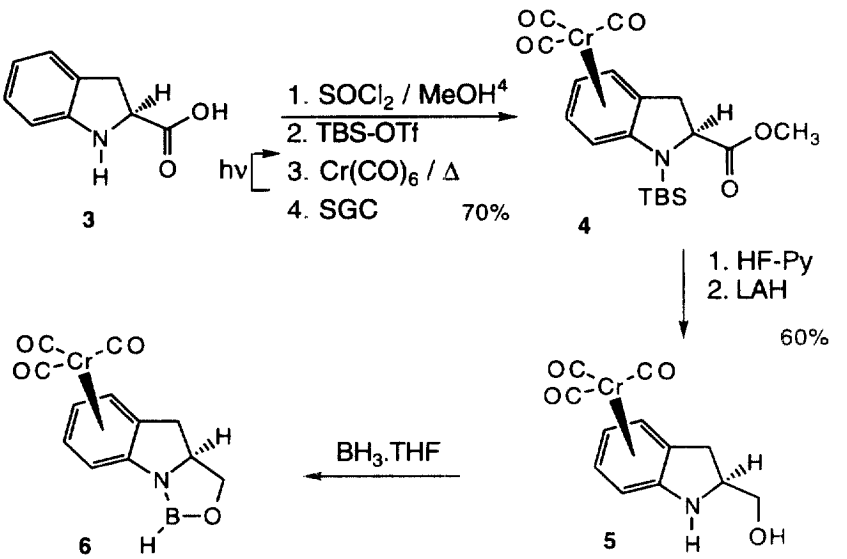
complexes in asymmetric processes lies in the fact that where the arene is *ortho* or *meta* disubstituted, on complexation two enantiomeric complexes are formed, by virtue of axial chirality conferred to the system. Resolution of such complexes can therefore be achieved giving access potentially to both enantiomers in optically pure form.[13] Until recently, the harnessing of the stereodirective effects of tricarbonyl (η^6-arene) chromium complexes in the form of asymmetric induction catalysts had not been exploited, having been used chiefly for either chiral template construction (via diastereoselective synthesis) or as stoichiometric controller groups to effect enantioselective transformations.[14]

Results and discussion

Mindful of the fact that strongly basic or acidic functionality is incompatible with arene chromium complexation conditions, we commenced synthesis of our initial catalyst systems by esterifying, then *N*-protecting commercially available (*S*)-indoline-2-carboxylic acid **3** (Scheme 1). On complexation a 1:1 mix of upper and lower face diastereomers was produced, which were separated with ease using standard silica gel chromatographic (SGC) methods. As is typical of such complexes, recrystallization and subsequent X-ray diffractive analysis allowed stereochemical assignment.[15] The lower face diastereomer was subjected to decomplexation, then recycled to eventually give an 80% isolated yield of desired complex **4**. *N*-Silyl deprotection, best accomplished using HF buffered with pyridine, was then followed by ester reduction to give catalyst precursor **5**. Treatment of this amino alcohol with borane in THF resulted in liberation of hydrogen, and *in situ* formation of desired oxazaborolidine **6**.



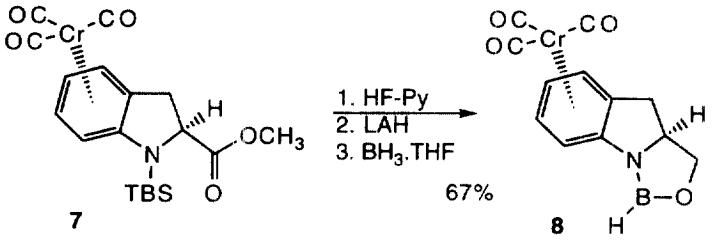
Scheme 1.

The catalytic efficiency of oxazaborolidine **6** in the reduction of a number of ketones was then examined, with reference to **2** (R=H), which was also prepared and used as a control element.[4] The results obtained (Table 1), indicate that the steric bulk of the metal carbonyl group does indeed impart additional enantiocontrol for the reduction of ketones when used under catalytic conditions, and that a moderate increase is obtained under stoichiometric conditions (entries 1–7). Under identical reaction conditions, the uncomplexed catalyst, (**2** R=H) gave consistently poor enantiocontrol at catalytic quantities, but improved appreciably under stoichiometric conditions (entries 8–9). Since the upper and lower face diastereomeric complexes **4** and **7** were separable, the oxazaborolidine derived from the lower face complex **8** was also prepared (Scheme 2). Significantly, this complex gave a lower e.e. for the reduction of acetophenone, but gave the identical enantiomeric (*R*) product alcohol (entry 10). Since the (*R*) product alcohols predominate in all cases, the results suggest that ketone substrates do

Table 1. Catalytic enantioselective reduction of ketones, using BH_3/oxazaborolidine catalysts

Entry	Catalyst	Equivs.	Substrate	Temp	% Yield	% e.e.
1	**6**	0.1	$PhCOCH_3$	25	95%	50% (R)
2	**6**	1.0	$PhCOCH_3$	25	93%	80% (R)
3	**6**	0.1	$PhCOnC_4H_9$	25	94%	55% (R)
4	**6**	0.1	2-naphthyl-$COCH_3$	25	91%	58% (R)
5	**6**	0.1	9-phenanthryl-$COCH_3$	25	97%	62% (R)
6	**6**	1.0	9-phenanthryl-$COCH_3$	25	97%	91% (R)
7	**6**	0.1	$PhCH_2CH_2COCH_3$	25	94%	19% (R)
8	**2** (R=H)	0.1	$PhCOCH_3$	25	91%	21% (R)
9	**2** (R=H)	1.0	$PhCOCH_3$	25	94%	76% (R)
10	**8**	0.1	$PhCOCH_3$	25	93%	25% (R)
11	**6**	0.1	$PhCOCH_3$	100	95%	41% (R)
12	**2** (R=H)	0.1	$PhCOCH_3$	100	93%	39% (R)

indeed coordinate to the oxazaborolidine such that the larger substituent (R_L) is positioned *anti* to the steric bulk of the metal carbonyl tripod. The similarity in product e.e. using catalyst **8** compared with uncomplexed catalyst **2** (R=H) suggests however that the *lower* face arene chromium tricarbonyl tripod exerts little stereochemical influence in the coordination of substrates.



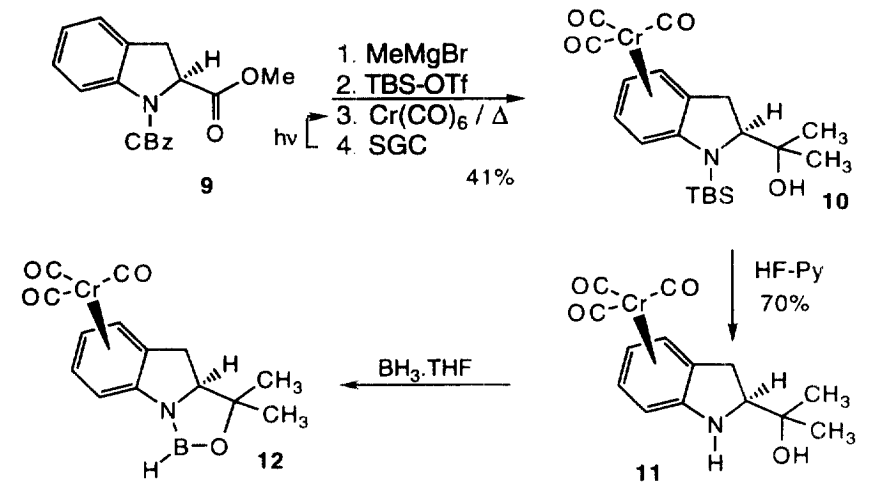
Scheme 2.

It has been reported that oxazaborolidines prepared *in situ* from amino alcohols using borane may exist in dynamic equilibrium between monomeric and dimeric forms, and that under elevated temperatures the more discriminating monomeric form is favored.[16] Accordingly, a reaction was run using **6** with borane at 100°C (entry 11), but the lack of improvement suggests that catalyst **6** is presumably monomeric even at at room temperature. This behavior is unsurprising based on the collosal steric bulk that the arene chromium tricarbonyl group imparts on the catalyst structure. Interestingly, the less encumbered catalyst (**2**, R=H) performed better at higher temperature (entry 12), supporting the dynamic equilibrium model.[17]

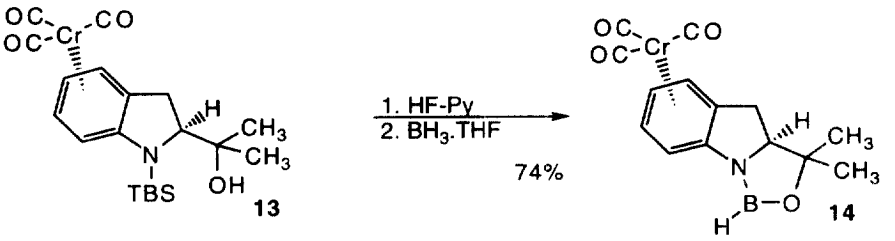
Since the arene chromium tricarbonyl group only conferred moderate steric demand in this system, synthesis of α,α-disubstituted analogs of **6** were pursued in order to probe the steric demand of the oxazaborolidine ring itself. Accordingly, CBz protected amino ester **9** was prepared, and subjected to the appropriate conditions shown in Scheme 3. The α,α-dimethyl carbinol was successfully prepared, then *N*-reprotected and complexed to give **10**, together with the lower face diastereomeric complex, which was accordingly decomplexed and recycled. *N*-Desilylation followed by treatment of amino alcohol **11** with borane thus allowed evaluation of analog **12**.

Since the upper and lower face diastereomers **10** and **13** were separable chromatographically, oxazaborolidine **14** was also prepared using identical methodology (Scheme 4).[15]

Catalyst **12** gave inferior enantioselection relative to catalyst **6** for the reduction of both acetophenone (20%) and 2-naphthylketone (21%) (Table 2). This contrasts with the uncomplexed analog of oxazaborolidine **12** i.e. **2** (R=Me), which gave superior enantiocontrol when compared to parent



Scheme 3.



Scheme 4.

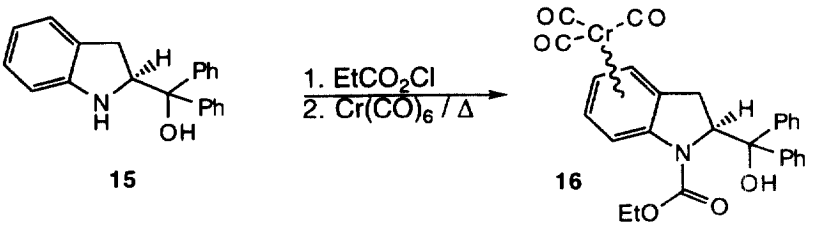
Table 2. Enantioselective reduction of ketones, using α,α-disubstituted oxazaborolidine catalysts

Entry	Catalyst	Equivs.	Substrate	Temp	% Yield	% e.e.
1	**12**	0.1	$PhCOCH_3$	25	96%	20% (R)
2	**12**	0.1	2-naphthyl-$COCH_3$	25	91%	21% (R)
3	**2** (R=CH_3)	0.1	$PhCOCH_3$	25	98%	40% (R)
4	**2** (R=CH_3)	0.1	2-naphthyl-$COCH_3$	25	95%	60% (R)
5	**2** (R=CH_3)	0.1	$(CH_3)_2CHCOCH_3$	25	94%	56% (R)
6	**14**	0.1	$PhCOCH_3$	25	92%	39% (R)
7	**18**	0.1	$PhCOCH_3$	25	91%	18% (R)
8	**2** (R=CH_3)	0.1	$PhCOCH_3$	70	90%	57% (R)
9	**12**	0.1	$PhCOCH_3$	70	90%	11% (R)
10	**14**	0.1	$PhCOCH_3$	70	92%	15% (R)

catalyst **2** (R=H) (Tables 1 and 2). Curiously, lower face oxazaborolidine **14** gave identical results to catalyst **2** (R=Me) giving insight to the likely transition state assembly (*vide infra*).

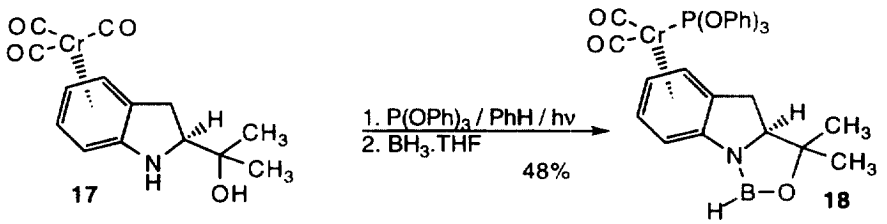
Numerous attempts to produce the α,α-diphenyl analog using the general route outlined in Scheme 3 proved unsuccessful, either due to product decomposition during complexation, or problems encountered during isolation. Additionally, carbamate protection then direct complexation of substrate **15**[4] gave **16** as an intractable mixture of diastereomers which proved impossible to separate and purify, either as the indicated carbamate or the free amine (Scheme 5).

Since ligand substitution of arene tricarbonyl chromium(0) complexes is a well versed process, a mixed ligand system bearing a triarylphosphite group was investigated, since the additional steric



Scheme 5.

bulk would be expected to have a greater impact on enantiodiscrimination than the tricarbonyl analog **14**.[18] Accordingly, carbinol **17** was transformed into the corresponding monophosphite complex via photolytic ligand substitution, then converted to oxazaborolidine **18** (Scheme 6). This lower face complex **18** gave inferior control relative to its tricarbonyl analog **14** (entry 7), suggesting that a gross change in catalyst architecture and/or substrate coordination had taken place (Table 2). As observed previously (Table 1), the uncomplexed system **2** (R=CH_3) proved responsive to increase in reaction temperature (entry 8) while the complexed catalysts were inferior (entries 9, 10).

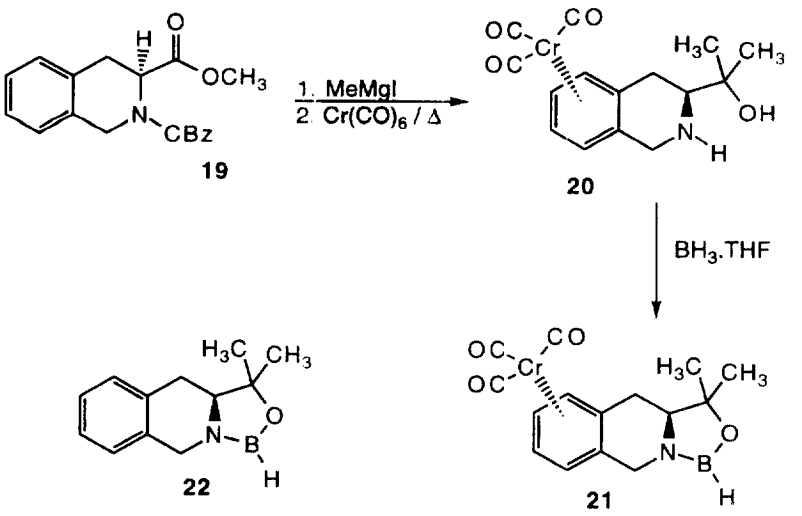


Scheme 6.

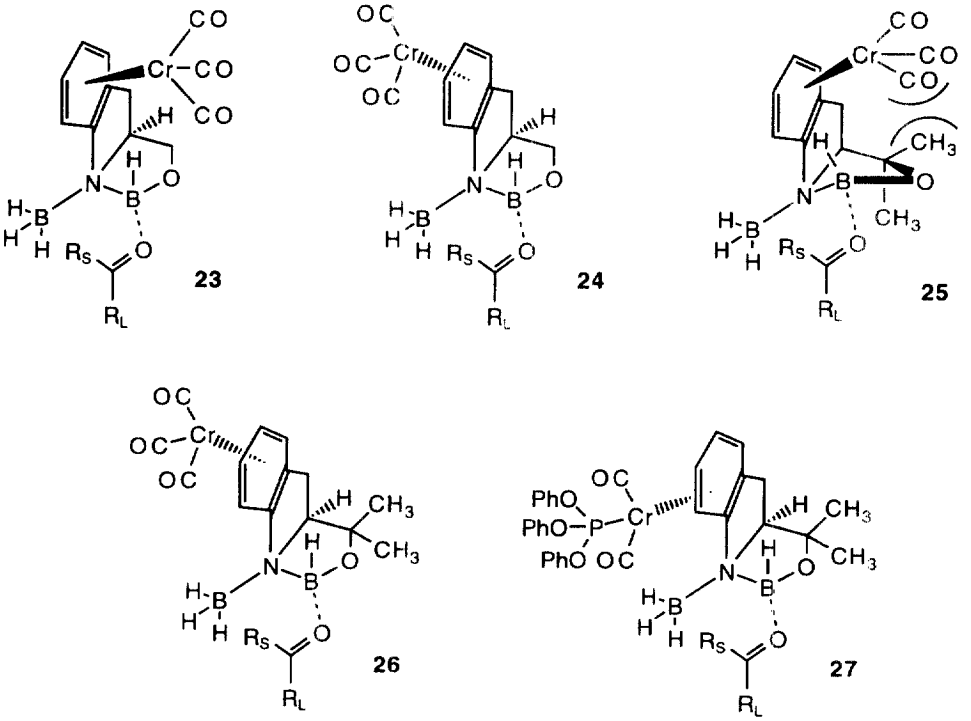
Finally, an isoquinoline derived variant was prepared using the methods outlined by Martens.[19] Precursor **19** is readily available from phenylalanine, using the classical Pictet–Spengler approach. Grignard addition followed by complexation and chromatographic resolution gave **20** in moderate yield (Scheme 7).[15] Formation of the metallocycle **21** was attempted, and its catalytic behaviour examined. In addition to giving a low yield (20%) of essentially racemic (3% e.e.) product in the reduction of acetophenone, chemical transformation of the catalyst occurred, giving a mixture of complexed amino alcohols. Fragmentation at the benzylic center adjacent to the amino group can be explained on the basis of generation of a metal carbonyl stabilized benzylic carbocation on treatment of the amine with borane. The role of the metal carbonyl appendage in this process was confirmed by repeating the sequence on a non-complexed version **22**, which, as expected, did not lead to cleavage and decomposition.[20]

Conclusion

The arene chromium carbonyl complexed indoline-2-carboxylic acid derived catalyst systems have allowed us to probe further the general constraints of oxazaborolidine mediated ketone reductions. Catalysts **6** and **8**, though superior to the non-complexed version **2** (R=H), did not demonstrate as significant an enhancement in enantiocontrol as could be expected.[5,6] It is clear that the major stereodirective influences on indoline-2-carboxylate derived oxazaborolidines emenate from the α,α-dialkyl or diaryl substituents on the heterocyclic ring. While the chromium tricarbonyl group imparts additional control relative to the α,α-unsubstituted catalyst, the presence of α,α-substituents in the case of the arene chromium carbonyl catalysts results either in no increase in selectivity (in the case of the lower face complex), or in a *drop* in selectivity in the case of the upper face complex.



Scheme 7.



One can thus conclude that the most likely transition state with the α,α-unsubstituted complexes involves substrate coordination to metallocycle–borane complex **23**. The arene chromium carbonyl group amplifies the steric butressing effect of the upper plane of the oxazaborolidine ring, encouraging the smaller of the two substrate ketone functions (Rs) to occupy the upper plane as shown. This then leads to borane delivery to the *si* face of the ketone, to yield *R* alcohols. In the case of the lower face complex **8**, the assembly shown in **24** is reasonable. Stereocontrol remains a function of the metallocycle plane, amplified to a much lesser degree by the arene metal carbonyl group, which nevertheless resides on the 'upper plane' of the catalyst. When α,α-disubstituted systems are prepared,

gross distortion of the catalyst framework in the case of upper face complex **12** results, as shown in **25**. In the case of lower face complex **14**, since the metal carbonyl group resides at a considerable distance to the α,α-appendages, less distortion of the oxazaborolidine ocurrs viz. **26**. The additional steric bulk present in complex **18** however presumably begins to reverse ketone coordinative preference, resulting in a concommitant lowering of product e.e., as depicted in **27**.

These findings are in agreement with the results of Martens, who found the α,α-diphenyl derivative **2** (R=Ph) to be essentialy as selective as the original CBS catalyst.[4] Confirmation that the predominant stereodirective element in this series is the α,α-appendage, coupled with the steric amplification/attenuation observed with the chromium carbonyl tripod may guide future effort in this class of catalyst.

Summary

A new family of transition metal carbonyl based enantioselective catalysts has been developed, which mediate the addition of coordinated borane to ketones with up to 91% enantioselectivity. The catalysts, prepared from commercially available (*S*)-indoline-2-carboxylic acid are potentially versatile and may lead to the development of highly discriminating systems.

Experimental section

All oxygen and moisture sensitive reactions described herein were performed in glassware which had been oven dried (140°C, 12 h) then flame dried (N_2 stream) immediately 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. Hexacarbonyl chromium was obtained from Strem chemicals and (*S*)-indoline-2-carboxylic acid from SAF Inc. All other reagents and solvents were purified according to standard convention. Unless indicated otherwise, silica gel chromatography (SGC) was perfomed on 70–240 mesh according to the method of Still. Analytical TLC was perfomed on glass backed 250 μ 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 Fisons Trio 1000 MS system. Chiral HPLC was conducted using an Isco 2350 isocratic pump coupled to an Isco V^4 UV 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 (OD, OJ; 4.6×250 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 HPLC retention and optical rotation data of known compounds.

(2S)-Methyl-2-indolinecarboxylate

(*S*)-Indoline-2-carboxylic acid (0.5 g, 3.06 mmol) was dissolved in dry methanol (10 mL), and cooled to 0°C for the dropwise addition of thionyl chloride (0.246 mL, 3.37 mmol). The mixture was heated at 40°C for 3 h, cooled to room temperature, then neutralized ($NaHCO_3$), and extracted with ethyl acetate (3×30 mL). The organic extracts were dried ($MgSO_4$), and the solvent removed under vacuum to yield the title compound (0.542 g, 99%) as a white crystalline solid, m.p. 148–150°C; $[\alpha]_D$=+17.8 (c=1.23, EtOH).[4]

*(2S)-Methyl-1-*tert*-butyldimethylsilyl-2-indolinecarboxylate*

Methyl-(*S*)-(+)-2-indolinecarboxylate (0.30 g, 1.69 mol)[4,17] was placed in a flame dried 50 mL flask with a magnetic stir bar and fitted with a septum. The flask was purged with dry nitrogen, 2,6-lutidine (0.593 mL, 5.1 mmol) added, and dry methylene chloride (30 mL) cannulated into the flask. The flask was cooled to −80°C and *tert*-butyldimethylsilyltriflate (0.47 mL, 2.04 mmol) added dropwise

over a 10 min. period with stirring. The cooling bath was removed and the reaction allowed to warm over 12 h. The reaction was neutralized with saturated aqueous sodium bicarbonate solution, extracted with methylene chloride (2×25 mL), dried over magnesium sulfate, and the solvent removed under vacuum. The crude product was purified by SGC (90% hexanes:10% ethyl acetate) to yield the title compound (0.44 g, 88%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) 7.03–6.96 (2H, m), 6.74 (1H, d, *J* 7.92 Hz), 6.64 (1H, t, *J* 7.29 Hz), 4.45 (1H, q, *J* 2.14 Hz) 3.73 (3H, s), 3.43 (1H, q, *J* 10.88 Hz), 0.93 (9H, s), 0.51 (3H, s), and 0.16 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) 233.2, 175.4, 151.8, 129.0, 127.2, 124.1, 117.9, 110.8, 62.9, 52.0, 35.3, 26.9, 20.5, −4.0, and −4.8; ν_{max} (Nujol) 3325, 2952, 1694, 1441, 1251, and 1208 cm^{-1}; (Found: C, 66.07; H, 8.79; N, 4.94. $C_{16}H_{25}NO_2SiCr$ requires C, 65.93; H, 8.65; N, 4.81%).

*(ηS,2S)-Methyl-1-*tert*-butyldimethylsilyl-2-indolinecarboxylate arene chromium carbonyl* **4**

(2*S*)-Methyl-1-*tert*-butyldimethylsilyl-2-indolinecarboxylate (0.295 g, 1.01 mmol) was thermolyzed with hexacarbonylchromium (0.667 g, 3.30 mmol) in a 10:1 mixture of *n*-butyl ether:THF (28 mL) for 3.5 h following the general complexation procedure.[6] On cooling, excess hexacarbonylchromium was filtered through a plug of silica gel, then the solution concentrated to dryness. Gravity column chromatography (70% hexanes:30% ethyl acetate) gave complex **4** (0.210 g, 49%) and isomer **7** (0.207 g, 48%) both of which were recrystallized from ethanol and subjected to X-ray analysis.[15] (**4**) Yellow crystals, m.p. 138–139°C; ^{1}H NMR (300 MHz, $CDCl_3$) 5.39–5.33 (2H, q, J 6.89 Hz), 5.17 (1H, t, J 6.11 Hz), 4.98 (1H, t, J 6.12 Hz), 4.26 (1H, m), 3.83 (3H, s), 3.23 (2H, m), 0.92 (9H, s), 0.55 (3H, s), and 0.19 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) 234.7, 173.6, 131.9, 97.0, 90.6, 89.6, 87.3, 80.7, 61.9, 52.7, 33.5, 26.9, 20.3, −4.0, and −4.8; ν_{max} (Nujol) 1947, 1870, 1848, 1743, 1455, and 1258 cm^{-1}; m/e 428.1 (M$^+$); (Found: C, 53.32; H, 5.85; N, 3.29. $C_{19}H_{25}NO_5SiCr$ requires C, 53.38; H, 5.89; N, 3.28%).

*(ηR,2S)-Methyl-1-*tert*-butyl-dimethylsilyl-2-indolinecarboxylate arene chromium carbonyl* **7**

Yellow crystals, m.p. 96°C; ^{1}H NMR (300 MHz, $CDCl_3$) 5.63 (1H, d, J 5.91 Hz), 5.32 (1H, m), 4.97 (1H, d, J 6.69 Hz), 4.85 (1H, t, J 6.36 Hz), 4.57 (1H, q, J 4.34 Hz), 3.71 (3H, s), 3.53–3.44 (1H, m), 2.98 (1H, m), 0.99 (9H, s), 0.38 (3H, s), and 0.30 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) 234.7, 138.0, 99.8, 93.9, 91.6, 84.1, 75.9, 63.4, 52.4, 34.5, 26.9, 20.0, −4.7, and −4.9; ν_{max} (Nujol) 1945, 1870, 1841, 1743, 1455, and 1258 cm^{-1}; m/e 428.1 (M$^+$); (Found: C, 53.43; H, 5.83; N, 3.31. $C_{19}H_{25}NO_5SiCr$ requires C, 53.38; H, 5.89; N, 3.28%).

(ηS,2S)-Methyl-2-indolinecarboxylate arene chromium carbonyl complex

Complex **4** (1.00 g, 2.34 mmol) was dissolved in dry acetonitrile (25 mL), and dry pyridine (1 mL), and HF/pyridine (1.5 mL of Aldrich 70% HF/pyridine) were added simultaneously. The mixture was stirred at 25°C for 1 h. The mixture was poured into HCl (1 M, 150 mL), and extracted with ethyl acetate (2×40 mL). The organic layer was washed with brine until the aqueous layer was approximately pH 7, then dried ($MgSO_4$) and the solvent removed under vacuum to yield the title compound (0.58 g, 79%) as a yellow oil; $[\alpha]_D$=+73.6 (c 0.1, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) 5.48 (1H, d, J 5.68 Hz), 5.30 (1H, s), 5.16 (1H, d, J 6.11 Hz), 4.42 (1H, s), 4.23 (1H, d, J 9.90 Hz), 3.86 (3H, s), and 3.47–3.20 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) 234.0, 172.8, 129.7, 96.5, 92.3, 90.6, 86.6, 75.8, 58.1, 53.1, and 31.5; ν_{max} (Nujol) 3430, 1947, 1827, and 1244 cm^{-1}; (Found: C, 50.06; H, 3.73; N, 4.16. $C_{13}H_{11}NO_5Cr$ requires C, 49.85; H, 3.54; N, 4.47%).

(η*R*,2*S*)-Methyl-2-indolinecarboxylate arene chromium carbonyl complex (83%) was accordingly produced as a yellow oil from compound **7** following identical procedure. $[\alpha]_D$=+67.8 (c 0.05, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) 5.61 (1H, d, J 6.16 Hz), 5.39 (1H, t, J 6.32 Hz), 4.98 (1H, d, 6.57 Hz), 4.83 (1H, t, J 6.16 Hz), 4.57 (1H, m), 4.20 (1H, s), 3.76 (3H, s), and 3.19–3.03 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) 234.2, 171.7, 131.8, 95.7, 94.7, 92.7, 84.3, 73.7, 59.6, 52.7, and 32.1; ν_{max} (Nujol) 3374, 1940, 1848, and 1216 cm^{-1}.

(ηS,2S)-2-hydroxymethylindoline arene chromium carbonyl 5

(ηS,2S)-Methyl-2-indolinecarboxylate arene chromium carbonyl (0.25 g, 0.80 mmol) was dissolved in THF (6 mL), and cannulated into a slurry of lithium aluminum hydride (0.061 g, 1.60 mmol) in dry ether (20 mL). The mixture was stirred for 0.5 h then quenched by the slow sequential addition of H_2O (0.061 mL), NaOH (15%, 0.061 mL), and then H_2O (0.183 mL). The mixture was filtered through a layer of Celite on a fritted funnel, the solution dried (Na_2SO_4), and the solvent removed under vacuum. The crude product was recrystallised from ether/hexane yielding **5** (0.173 g, 76%) as fine yellow crystals, m.p. 84–85°C; $[\alpha]_D$=+774.3 (c 0.01, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) 5.61 (1H, d, J 6.27 Hz), 5.39 (1H, t, J 6.43 Hz), 4.99 (1H, d, J 6.80 Hz), 4.84 (1H, t, J 6.28 Hz), 4.26 (1H, s), 4.10–4.00 (2H, m), 3.58 (1H, m), 3.14–3.05 (1H, m), and 2.65–2.50 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) 235.2, 133.2, 96.3, 94.8, 93.8, 84.3, 74.0, 63.3, 58.3, and 30.6; ν_{max} (Nujol) 3395, 1940, 1848, and 1040 cm^{-1}; (Found: C, 50.87; H, 3.96; N, 4.74. $C_{12}H_{11}NO_4Cr$ requires C, 50.53; H, 3.89; N, 4.91%).

(ηR,2S)-2-hydroxymethylindoline arene chromium carbonyl was produced from (ηR,2S)-methyl-2-indolinecarboxylate arene chromium carbonyl complex (80%) as yellow crystals, m.p. 75–76°C; $[\alpha]_D$=+508 (c 0.005, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) 5.65 (1H, d, J 5.32 Hz), 5.42 (1H, s), 4.99 (1H, s), 4.86 (1H, s), 4.17 (2H, m), 3.83 (1H, br s), 3.62 (1H, br s), and 2.83 (2H, br s); ^{13}C NMR (75 MHz, $CDCl_3$) 234.7, 133.4, 98.3, 94.9, 93.3, 84.4, 74.0, 64.0, 60.7, 30.6; ν_{max} (Nujol) 3556, 3381, 3262, 1935, and 1848 cm^{-1}.

(S)-1-Benzyloxycarbonyl-2-indolinecarboxylic acid

(S)-(−)-Indoline-2-carboxylic acid (1.00 g, 6.13 mmol) was added, with stirring, to a 50 mL flask containing NaOH (2 M, 3.16 mL) at a temperature of −5°C. The solution was stirred until all acid had dissolved, then benzyl chloroformate (1.12 mL, 12.3 mmol) was added, followed by the dropwise addition of NaOH (4 M, 2.15 mL). The reaction was stirred for an additional 1 h at 0°C, then washed with ether (2×15 mL), and the aqueous phase acidified to pH 2 with HCl (6 M). The aqueous phase was then saturated with Na_2SO_4 and extracted with ethyl acetate (2×30 mL). The organic extracts were washed with brine (2×30 mL), dried ($MgSO_4$), and the solvent removed under vacuum giving the title compound (1.802 g, 99%) as a foamy solid; ^{1}H NMR (300 MHz, $CDCl_3$) 11.28 (1H, br s), 7.92–6.83 (9H, m), 5.35–5.20 (2H, m), 4.99 (1H, s), 3.55 (1H, m), and 3.21 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) 218.7, 177.7, 128.5, 128.2, 127.9, 127.7, 124.4, 123.2, 114.9, 81.0, 67.4, 59.7, and 32.8; ν_{max} (Nujol) 1715, 1495, 1271, and 1152 cm^{-1}.

(2S)-Methyl-1-benzyloxycarbonyl-2-indolinecarboxylate 9

(2S)-1-Benzyloxycarbonyl-2-indolinecarboxylic acid (1.51 g, 5.08 mmol) was dissolved in dry methanol (15 mL), then $BF_3 \cdot Et_2O$ (0.926 mL, 7.52 mmol) added. The mixture was refluxed for 2 h then the solvent removed under vacuum. Iced H_2O (10 g) was added, and the mixture was extracted with ethyl acetate (2×25 mL). The organic extracts were washed with saturated aqueous sodium bicarbonate (35 mL), dried ($MgSO_4$), then the solvent removed under vacuum to give **9** (1.566 g, 99%) as a light brown gum; ^{1}H NMR (300 MHz, $CDCl_3$) 7.95–6.75 (9H, m), 5.32–5.12 (2H, m), 4.94 (1H, m), 3.74–3.47 (4H, m), and 3.17–3.10 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) 171.8, 151.9, 141.9, 140.7, 135.7, 128.3, 128.0, 127.8, 124.6, 124.2, 122.7, 114.5, 67.9, 67.0, 59.8, 52.0, 32.6, and 31.8; ν_{max} (Nujol) 1715, 1495, 1271, and 1152 cm^{-1}; (Found: C, 69.41; H, 5.50; N, 4.54. $C_{18}H_{17}NO_4$ requires C, 69.44; H, 5.50; N, 4.50%).

(2S)-α,α-Dimethyl-(indolin-2-yl)methanol

(2S)-Methyl-1-benzyloxycarbonyl-2-indolinecarboxylate (0.107 g, 0.343 mmol) was dissoled in a 2:1 THF:ether (0.7 mL) mixture, and cannulated at −10°C into a pre-cooled solution of methylmagnesium iodide (0.5 M, 5.50 mL, 2.75 mmol in ether). The reaction was stirred for 8 h then poured onto saturated aqueous ammonium chloride (10 mL). The mixture was dissolved in ether (45 mL),

washed with H_2O, then brine, dried (Na_2SO_4), filtered, and the solvent removed under vacuum. The crude product was purified by SGC (70% hexane:30% ethyl acetate) yielding the title compound (0.047 g, 77%) as a white solid; ^1H NMR (300 MHz, $CDCl_3$) 7.09–7.00 (2H, m), 6.73 (1H, t, J 7.37 Hz), 6.64 (1H, d, J 7.73 Hz), 3.81 (1H, t, J 9.55 Hz), 3.06–2.93 (2H, m), 1.25 (3H, s), and 1.19 (3H, s); ^{13}C NMR (300 MHz, $CDCl_3$) 150.7, 129.3, 127.1, 124.6, 119.1, 109.6, 70.7, 68.5, 30.9, 28.2, and 24.4; ν_{max} (Nujol) 3508, 3353, 1602, 1490, 1469, and 1251 cm^{-1}; (Found: C, 74.25; H,8.48; N, 7.84. $C_{11}H_{15}NO$ requires C, 74.54; H, 8.53; N, 7.90%).

*(2S)-α,α-Dimethyl-(1-*tert*-butyldimethylsilyl-2-indolinyl)methanol*

(2*S*)-α,α-Dimethyl-(indolin-2-yl)methanol (1.02 g, 5.76 mmol) was dissolved in dry methylene chloride (20 mL) and 2,6-lutidine (4 mL, 34.56 mmol) added, and the flask was cooled to −80°C, for the dropwise addition of *tert*-butyldimethylsilyl triflate (1.72 mL, 7.49 mmol). The mixture was warmed to room temperature, stirred for 2 h, then poured into HCl (2 M, 50 mL) and extracted with ethyl acetate (2×25 mL). The organic extracts were washed with water (2×40 mL) and brine (1×40 mL), dried (Na_2SO_4), filtered, and the solvent removed under vacuum. The crude product was purified by SGC (hexane:ethyl acetate) to yield the title compound (1.66 g, 99%) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) 7.08–6.95 (2H, m), 6.65–6.55 (2H, m), 3.76 (1H, t, J 8.25 Hz), 3.06–2.75 (2H, m), 1.18 (6H, d, J 15.0 Hz), 0.85 (9H, s), and 0.07 (6H, d, J 6.71 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) 151.2, 128.7, 127.2, 124.5, 118.0, 108.5, 75.9, 69.0, 31.7, 26.1, 25.8, 248, 18.1, and −2.0; ν_{max} (neat) 3460, 2954, 1223, and 833 cm^{-1}; (Found: C, 70.31; H, 10.19; N, 4.63. $C_{17}H_{29}NOSi$ requires C, 70.04; H, 10.03; N, 4.81%).

*(ηS,2S)-α,α-Dimethyl-(1-*tert*-butyldimethylsilyl-2-indolinyl)methanol arene chromium carbonyl* ***10***

(*S*)-α,α-Dimethyl-(1-*tert*-butyldimethylsilyl-2-indolinyl)methanol (1.315 g, 4.51 mmol) was thermolyzed with hexacarbonylchromium (2.0 g, 9.09 mmol) in a 10:1 mixture of *n*-butyl ether:THF (55 mL) for 5 h following the general complexation procedure.[6] On cooling, excess hexacarbonylchromium was filtered through a plug of silica gel, then the solution concentrated to dryness. SGC (70% hexanes:30% ethyl acetate) gave complexes **10** and **13** in an approximately 9:1 ratio. **10** (1.04 g, 54%), as yellow crystals, m.p. 135–136°C; $[\alpha]_D$=+348 (c 0.001, EtOH); ^1H NMR (300 MHz, $CDCl_3$) 5.58 (1H, d, J 5.64 Hz), 5.36 (1H, s), 4.89 (1H, d, J 6.26 Hz), 4.77 (1H, s), 3.88 (1H, t), 3.73 (1H, s), 2.76 (2H, s), 1.17 (6H, d, J 11.07 Hz), 0.81 (9H, s), and 0.06 (6H, d, J 5.42 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) 234.9, 133.0, 97.3, 95.0, 93.3, 83.6, 74.3, 72.8, 69.1, 30.3, 26.6, 25.7, 18.3, and −2.1; ν_{max} (Nujol) 3402, 1954, 1933, 1834, 1560, and 1047 cm^{-1}; (Found: C, 56.37; H, 6.93; N, 3.15. $C_{20}H_{29}NO_4SiCr$ requires C, 56.19; H, 6.84; N, 3.28%). Also obtained (η*R*,2*S*)-α,α-dimethyl-(1-*tert*-butyldimethylsilyl-2-indolinyl)methanol arene chromium carbonyl (**13**) (0.116 g, 6%), as yellow crystals, m.p. 54–56°C; $[\alpha]_D$=+161 (c 0.05, EtOH); ^1H NMR (300 MHz, $CDCl_3$) 5.85 (1H, s), 5.66 (1H, s), 5.30 (1H, s), 5.08 (1H, s), 3.87 (2H, s), 2.87 (2H, m), 1.19 (6H, s), 0.84 (9H, s), and 0.10 (6H, s); ^{13}C NMR 233.5, 136.2, 97.3, 93.9, 83.7, 75.7, 74.0, 70.0, 31.0, 26.3, 25.8, 24.5, 18.0, and −2.1; ν_{max} (Nujol) 3394, 1960, 1844, and 1043 cm^{-1}.

(ηS,2S)-α,α-Dimethyl-(indolin-2-yl)methanol arene chromium carbonyl ***11***

Complex **10** (0.5023 g, 1.18 mmol) was dissolved in dry pyridine (6 mL), and HF–pyridine (5 mL, 70% HF in pyridine) was then added dropwise and the reaction stirred for 5 h. The mixture was poured into saturated aqueous sodium bicarbonate (150 mL) and extracted with ethyl acetate (2×25 mL). The organic extracts were washed with brine (2×35 mL), dried (Na_2SO_4), and the solvent removed under vacuum. The crude product was purified by SGC (70% hexane:30% ethyl acetate) to yield **11** (0.258 g, 70%) as a yellow crystalline solid, m.p. 118–120°C; $[\alpha]_D$=+251 (c 0.03, EtOH); ^1H NMR (300 MHz, $CDCl_3$) 5.60 (1H, d, J 5.41 Hz), 5.37 (1H, s), 4.96 (1H, d, J 6.04 Hz), 3.89 (1H, s), 2.94–2.77 (2H, m), 1.23 (3H, s), and 1.16 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) 234.6, 133.1, 98.6, 94.7, 93.0, 84.6, 74.0, 70.4, 68.1, 29.7, 28.1, and 24.6; ν_{max} (Nujol) 3354, 1965, 1850, and 1047 cm^{-1}; (Found: C, 53.86; H, 4.91; N, 4.28. $C_{14}H_{15}NO_4Cr$ requires C, 53.67; H, 4.83; N, 4.47%).

Diastereomer **17** (74%), produced from complex **13** using an identical protocol, was isolated as a yellow crystalline solid, m.p. 109–110°C; $[\alpha]_D$=+271 (c 0.03, EtOH); ^{1}H NMR (300 MHz, acetone-d_6) 5.97 (1H, d, J 6.23 Hz), 5.52 (1H, t, J 6.68 Hz), 5.30 (1H, d, J 6.74), 4.91 (1H, t, J 6.16 Hz), 3.97 (1H, t, J 9.92 Hz), 3.31 (1H, s), 3.07–2.89 (3H, m), and 1.20 (6H, d, J 4.59 Hz); ^{13}C NMR (75 MHz, acetone-d_6) 236.7, 139.7, 99.3, 96.3, 84.0, 75.3, 71.6, 69.7, 31.0, 27.0, and 25.0; ν_{max} (Nujol) 3360, 1972, 1908, and 1064 cm^{-1}.

(ηR,2S)-α,α-Dimethyl-(indolin-2-yl)methanol arene chromium monotriphenylphosphine dicarbonyl

Complex **17** (0.059 g, 0.189 mmol) was dissolved in dry benzene (5 mL) in a quartz test tube. Triphenylphosphite (0.292 g, 0.943 mmol) was added and the mixture was deoxygenated using triple freeze-thaw cycles. The solution was photolyzed (Hanovia 450W) for 5 h under an argon atmosphere, the solvent evaporated under vacumm, and the mixture purified by SGC (80:20 hexane:ethyl acetate eluent) to afford the title compound (0.054 g, 48%) as a yellow oil. $[\alpha]_D$=+276.0 (c=0.01, $CHCl_3$); ^{1}H NMR (300 MHz, $CHCl_3$) δ 7.36–7.24 (br, 12H, 12Hz), 7.15–7.06 (br, 3H, 9 Hz), 5.28 (s, 1H), 5.18–5.09 (d, 2H, 9 Hz), 4.56 (s, 1H), 3.81–3.75 (d, 2H, 6 Hz), 2.72–2.66 (m, 1H, 6 Hz), 2.35–2.29 (m, 1H, 6 Hz), 1.84 (br, 1H), 1.17–1.08 (d, 6H, 9 Hz); ^{13}C NMR (75 M Hz, $CHCl_3$) δ 237.5, 152.4, 129.4, 124.6, 121.8, 97.2, 90.9, 88.6, 84 3, 72.5, 70.3, 67.5, 29.8, 28.1, 24.4; IR (neat) 3387.2, 3310.6, 3072.3, 2978.7, 2936.2, 2876.6, 2374.5, 1966.0, 1897.9, 1846.8, 1727.7, 1600.0, 1489.4, 1387.2, 1217.0, 876.6, 783.0, and 697.9 cm^{-1}; MS (m/e) 595 (M^+, 100%).

General experimental procedure for the enantioselective reduction of ketones using oxazaborolidines

Complex **5** (30 mg, 0.105 mmol) was placed in a flame dried 10 mL round bottomed flask fitted with a reflux condensor and magnetic stir bar and the unit sealed with a predried septum. The flask was purged with dry nitrogen and BH_3·THF (5.25 mL, 5.25 mmol, 1 M in THF) added. Addition of borane was accompanied by bubbling as hydrogen gas is produced. The vessel was then placed in a 70°C oil bath for 2 h, after which time the flask was cooled to room temperature and acetophenone (0.122 mL, 1.05 mmol) was added over a 10 min. period. The reaction was stirred for an additional 10 min. then quenched by slow addition of methanol (5 mL). The solvents were concentrated to a volume of 0.5 mL under vacuum, then poured into HCl (1%, 25 mL) and extracted with ethyl acetate (3×25 mL). The organic extracts were washed with water (25 mL), brine (25 mL), then concentrated under vacuum and the crude product purified by SGC (80:20 hexane:ethyl acetate eluent) to give (*R*)-1-(phenyl)propan-1-ol (0.122 g, 95%) as a colorless oil. HPLC (OD column, 2.5% isopropanol 97.5% hexane, 1mL/min. flow rate) 13.2 min (*R*); 15.8 min (*S*).

(3S)-α,α-Dimethyl-(1,2,3,4-tetrahydroisoquinolin-3-yl)methanol

(3*S*)-Methyl-2-benzyloxycarbonyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate **19** (2.68 g, 8.25 mmol)[19] was placed in a flame dried 10 mL flask fitted with a septum, purged with dry nitrogen, and a 9:1 mixture of ether:THF (10 mL) added. The contents were cannulated slowly into a flask containing methylmagnesium iodide (66.0 mL, 66.0 mmol, 1 M in ether) at 0°C. The mixture was warmed to room temperature and stirred for 8 h. The reaction was quenched by the addition of water (10 mL), and extracted with ethyl acetate (3×25 mL), the organic extracts dried (Na_2SO_4), and the solvent removed under vacuum. The crude product was purified by SGC (85% hexane:15% ethyl acetate eluent) yielding the title compound (1.34 g, 85%) as a white solid, m.p. 114–116°C; $[\alpha]_D$=−89.6 (c=0.02, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) 7.22–7.09 (4H, m), 4.83 (1H, m), 4.28 (2H, m), 3.50 (1H, m), 3.07–3.00 (2H, m), 1.51 (3H, s), and 1.44 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) 128.0, 127.9, 127.1, 127.8, 126.3, 125.4, 67.7, 59.2, 45.5, 29.4, 27.7, and 26.0; ν_{max} (Nujol) 3459 and 1659 cm^{-1}; (Found: C, 75.68; H, 9.07; N, 7.11. $C_{12}H_{17}NO$ requires C, 75.35; H, 8.96; N, 7.32%).

*(3S)-α,α-Dimethyl-(1,2,3,4-tetrahydroisoquinolin-3-yl)methanol arene chromium carbonyl **20***

(3*S*)-α,α-Dimethyl-(1,2,3,4-tetrahydroisoquinolin-3-yl)methanol (0.478 g, 0.0025 mol) was reacted with chromium hexacarbonyl (1.1 g, 0.005 mol) following the general complexation procedure, to give

a mixture of diastereomers. The mixture was purified by SGC (70% hexane:30% ethyl acetate eluent) to yield diastereomer **20** (0.524 g, 64%) as yellow powder, m.p. 152–153°C; $[\alpha]_D$=+318 (c=0.02, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) 5.26 (4H, m), 4.65–4.19 (2H, q, J 16.5 Hz), 3.48 (1H, m), 2.92 (1H, m), 2.57 (1H, m), 1.50 (3H, s), and 1.42 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) 232.2, 103.0, 92.6, 91.6, 91.1, 90.1, 81.0, 59.3, 43.0, 28.1, 27.6, and 22.0; ν_{max} (Nujol) 3440, 1947, 1870, 1743, and 1082 cm^{-1}; (Found: C, 55.31; H, 5.36; N, 4.16. $C_{15}H_{17}NO_4Cr$ requires C, 55.05; H, 5.23; N, 4.28%). The upper face diastereomer was isolated as an unstable yellow oil which could not be fully characterized.

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20. Prepared and manipulated as described in Ref. 19.

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