Diastereoselective Transformation of Arenes into Highly Enantiomerically Enriched Substituted Cyclohexadienes

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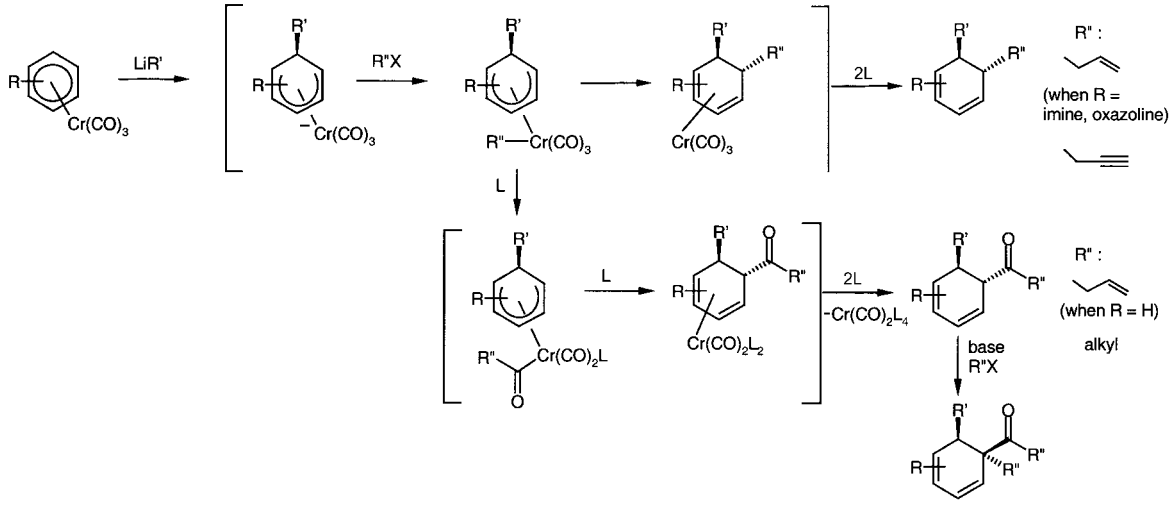
Abstract: Sequential addition of a C-nucleophile and a C-electrophile to enantiomerically pure arene tricarbonyl chromium complexes **3a**,**b, 6**, and **8b**, containing aryl bound chiral oxazoline, SAMP-hydrazone and chiral imine auxiliaries affording substituted cyclohexadienes. C-Nucleophiles included alkyl-, vinyl-, and phenyl-lithium reagents. C-Electrophiles included methyl iodide, allyl bromide, benzyl bromide, and propargyl bromides. The 1,3-cylohexadienes were obtained with a 1,5,6-substitution pattern. The results are consistent with a diastereoselective *exo*-nucleophilic addition to an *ortho* position of the complexed arene, followed by addition of the electrophile to the metal center. With allyl, ben-zyl, and propargyl groups, direct reductive elimination then yielded trans-5,6-substituted products. With methyl iodide, reductive elimination was preceded by CO insertion and acetyl cyclohexadienes were formed exclusively whose in situ deprotonation/alkylation gave products in which three C-substituents had been added across an arene double bond with complete regio- and stereocontrol. The two path-ways reflect migratory aptitude to carbonylation. An X-ray structure determination of the phenyl oxazoline complex **3a** allowed a rationalization of observed diastereoselectivity. Asymmetric induction was very high with the oxazoline and the SAMP-hydrazone complexes (>90% de) whereas the chiral benzaldehyde imine complex **8b** afforded the substituted diene aldehydes in moderate enantiomeric purity (34–58% ee). Changing the reaction medium from THF to toluene in reactions with **8b** resulted in products of the opposite chirality.

Key words: diastereoselective dearomatization, cyclohexadiene, arene $Cr(CO)_3$ complexes, imine , oxazoline, SAMP-hydrazone

Introduction

The search for expedient chemo- and regioselective transformations of simple starting materials is an important task in organic synthesis. Arenes, the subject of this study, are widely available, highly stable and readily derivatized through reactions such as electrophilic aromatic substitution, nucleophilic aromatic substitution,[1] *ortho*-lithiation followed by reaction with electrophiles,[2] and metal catalyzed substitution and coupling reactions.[3] Routes to differentially substituted aromatic products are thus well established. Benzene and its derivatives are attractive starting materials because they have the potential to provide a rapid entry into complex alicyclic synthetic building blocks containing unmasked functionality, new carbon-carbon bonds and new stereogenic centers.[4] However, this route to functionalized non-aromatic six-membered carbocycles is not common because substitutive dearomatization reactions require disruption of the aromatic π-system and this severely limits the scope of viable methodologies.

Our research in this area has focused on (arene) $Cr(CO)_3$ complexes. The dearomatization sequence involves nucleophilic addition to the arene, electrophile (H, alkyl, allyl, propargyl) addition to the metal, followed by reductive elimination and decomplexation to give the



Scheme 1

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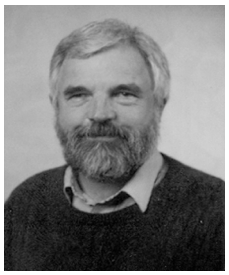
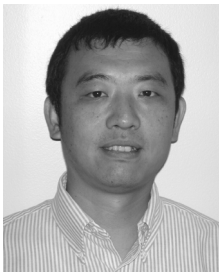
Biographical Sketches

Gérald Bernardinelli was born in 1945 in Nice, France. He studied chemical engineering at the School of Engineering in Geneva (diploma 1968) and then chemistry at the University of Geneva. He received his diploma degree in chemistry in 1973 and his PhD in 1978 in the domain of structural chemistry of macrocyclic musks. From 1978 to 1983, he was a Research Chemist in the field of X-ray crystallography. Since 1983 he is Head of the X-ray structure determination unit for organic and organometallic compounds of the Faculty of Sciences of the University of Geneva. His scientific interests are X-ray diffraction analysis in relation to structural chemistry of small and medium-sized molecules.

Sandra Gillet was born in 1974 in Voiron, France. She studied chemistry at the University Joseph Fourier in Grenoble, France and obtained her M.S. degree (DEA) in 1997 with a research project on the asymmetric synthesis of (3*S*,4*S*)-4-amino-3-hydroxy-5-phenyl-pentanoic acid. This work was carried out under the direction of Dr. Andrew E. Greene. Following a research period at Rhône-Poulenc Agro in Lyon, she joined the group of Prof. E. P. Kündig in Geneva for a year and contributed to the research results presented in this article.



E. Peter Kündig was born in 1946 in Weinfelden, Switzerland. He studied chemistry at the Federal Institute of Technology (ETH) in Zurich and obtained the diploma degree in 1971. In the same year he moved to the University of Toronto where he carried out research on transition metal carbonyl and dinitrogen complex fragments by matrix isolation techniques under the guidance of Prof. G. A. S. Ozin. He obtained his PhD degree in Toronto in 1975 and then took up a postdoctoral position at the University of Bristol, UK, with Dr. P. L. Timms. His studies there focused on the synthesis of organometallics via metal vapor/ligand cocondensation. Thereafter, he joined the University of Geneva, Switzerland, where he started his own research in 1978 and where he is now Professor of Organic Chemistry. His current research interests center on the development of new asymmetric methodologies via transition metals, their application in organic synthesis and on the design of new chiral ligands and asymmetric catalysts.



Ronggang Liu was born in 1962 in Tianjin, China. He received his B.S. in 1983 and his M.S. in 1986 from Nankai University, China. He carried out research at the Institute of Chemistry of the Academica Sinica in Beijing as research assistant (1986–89) and then joined the group of Prof. E. P. Kündig in Geneva as graduate student working on the dearomatization of $Cr(CO)_3$ bound arenes. After receiving his PhD from the University of Geneva, Switzerland, in 1993, he moved to the University of Virginia as a postdoctoral fellow in the group of Prof. W. Dean Harman. He is currently working as investigator at GlaxoSmithKline Pharmaceuticals, Inc. in King of Prussia, Pennsylvania.

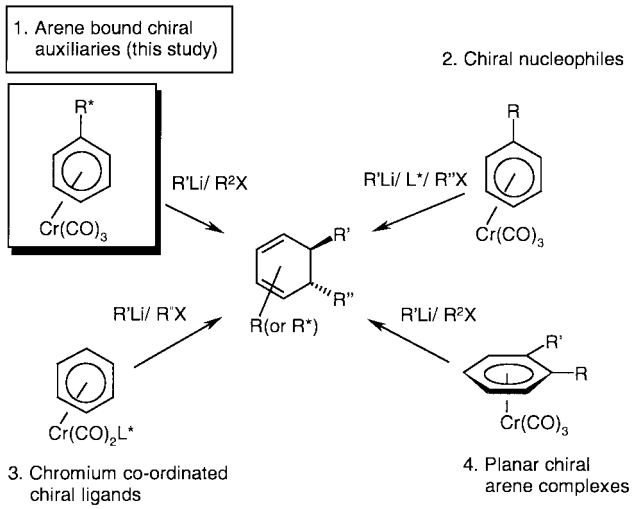
Alberto Ripa was born in 1962 in Milan, Italy. He received his „Laurea“ in Chemistry from the University of Milan in 1985, working under the guidance of Prof. C. Scolastico. He spent two years (1986–88) at the Istituto di Ricerche Farmacologiche Mario Negri of Milan, working with Prof. E. Mussini on asymmetric synthesis of α-aminophosphonic acids. Following a short stay at the University of Milan with Prof. G. Jommi, he moved to the University of Geneva in 1988 to join Prof. E. P. Kündig's group. In 1991 he was appointed „Maître Assistant“. During the five-year stay in Geneva he carried out research on the transformation of arene tricarbonyl chromium complexes into cylcohexadienes and on the synthesis of new chiral ligands. He returned to Italy in early 1995 and joined the Politecnico of Milan as „Ricercatore“ (Assistant Professor), working on transition-metal-mediated stereospecific polymerization of 1-alkenes and 1,3-dienes. In 1996, he took up a position at the Central Laboratories of REDA S.p.a., Milan, where he is now Research and Development Manager. His current research interests focus on the development of new materials based on polymers.

Lionel Saudan was born in Geneva, Switzerland in 1968. He completed his undergraduate studies in Chemistry at the University of Geneva in 1993. He carried out graduate studies on the asymmetric synthesis of new chiral amines and their use in organic and organometallic synthesis at the University of Geneva under the supervision of Prof. E. P Kündig and obtained his doctoral degree from the University of Geneva in 1998. With a postdoctoral grant from the Swiss National Science Foundation he then joined the group of Prof. J. M. Tour at the University of South Carolina and the following year at Rice University, Houston, working on the synthesis of new macromolecules. He is currently member of the Research Division of Firmenich S.A. in Geneva and works on the development of new organometallic catalysts for the synthesis of perfumery ingredients.

trans disubstituded cyclohexadiene. With alkyl halides reductive elimination is preceded by migratory CO insertion. Both the complexation and the one-pot procedure of addition of two substituents across an arene double bond in a regio- and stereoselective manner are reactions that occur in high yield (Scheme 1).[5]

Resonance donor substituents on the ring direct attack to the *meta* position[6–8] while bulky substituents and acceptor substituents direct preferentially *para*.[9] Functional groups that can efficiently coordinate the incoming organolithium reagent direct *ortho*.[10]

In this article we report details of our studies of asymmetric variants of one of the four chiral dearomatization approaches that have been realized using this reaction sequence. (Scheme 2)[11–13]



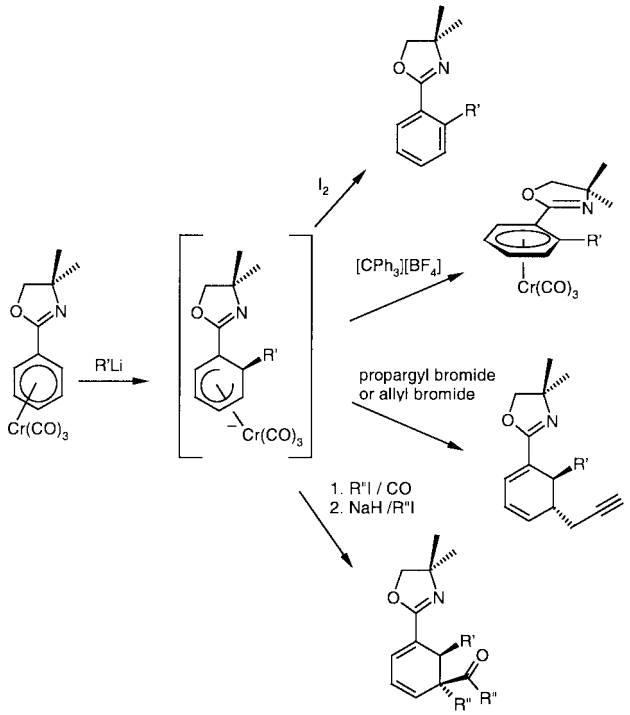
Scheme 2

The methodology described here is an arene bound chiral auxiliary approach, with the auxiliary chosen to lead to diastereoselective *ortho*-addition to the complexed arene (1. in Scheme 2)[14,15]

Aryl oxazoline (and also benzylidene cyclohexylamine) complexes have been shown previously to undergo selective *ortho*-additions of C-nucleophiles. While the intermediate anionic complex can be isolated and has been structurally characterized,[16] for the transformations with the electrophiles shown in Scheme 3 this is not required and in situ procedures have been used throughout.[17]

Results and discussion

For a diastereoselective approach we selected the chiral phenyl oxazoline complexes 3a and 3b derived from L-valinol and L-*tert*-leucinol,[18] the chiral phenyl SAMP-hydrazone[19] complex 6 and the chiral imine complexes 8a and 8b. We anticipated that the addition of a C-nucleophile could be directed preferentially to one of the diastereotopic *ortho*-positions of the complexed benzene. The data reported here confirm this hypothesis and show that the absolute configuration of the two new stereogenic centers can be easily controlled via the chiral auxiliaries.

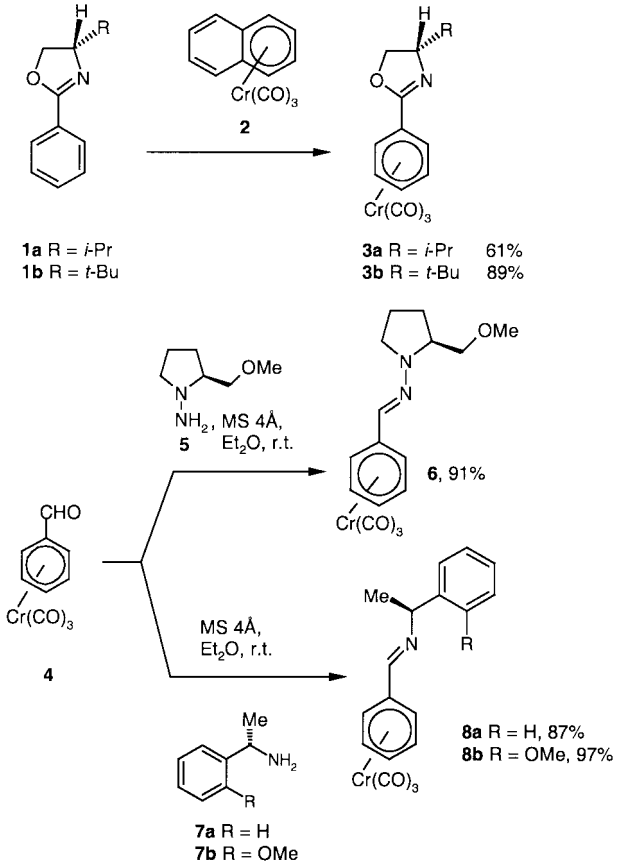


Scheme 3

Complexes **3a** and **3b** were synthesized by arene exchange with (naphthalene) $Cr(CO)_3$ **2**.[20] The SAMP hydrazone complex **6** and the benzaldehyde imine complexes **8a** and **8b** were obtained by condensation of (*S*)-1-amino-2-methoxymethylpyrrolidine (SAMP) **5**, and the enantiomerically pure amines **7a**,**b** with (benzaldehyde) $Cr(CO)_3$ **4** (Scheme 4).

Oxazoline complexes **3a** and **3b** reacted with alkyl-, vinyl-, and phenyl-lithium reagents to give the corresponding anionic cyclohexadienyl complexes **9**. In situ alkylation, allylation and propargylation afforded, after oxidative decomplexation (by exposure to air), the highly diastereomerically enriched cyclohexadienes **10–22**. The one-pot sequence was applied to a number of reactive nucleophiles and electrophiles (Scheme 5, Table 1) and led to products of high synthetic potential, given that oxazolines are readily cleaved by *N*-alkylation and $NaBH_4$ reduction to give the corresponding aldehydes.[21]

The organolithium reagents MeLi, BuLi, vinylLi and PhLi selectively added to the arene *ortho* position (1,4 addition reaction), no products arising from 1,2 addition or from arene lithiation were observed.[22] High diastereoselectivities were obtained with MeLi, BuLi and vinylLi, whereas PhLi gave an approximate 4:1 mixture of diastereoisomers in the reaction with complex **3a** (entry 4) and a much enhanced 11.5:1 mixture of diastereoisomers in



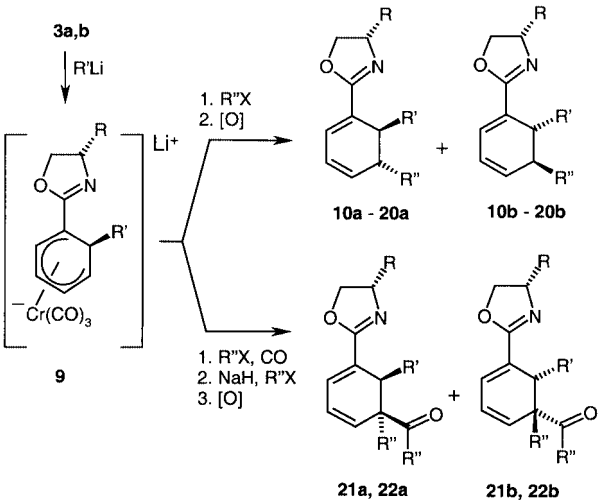
Scheme 4

Table 1 Cyclohexadienes **10**–**22** Obtained by Alkylation, Allylation or propargylation from **3**

Entry	R	R'Li[a]	R"X	Product	Diast. ratio[b]	Yield [%]
1	*i*-Pr (**3a**)	MeLi	allylBr	**10a**,**b**	96: 4	61
2	'	*n*-BuLi	allylBr	**11a**,**b**	96:4	54
3	'	vinylLi	allylBr	**12a**,**b**	96:4	48
4	'	PhLi	allylBr	**13a**,**b**	81:19	60
5	'	vinylLi	TMS-≡-CH_2Br[c]	**14a**,**b**	85:15	86
6	'	MeLi	TMS-≡-CH_2Br[c]	**15a**,**b**	93:7	77
7	'	MeLi	benzylBr	**16a**,**b**	95:5	51
8	'	MeLi	MeI[d]	**21a**,**b**	95:5	54
9	*t*-Bu (**3b**)	MeLi	allylBr	**17a**,**b**	>98:2	58
10	'	*n*-BuLi	allylBr	**18a**,**b**	>98:2	62
11	'	PhLi	allylBr	**19a**,**b**	92:8	54
12	'	MeLi	propargylBr[c]	**20a**,**b**	>98:2	79
13	'	MeLi	MeI[d]	**22a**,**b**	>98:2	58

[a] Reactions were carried out in THF or in THF-toluene, see experimental section.
[b] Diastereomeric ratios were determined by ^{1}H NMR in the crude product. The indication >98:2 means that a single diastereoisomer was observed. The major diastereoisomers are **10a**–**22a**.
[c] Addition of HMPA together with the electrophile. This improved yields by about 20%.
[d] Addition of MeCN together with the electrophile gave a cleaner reaction and improved yield.

the reaction with complex **3b** (entry 11). Higher diastereoselectivities in reactions with **3b** compared to those with **3a** are also apparent with MeLi and BuLi (compare entries 1 with 9 and 2 with 10). The lower diastereoselectivity of the phenyl lithium reaction compared to the alkyl lithium additions may reflect the lower degree of aggregation of PhLi in THF and its resulting higher reactivity.[23] Trapping with allyl bromide, propargyl bromide, or trimethylsilyl propargyl bromide afforded the products **10**–**20**. As found previously and in keeping with the low migratory aptitude to carbonylation of the propargyl group, propargylation at the metal is followed by reductive elimination without prior migratory CO insertion.[1,7] The situation is less clear-cut for the allyl group. In the substituted complexes used in this study, the major products in the crude reaction mixture, and the only products isolated after chromatography, are the products without carbonylation. In contrast, the sequential addition of dithiane Li and allyl bromide to (benzene) $Cr(CO)_3$ exclusively yielded the carbonylated product.[24] Secondary products were observed in the crude reaction mixtures of the reactions in entries 1–4, 7, and 9–11 in amounts varying between 5% and 15%. They were tentatively identified as the carbonylated products and while their isolation was not practical, they account for the lower yields of the allyl products compared to the propar-



Scheme 5

gyl products **14** and **15**. Methyl iodide gave carbonylated products exclusively. Enolate formation and methylation from the sterically more accessible face then afforded products **21** and **22**. The relative configuration of the two new stereogenic centers with respect to that of the auxiliary was established unambiguously by a crystal structure determination of **21a**.[14a] A rationale for the observed diastereoselectivity and its increase on going from the *i*-propyl oxazoline complex **3a** to the *t*-butyl oxazoline complex **3b** is provided by the X-ray structure of complex **3a** (Figure 1).[25,26]

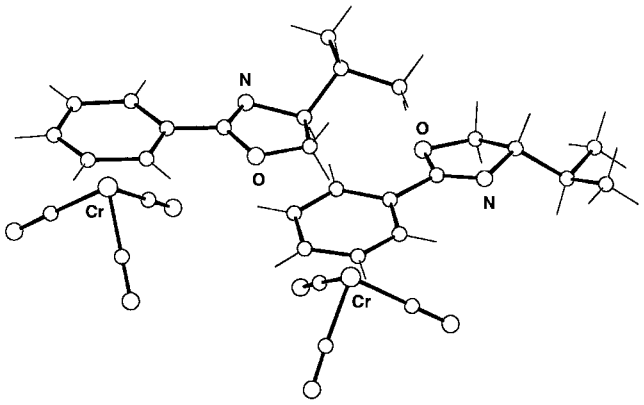
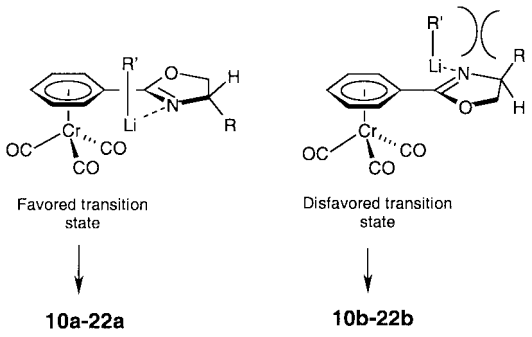


Figure 1 Perspective view of the crystal structure of **3a** showing the *syn*- (bottom) and *anti*-conformers (top)

The structure shows that both the *syn*-rotamers and the *anti*-rotamers are present in the unit cell in a ratio of 1:1. In the *syn*-rotamer the *i*-propyl group is located far away from the $Cr(CO)_3$ group so that there is no adverse steric interaction between these two fragments. It is therefore unlikely that one of the rotamers of **3a** is strongly favored and this should also hold for **3b**. The organolithium reagent coordinates to the oxazoline nitrogen and then adds to the *exo*-face of the arene. Product stereochemistry reflects a transition state in which the R substituent of the chiral auxiliary *syn* to the metal fragment (Scheme 6). The transition state arising from the *anti*-rotamer is disfavored because of steric interactions between the R and R′ groups (as usual, the organolithium reagents are represented as monomers, even though aggregates may be the reacting species). These interactions become more important with the size of R and this readily accounts for the higher induction by the *t*-butyl oxazoline in **3b** compared to the *i*-propyl analogue **3a**. The model shown is in accordance with the observed diastereoselectivity, with the observation of better induction by R = *t*-Bu than *i*-Pr and with the subsequent finding of the same mode of action in chiral oxazoline mediated diastereoselective *ortho* deprotonations of ferrocenes.[27]



Scheme 6

In an earlier study, the SAMP-hydrazone complex **6** has been shown to react with alkyl- and phenyl lithium reagent selectively at one of the two diastereotopic *ortho*-positions. The resulting cyclohexadienyl complex could be rearomatized by hydride abstraction without cleavage of the arene Cr bond. Removal of the auxiliary then provided enantiomerically pure planar chiral *ortho*-substituted benzaldehyde complexes.[28] Figure 2 shows an X-ray structure determination of **6** with the presence of two rotamers (*syn* and *anti*) in the unit cell in a 1:1 ratio.[29]

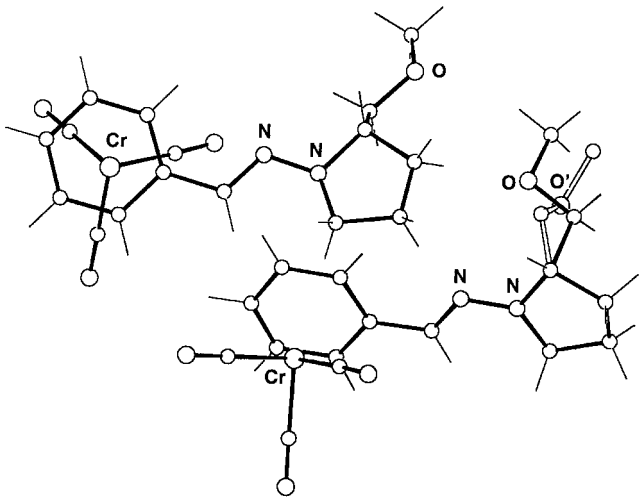
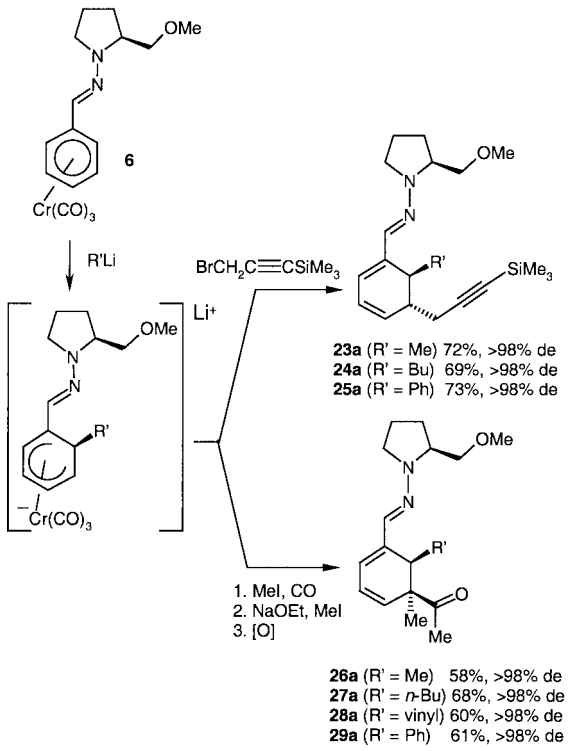


Figure 2 Perspective view of the crystal structure of **6** showing the *syn*- (top) and *anti*-conformers (bottom)

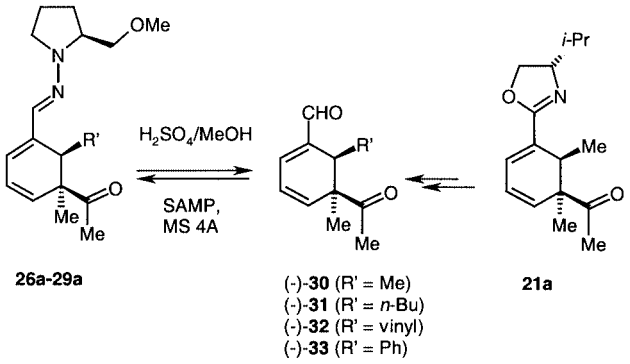
Dearomatization via sequential nucleophile/electrophile addition to the phenyl SAMP-hydrazone complex **6** is shown in Scheme 7.

Analysis of the crude reaction mixture by ^{1}H NMR spectroscopy showed that the diastereoselectivity was very high and often exceeded the value given in the scheme. The diastereomeric excess was probed by ^{1}H NMR integration of the C-H singlet of the hydrazone function. This method is reliable because conversion of the racemic aldehydes **30**–**33**[17] had shown that singlets associated with these hydrogens are distinct for each diastereoisomer.

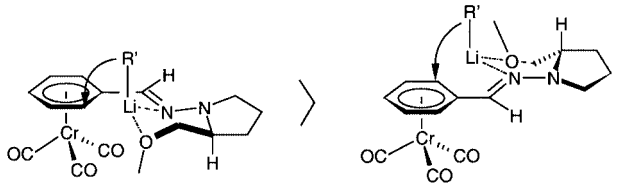
Hydrolysis of **26a** to **29a** (50% H_2SO_4/MeOH) afforded the highly enantioenriched aldehydes (–)-**30**–(–)-**33** (Scheme 8). The reverse reaction, treatment of (–)-**30** with



Scheme 7



Scheme 8



Scheme 9

SAMP-hydrazine gave **28a** in 99% diastereomeric purity, confirming that no partial racemization had occured during SAMP hydrolysis. This analysis was also carried out with **31**–**33**. Structural assignment of the aldehydes (–)-**30**–(–)-**33** as shown in Scheme 8 is based on the comparison of the sign of rotation of (–)-**30** with that of the same product obtained by conversion of **21a**. This was done via ketone protection of **21a** as a dioxolane (ethylene glycol, TsOH, toluene), followed by oxazoline *N*-alkylation (MeOTf) and reduction ($NaBH_4$).

With the absolute configuration of (–)-**30** known,[14a] the relative stereochemistry of **26**–**29a** must be as shown in Scheme 8. Asymmetric induction in the 1,4-addition of organolithium reagents to complex **6** is interpreted in terms of a preference of a chair-like transition state over the boat-like transition state that is adopted in the addition of the chelated organolithium reagent (Scheme 9).

We next turned our attention to chiral imine auxiliaries. Imines offer the advantage of being readily hydrolyzed and do not require additional steps for removal. Moreover, excellent *ortho*-selectivity in $Cr(CO)_3$ complexed benzaldehyde imines has been demonstrated in both nucleophilic addition reactions and in lithiation reactions.[16,17,28,30]

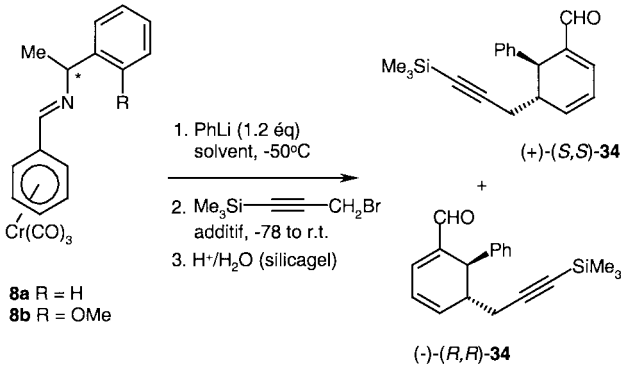
First data with complexes **8a** and **8b** are shown in Scheme 10 and Table 2. The imine complex **8a** afforded product **34** in good yield but as a racemate (entry 1). This was not wholly unexpected because coordination of the incoming organolithium compound to the imine nitrogen is not likely to result in a transition state that favors selective addition to either of the two diastereotopic *ortho* positions of the arene. A more rigid transition state can be expected by the incorporation of a function capable of chelating the incoming PhLi reagent. Our choice fell on complex **8b** and as shown in entries 2–4, this led to moderate asymmetric induction. A polar additive, HMPA or, preferably DMPU because of its non-carcinogenic nature, after the stereodefining nucleophilic addition reaction gives a higher product yield because it increases the efficiency of the electrophile addition step (entries 2 and 3 versus entry 4). Entries 2 and 3 also show that the reaction is stereospecific. Changing the reaction medium to toluene resulted in a drop in yield presumably because the S_N2 reaction between the anionic cyclohexadienyl intermediate and the electrophile is very slow.[24] Remarkably, asymmetric induction, while modest, is opposite in toluene from that found in THF (entries 4 and 5). Models of transition states

Table 2 Formation of Chiral Compounds **34**

Entry	Complex	Solvent	Additive	(*S*,S)-**34**: (*R*,*R*)-**34**[a]	ee (%)	Yield (%)
1	(*S*)-**8a**	THF	HMPA	50:50	0	70
2	(*S*)-**8b**	THF	HMPA	23:77	54	71
3	(*R*)-**8b**	THF	DMPU	79:21	58	78
4	(*S*)-**8b**	toluene	HMPA	69:31	38	50
5	(*R*)-**8b**	toluene	DMPU	67:33	34	50

[a] The ratio of enantiomers was determined by HPLC (column Daicel OD). The absolute configuration was assigned on the basis of the sign of optical rotation.

based on Li-chelation can be drawn up for the nucleophilic addition but the dataset at this stage is too small to make valid proposals. The switch in asymmetric induction on going to a less polar solvent where chelation is stronger but where the agglomeration state of the organolithium reagent also is larger indicates a change in transition state geometry. The question is intriguing and will be investigated more fully. While the results are preliminary, we feel that their inclusion in this article is useful.



Scheme 10

In conclusion, we have shown that chiral auxiliaries capable of coordinating to the incoming organolithium reagent can lead to high diastereoselectivity in the $Cr(CO)_3$ mediated dearomatization. With all three auxiliaries, reactions are highly chemoselective (the organolithium reagents act as nucleophiles rather than as bases) and regioselective (exclusive 1,4-addition rather than 1,2-addition). The synthetic protocols described in this article are useful for the transformation of simple aromatics into highly enantiomerically enriched alicyclic compounds with functionality suitable for their use as a building block for complex synthesis.

Reactions and manipulations involving organometallics were carried out under an atmosphere of purified nitrogen using an inert gas/vacuum double manifold and standard Schlenk techniques.[31] Column chromatography (f.c.) was carried out in air by the flash method described by Still (Silicagel: Merck 60).[32]

All 200 MHz or 400 MHz ^{1}H and 50.3 or 100.5 MHz ^{13}C NMR Spectra were recorded at room temperature on a Varian-XL-200 spectrometer or a Brucker 400 MHz spectrometer as indicated. Chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane as the internal standard and referenced to the proton signal for the residual solvent (C_6D_6, $\delta = 7.15$ for ^{1}H and $\delta = 128.0$ for ^{13}C). Mass spectra were obtained on a Varian CH 4 or SM 1 spectrometer, relative intensities are given in parentheses. High-resolution mass spectra were measured on a VG analytical 7070E instrument (data system 11 250, resolution 7000). IR spectra were recorded using NaCl cells on a Perkin-Elmer 1650 FT-IR spectrometer. Melting points were determined on a Büchi 510 apparatus and are not corrected. Elemental analyses were performed by H. Eder, Service de Microchimie, Institut de Chimie Pharmaceutique, Université de Genève.

$Cr(CO)_6$ was obtained from Strem Chemicals and used as received. THF and diethylether were dried and distilled from sodium/benzophenone ketyl under nitrogen before use. Toluene was distilled over Na under nitrogen. BuLi (Fluka, 1.7 M), MeLi (Fluka, 1.6 M), PhLi (Fluka, 1.6 M) were titrated before use.[33] Tetravinyltin (Aldrich) was used as received. (*S*)-Valinol and (*S*)-*tert*-leucinol were prepared by a literature method.[18] (4*S*)-4,5-Dihydro-4-(1,1-dimethylethyl)-2-phenyloxazole **1b** was prepared by using *Meyers* procedure.[34] (–)-1-(*S*)-(2-Methoxy-phenyl)-ethyl)-amine [(–)-(*S*)-**7b**][35] was synthesized using a method previously described for the preparation of chiral non-racemic benzylic amines via alkylation of chiral imines.[36] (η^6-Naphthalene) $Cr(CO)_3$ **2**,[20,37] and (η^6-benzaldehyde) $Cr(CO)_3$[10b,38]**4** were prepared as previously described. All other chemicals were purchased from Aldrich or Fluka and were purified following standard literature procedures.[39]

Synthesis of Chiral [(arene) $Cr(CO)_3$] Complexes 3, 6, and 8

Tricarbonyl{η^6-[(4*S*)-4,5-dihydro-4-(1-methylethyl)oxazol-2-yl]benzene}chromium (3a)

In a 50 mL anhyd reactor a mixture of **1a** (5.33 g, 28.16 mmol) and (η^6-naphthalene) $Cr(CO)_3$ **2** (3.720 g, 14.08 mmol) in anhyd THF (35 mL) was submitted to three freeze/pump/thaw cycles and then heated at 70 °C under stirring and under nitrogen atmosphere in the absence of light. After 16 h the reaction mixture was allowed to cool to r.t. and the solvent was evaporated under vacuum. The residue was dissolved in anhyd Et_2O (10 mL) and filtered through celite under N_2. The orange solution was concentrated under vacuum. The crude product was purified by flash chromatography (hexane–Et_2O, 5:1). The yellow orange band was collected. Recrystallization of the oily crude product from hexane–Et_2O, 1:1 at −78 °C afforded **3a** (2.910 g, 61%) as a yellow solid; 3.25 g of ligand **1a** (88% based on unconverted ligand) was recovered, mp = 51–52 °C.

$[\alpha]^{20}_D$ –140 (c 0.48, $CHCl_3$).

IR (hexane): 1926vs, 1922vs cm^{-1}.

^{1}H NMR (C_6D_6, 200 MHz): $\delta = 0.77$ (d, 3 H, $J = 6.7$ Hz), 0.93 (d, 3 H, $J = 6.7$ Hz), 1.45–1.55 (m, 1 H, $J = 6.7$Hz), 3.60–3.90 and 4.20–4.42 (m, 6 H), 5.70–5.77 (bd, 1 H, $J = 6.6$ Hz), 5.78–5.85 (bd, 1 H, $J = 6.2$ Hz).

MS: *m/z* (%) 325 (3), 269 (2), 241 (33), 52 (100).

Anal. Calcd for $C_{15}H_{15}CrNO_4$: C, 55.38; H, 4.58; N, 4.31. Found: C, 55.42; H, 4.65; N, 4.38.

(4*S*)-4,5-Dihydro-4-(1,1-dimethylethyl)-2-phenyloxazole (1b)

A 250 mL two necked round bottom flask, equipped with a reflux condenser, magnetic bar and rubber septum, were dried under vacuum with a heating gun. After cooling to r.t. under N_2, the flask was charged with anhyd CH_2Cl_2 (100 mL) and benzoylchloride (4.16 mL, 35.8 mmol). To this resulting solution was added via syringe a solution of (*S*)-(+)-*tert*-leucinol (4.200 g, 35.8 mmol) and Et_3N (5 mL, 35.8 mmol) in CH_2Cl_2 (22 mL) at 0 °C under N_2. The flask was protected from light with aluminum paper and the solution was stirred at room temperature overnight. The solvent was removed on a rotary evaporator. The white solid was treated with $SOCl_2$ (8.60 mL) at 0 °C under N_2. After stirring for 5 h at r.t., the solution was diluted with Et_2O (50 mL), cooled to 0 °C and carefully treated with aq NaOH (20%) until pH 7. The phases were separated and the aq phase extracted with Et_2O (3×50 mL). The combined organic phases were dried ($MgSO_4$), filtered, and evaporated. Bulb to bulb distillation afforded **1b** (6.520 g, 89%) as a white solid, mp = 32–33 °C.

$[\alpha]^{20}_D$ –99.4 (c 1.3, $CHCl_3$).

IR (CH_2Cl_2): 2960s, 2905m, 2870m, 1652vs, 1495m, 1479m, 1450m, 1394m, 1356s, 1340m, 1306m, 1088s, 1072m, 1056m, 1024s, 996s cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.94 (s, 9 H, $C(CH_3)_3$), 4.30 (dd, 1 H, *J* = 7.5 Hz), 4.22 (dd, 1 H, *J* = 7.5, 8.5 Hz), 4.34 (dd, 1 H, *J* = 8.5, 10 Hz), 7.34–7.52 (m, 3 H), 7.91–7.99 (m, 2H).

MS: *m/z* (%) 203 (3), 188 (3), 146 (100), 118 (19), 105 (20), 91 (21), 77 (18).

HRMS: *m/z* calcd for $C_{13}H_{17}NO$: 203.1310. Found: 203.1305.

Tricarbonyl{η^6-[(4*S*)-4,5-dihydro-4-(1,1-dimethylethyl)oxazol-2-yl]benzene}chromium (3b)

Phenyloxazoline **1b** (6.20 g, 30.50 mmol), (η^6-naphthalene) $Cr(CO)_3$ **2** (4.03 g, 15.25 mmol), and THF (60 mL) were placed in a 100 mL anhyd flask equipped with a reflux condenser, a magnetic stirring bar and submitted to three freeze-pump-thaw cycles. The solution was then refluxed in the dark for 24 h by means of an oil bath at 80 °C. The dark reaction mixture was allowed to cool to r.t. and stripped of volatiles in vacuum. The residue was taken up in anhyd Et_2O (50 mL) and the solution filtered over celite. After removal of solvent, the yellow-orange oily residue was purified by flash chromatography. After elution of ligand **1b** and a first orange-red band with hexane–Et_2O, 6:1, a second yellow-orange band containing **3b** was eluted with pure Et_2O. The crude product was recrystallized from hexane–Et_2O (ca. 4:1) at −78 °C to yield complex **3b** (4.12 g, 80%) as orange crystals, mp = 66–67 °C. Excess of ligand **1b** was recovered quantitatively.

$[\alpha]^{20}_D$ –176.5 (c 1, $CHCl_3$).

IR (CH_2Cl_2): 1985vs, 1925vs, 1889m, 1657s cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.92 (s, 9 H), 3.98 (dd, 1 H, *J* = 8, 10 Hz), 4.22 (t, 1 H, *J* = 8Hz), 4.32 (dd, 1 H, *J* = 8, 10 Hz), 5.27 (t, 1 H, *J* = 6.1 Hz), 5.29 (t, 1 H, *J* = 6.6 Hz), 5.99 (d, 1 H, *J* = 6.6 Hz), 6.10 (d, 1 H, *J* = 6.1 Hz).

MS: *m/z* (%) 339 (10), 283 (5), 255 (100), 171 (10), 155 (35), 52 (100).

HRMS: *m/z* calcd for $C_{16}H_{17}CrNO_4$: 339.0562. Found: 339.0542.

Anal. Calcd. for $C_{16}H_{17}CrNO_4$ (339.31): C, 56.63; H, 5.05; N, 4.13. Found: C, 56.64; H, 5.11; N, 4.11.

[η^6-Benzylidene-(1*S*)-(2-methoxymethyl-pyrrolidin-1-yl)-amine] tricarbonyl chromium (6)

(η^6-Benzaldehyde) $Cr(CO)_3$ (3.400 g, 14.0 mmol), (*S*)-1-amino-2-(methoxymethyl)-pyrrolidine (SAMP, 1.900 g, 14.7 mmol), molecular sieves (4 Å, 1 g) and freshly distilled and degassed Et_2O (50 mL) were placed into a Schlenk tube and stirred under N_2 in the dark at r.t. for 18 h. After filtration over celite, volatiles were removed in vacuum and the yellow residue was recrystallized (hexane-Et_2O, 1:1) to give (–)-**6** (5.510 g, 91%) as a yellow solid, mp 74–76 °C.

$[\alpha]^{20}_D$ –10.0 (c 10, CH_2Cl_2).

IR (CH_2Cl_2): 1962vs, 1890vs, 1560s, 1460m, 1330m, 1220m, 1120m cm^{-1}.

^{1}H NMR (400 MHz, C_6D_6): δ = 1.40–1.50 (m, 1 H), 1.60–1.75 (m, 3 H), 2.58–2.68 (m, 1 H), 2.85–2.92 (m, 1 H), 3.18 (s, 3 H), 3.38 (dd, 1 H, *J* = 6.8,9.4 Hz), 3.54 (dd, 1 H, *J* = 3.3,9.4 Hz), 3.62–3.70 (m, 1 H), 4.41 (t, 1 H, *J* = 6.4 Hz), 4.71 (t, 2 H, *J* = 6.4 Hz), 5.27 (d, 2 H, *J* = 6.4 Hz), 6.24 (s, 1 H).

MS *m/z* (%): 354 (17), 298 (2), 270 (12), 165 (100), 52 (68).

HR-MS: *m/z* calcd for $C_{16}H_{18}CrN_2O_4$: 354.0671. Found: 354.0399.

[η^6-Benzylidene-(1-(*S*)-phenyl-ethyl)-amine]tricarbonyl-chromium (8a)

(η^6-Benzaldehyde) $Cr(CO)_3$ (2.425 g, 10.0 mmol), (−)-1-(*S*)-phenyl-ethylamine (1.4 mL, 11.01 mmol, Fluka ee 96%), $MgSO_4$ (10 g) and freshly distilled and degassed diethyl Et_2O (25 mL) were placed into a Schlenk tube and stirred under N_2 at r.t. for 43 h. After filtration over celite, volatiles were removed in vacuum and the red residue was recrystallized from hexane at −10 °C to give (+)-**8a** (3.041 g, 87%) as an orange solid.

$[\alpha]^{20}_D$ +158.8 (c 0.17, $CHCl_3$).

IR ($CHCl_3$): 1977s, 1909s, 1645w cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.56 (d, 3 H, *J* = 6.4 Hz), 4.52 (q, 1 H, *J* = 6.4 Hz), 5.4–5.5 (m, 3 H), 5.75 (d, 1 H, *J* = 6.7 Hz), 5.81 (d, 1 H, *J* = 6.1 Hz), 7.2–7.4 (m, 5 H), 7.87 (s, 1 H).

MS *m/z* (%): 345 (1, M^+), 289 (29), 261 (100), 209 (10), 155 (93), 129 (12), 105 (33), 77 (8), 52 (79).

{η^6-Benzylidene-[1-(*S*)-(2-methoxy-phenyl)-ethyl]-amine}tricarbonylchromium (8b)

(η^6-Benzaldehyde) $Cr(CO)_3$ (1.602 g, 6.61 mmol), (–)-1-(*S*)-(2-methoxy-phenyl)-ethyl)amine ((–)-(*S*)-**7b**) (1.090 g, 7.20 mmol, ee 96%), $MgSO_4$ (10 g) and freshly distilled and degassed Et_2O (50 ml) were placed into a Schlenk tube and stirred under N_2 at r.t. for 24 h. After filtration over celite, volatiles were removed in vacuum at –20 °C to give (+)-**8b** (2.416 g, 97%) as an orange solid, mp 70–72 °C.

$[\alpha]^{20}_D$ +94.6 (c 0.24, CH_2Cl_2).

IR (CH_2Cl_2): 1973s, 1900s, 1643w cm^{-1}.

^{1}H NMR (400 MHz, C_6D_6): δ = 1.64 (d, 3 H, *J* = 6.9 Hz), 3.43 (s, 3 H), 4.36–4.48 (m, 3 H), 5.03 (q, 1 H, *J* = 6.9 Hz), 5.11 (d, 1 H, *J* = 6.4 Hz), 5.42 (d, 1 H, *J* = 6.4 Hz), 6.62 (d, 1 H, *J* = 7.4 Hz), 7.03 (dt, 1 H, *J* = 7.4, 1 Hz), 7.15 (dt, 1 H, *J* = 7.4, 1.5 Hz), 7.38 (s, 1 H), 7.79 (dd, 1 H, *J* = 7.4, 1.5 Hz).

^{13}C NMR (100 MHz, C_6D_6): δ = 23.6, 54.8, 62.4, 91.0, 91.2, 92.6, 92.9, 93.3, 100.9, 110.6, 121.1, 127.6, 128.1, 132.9, 155.5, 156.7, 232.5.

MS: *m/z* (%) 319 (32; M^+ – 2CO), 291 (95), 276 (29), 262 (3), 186 (11), 171 (18), 155 (87), 135 (36), 129 (12), 105 (11), 91 (12), 77 (10), 52 (100).

HR-MS: *m/z* calcd for $C_{16}H_{17}NOCr$: 291.0715. Found: 291.0731.

Sequential Nucleophile/Electrophile Additions to Complexes 3a and 3b

(–)-(4*S*)-2-[(5*R*,6*S*)-5-Allyl-6-methyl-cyclohexa-1,3-dienyl]-4-isopropyl-4,5-dihydro-oxazole (10a)

To a stirred solution of complex **3a** (335.3 mg, 0.988 mmol) in THF (10 mL) at −90 °C under N_2 was added dropwise MeLi (0.732 mL of a 1.62 M Et_2O solution, 1.185 mmol). The solution was warmed to –78 °C over a period of 3 h and then allylbromide (0.865 mL, 10 equiv, freshly distilled from P_2O_5) was added. The solution was slowly warmed to r.t. overnight and then the volatiles were removed in vacuum. The residue was dissolved in Et_2O (40 mL) and washed with sat. aq NH_4Cl (10 mL) and H_2O (2 × 5mL). The combined aq. phases were extracted with Et_2O (3 × 10 mL). The combined organic phases were dried ($MgSO_4$), exposed to sunlight for a few hours, filtered through celite and evaporated. HPLC analysis (hexane–EtOAc, 40:1; 5mL/min) showed a 95:5 ratio of the diastereoisomers **10a** (major, 11.1 min) and **10b** (10.1 min). Flash chromatography (hexane-Et_2O, 7:1) afforded **10a** (148.7 mg, 61%).

$[\alpha]^{20}_D$ –517.4 (c 1.04, $CHCl_3$).

IR (CH_2Cl_2): 3075w, 3065w, 3055w, 3050w, 3040w, 2965s, 2925m, 2910m, 2875m, 1652m, 1611s, 1466w, 1455w, 1404w,

1385w, 1362m, 1344m, 1307w, 1270m, 1241w, 1044m, 1018m, 1007m, 985m, 963m, 918m cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 0.85 (d, 3 H, *J* = 6.8 Hz), 0.94 (d, 3 H, *J* = 6.8 Hz), 1.04 (d, 3 H, *J* = 6.8 Hz), 1.83–1.92 (m, 1 H), 1.93–2.16 (m, 3 H), 2.84 (bq, 1 H, *J* = 6.8), 3.95–4.27 (m, 3 H), 4.94–5.02 (m, 2 H), 5.70–5.82 (m, 1 H), 5.96 (ddt, 1 H, *J* = 1,5,9 Hz), 6.01 (dd, 1 H, *J* = 5,9 Hz), 6.59 (dd, 1 H, *J* = 1,5 Hz).

MS: *m/z* (%) 245 (5), 244 (5), 204 (9), 160 (15), 119 (100), 91 (52).

HR-MS: *m/z* calcd for $C_{16}H_{23}NO$: 245.1779. Found: 245.1816.

(–)-(4*S*)-2-[(5*R*,6*S*)-5-Allyl-6-butyl-cyclohexa-1,3-dienyl]-4-isopropyl-4,5-dihydro-oxazole (11a)

The reaction was carried out as described for **10a** with BuLi and allylbromide on a scale of 1.026 mmol of **3a** in THF−toluene [1:10 (11 mL), for the nucleophilic addition; 6:10 (16 mL) for the electrophile addition]. HPLC analysis (Silica spheri 5 mm, hexane−EtOAc, 20:1; 5mL/min) showed a 95:5 ratio of products assigned to the diastereoisomers **11a** (major, 6.5 min) and **11b** (7.8 min). Flash-chromatography (hexane−Et_2O, 6:1) afforded **11a** (52.5 mg) and a mixture of **11a** and **11b** (30.1 mg, 62%).

An analogous experiment was carried out as above but in THF as solvent to give a 94:6 mixture of **11a** and **11b**

11a

$[\alpha]^{20}_D$ –477 (c 2.32, $CHCl_3$).

IR (CH_2Cl_2): 3080w, 3040w, 2960vs, 2930vs, 2880s, 1648s, 1611vs, 1570w, 1480w, 1467m, 1440w, 1400w, 1385m, 1370w, 1348m, 1300w, 1266w, 1230w, 1045s, 1005m, 974m, 963m, 920s cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 0.85 (d, 3 H, *J* = 6.8Hz), 0.86 (t, 3 H, *J* = 6.8Hz), 0.95 (d, 3 H, *J* = 6.8Hz), 1.20–1.50 (m, 6 H), 1.80–1.92 (m, 1 H), 1.94–2.03 (m, 1 H), 2.08–2.17 (m, 1 H), 2.26–2.34 (m, 1 H), 2.72–2.77 (m, 1 H), 3.96–4.10 and 4.14–4.25 (m, 3 H), 4.94–5.02 (m, 2 H), 5.70–5.82 (m, 1 H), 5.93 (dd, 1 H, *J* = 6,9 Hz), 5.99 (dd, 1 H, *J* = 5,9 Hz), 6.60 (d, 1H, *J* = 5Hz).

MS: *m/z* (%) 287 (15), 246 (100), 190 (30), 161 (28), 105 (30).

HR-MS: *m/z* calcd for $C_{19}H_{29}NO$: 287.2249. Found: 287.2235.

(–)-(4*S*)-2-[(5R,6*S*)-5-Allyl-6-vinyl-cyclohexa-1,3-dienyl]-4-isopropyl-4,5-dihydro-oxazole (12a)

Vinyllithium was prepared by adding MeLi dropwise (1.358 mL of a 1.62 M Et_2O solution, 2.2 mmol) to a stirred solution of tetravinyltin (0.133 mL, 0.73 mmol) in 10 mL of THF at −78 °C under N_2. After 1 h the solution was cooled to −90 °C and complex **5a** (339 mg, 1.00 mmol) was added as a solid, and the resulting solution was gradually warmed to −78 °C over a period of 3 h. The reaction was then carried out as described for **10a** with allylbromide and **3a**. HPLC analysis showed two products, **12a** (5.8 min) and **12b** (6.5 min) in a 95:5 ratio. Flash chromatography (hexane−Et_2O, 6:1) gave a mixture of **12a** and **12b** (131 mg, 48%) as a colorless oil.

$[\alpha]^{20}_D$ -388.38, (c 2.22, $CHCl_3$).

12a

IR (CH_2Cl_2): 3079w, 3042w, 2963s, 2927m, 2904m, 2863m, 1650s, 1637s, 1612vs, 1574w, 1467w, 1438w, 1401w, 1384w, 1346w, 1300w, 1231w, 1045w, 995m, 960m, 918s cm^{-1}.

1H NMR ($CDCl_3$, 200 MHz): δ = 0.84 (d, 3 H, *J* = 6.8 Hz), 0.92 (d, 3 H, *J* = 6.8 Hz), 1.70–2.40 (m, 4 H), 3.45 (d, 1 H, *J* = 6 Hz), 3.95–4.28 (m, 3 H), 4.90–5.13 (m, 4 H), 5.65–6.10 (m, 4 H), 6.71 (dd, 1 H, *J* = 1.5, 5.0 Hz).

MS: *m/z* (%) 257 (8), 256 (10), 216 (73), 172 (22), 146 (21), 131 (100).

HR-MS: *m/z* calcd for $C_{17}H_{23}NO$: 257.1779. Found: 257.1783.

(–)-(4*S*)-2-[(5*R*,6*S*)-5-Allyl-6-phenyl-cyclohexa-1,3-dienyl]-4-isopropyl-4,5-dihydro-oxazole (13a) and (+)-(4*S*)-2-[(5*S*,6*R*)-5-Allyl-6-phenyl-cyclohexa-1,3-dienyl]-4-isopropyl-4,5-dihydro-oxazole (13b)

The reaction was carried out as described for **10a** on a scale of 1.0 mmol of **3a** in THF-toluene (1:5, 48mL) at −78 °C with PhLi (601 mL of a 2 M cyclohexane solution, 1.202 mmol) and allylbromide. ^1H NMR analysis showed a 81:19 mixture of diastereoisomers **13a** and **13b** (199.8 mg, 62%). Flash chromatography (hexane−Et_2O, 6:1) afforded pure samples of both diastereoisomers. An analogous experiment was carried out exactly as before but in THF as solvent. This afforded a mixture of **13a** and **13b** in the ratio of 75:25 in 52% yield.

13a

$[\alpha]^{20}_D$ –486 (c 1.22, $CHCl_3$).

IR (CH_2Cl_2): 3085w, 3070w, 3060w, 3050w, 3035w, 2965s, 2925m, 2905m, 2880m, 1652m, 1641m, 1620vs, 1578w, 1500m, 1485w, 1470w, 1455w, 1422w, 1407w, 1385w, 1352m, 1305w, 1280w, 1262w, 1233m, 1052s, 1008m, 960m, 920m cm^{-1}.

1H NMR ($CDCl_3$, 400 MHz): δ = 0.81 (d, 3 H, *J* = 6.8Hz), 0.90 (d, 3 H, *J* = 6.8Hz), 1.82 (m, 1 H), 2.13–2.22 (m, 1 H), 2.24–2.32 (m, 1 H), 2.44–2.51 (m, 1 H), 3.88–4.00 and 4.10–4.16 (m, 3 H), 4.08 (s, 1 H), 5.04–5.13 (m, 2 H), 5.79–5.93 (m, 2 H), 6.11 (dd, 1 H, *J* = 5.2, 9.2 Hz), 6.93 (d, 1 H, *J* = 5.2 Hz), 7.13–7.27 (m, 5 H).

MS: *m/z* (%) 307 (3), 266 (100), 181 (40), 153 (19), 91 (8), 77 (10).

HR-MS: *m/z* calcd for $C_{21}H_{25}NO$: 307.1936. Found: 307.1910.

13b

$[\alpha]^{20}_D$ +528 (c 1.035, $CHCl_3$).

IR (CH_2Cl_2): 3080w, 3043w, 2963s, 2904m, 2873m, 1652m, 1614vs, 1576w, 1493m, 1481w, 1467w, 1452w, 1402w, 1385w, 1367m, 1348w, 1300w, 1283w, 1231m, 1047s, 1001m, 959m, 919m cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): δ = 0.57 (d, 3 H, *J* = 6.8 Hz), 0.63 (d, 3 H, *J* = 6.8 Hz), 1.50–1.65 (m, 1 H), 2.15–2.40 (m, 2 H), 2.45–2.60 (m, 1 H), 3.85–4.20 (m, 3 H), 3.98 (bs,1 H), 5.01–5.14 (m, 2 H), 5.75–6.00 (m, 2 H), 6.12 (dd, 1 H, *J* = 5.5, 9.5 Hz), 6.89 (d, 1 H, *J* = 5.5 Hz), 7.10–7.30 (m, 5 H).

MS: *m/z* (%) 307 (3), 266 (100), 224 (8), 181 (42), 153 (18), 91 (10), 77 (8).

HR-MS: *m/z* calcd for $C_{21}H_{25}NO$: 307.1936. Found: 307.1910.

(4*S*)-4-Isopropyl-2-[(5*R*,6*S*)-5-(3-trimethylsilanyl-prop-2-ynyl)-6-vinyl-cyclohexa-1,3-dienyl]-4,5-dihydro-oxazole (14a) and (4*S*)-4-Isopropyl-2-[(5*S*,6*R*)-5-(3-trimethylsilanyl-prop-2-ynyl)-6-vinyl-cyclohexa-1,3-dienyl]-4,5-dihydro-oxazole (14b)

The reaction was carried out as described for **12a** with vinyl lithium on a scale of 1.0 mmol of **3a** in THF. HMPA (1.74 mL, 10 equiv) was added immediately prior to the addition of trimethylsilyl propargyl bromide. Flash chromatography (SiO_2, hexane-Et_2O, 7:1) gave an inseparable mixture of the diastereoisomers **14a** and **14b** in the ratio of 85:15 (283 mg, 86%).

14a (partial data)

^1H NMR ($CDCl_3$, 200 MHz): δ = 0.13 (s, 9 H), 0.84 (d, 3 H, *J* = 6.8 Hz) 0.93 (d, 3 H, *J* = 6.8 Hz) 1.70–1.95 (m, 1 H), 2.10–2.40 (m, 2 H), 2.45–2.58 (m, 1 H), 3.61 (d, 1 H, *J* = 6.0 Hz), 3.90–4.30 (m, 3 H), 4.98 (dt, 1 H, *J* = 1.5, 10.0 Hz), 5.07 (dt, 1 H, *J* = 1.5, 16.5 Hz), 5.80 (ddd, 1 H, *J* = 6.0, 10.0, 16.5 Hz), 5.96–6.11 (m, 2 H), 6.71 (bd, 1 H, *J* = 6.0 Hz).

MS: *m/z* (%) 376 (6), 326 (8), 216 (83), 201 (32), 131 (100), 103 (71), 73 (95).

HR-MS: *m/z* calcd for $C_{20}H_{19}NOSi$: 327.2018. Found: 327.2014.

(4S)-4-Isopropyl-2-[(5R,6S)-6-methyl-5-(3-trimethylsilanyl-prop-2-ynyl)-cyclohexa-1,3-dienyl]-4,5-dihydro-oxazole (15a)

The reaction was carried out in THF as described for **10a** with MeLi on a scale of 1.0 mmol of **3a**. HMPA (1.74 mL, 10 equiv) was added immediately prior to the addition of trimethylsilyl propargyl bromide. GC analysis (initial T: 100 °C; initial time: 5 min; 10 °C/min; major diastereoisomer **15a** (19.6 min); minor diastereoisomer **15b** (19.8 min)) showed the formation of two products in the ratio of 93:7. Purification by flash chromatogaraphy (hexane−Et_2O, 7:1 to 5:1) afforded the mixture of diasteroisomers (242.9 mg, 77%).

15a

$[\alpha]^{20}_D$ –301.6 (c 0.98, $CHCl_3$)

IR (CH_2Cl_2): 3042w, 2961vs, 2927m, 2900m, 2873m, 2171m, 1651m, 1612s, 1574m, 1467m, 1425m, 1044m, 1386m, 1364m, 1345m, 1301m, 1274s, 1252s, 1048m, 1019m, 973m, 909m, 845vs cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): δ = 0.13 (s, 9 H), 0.85 (d, 3 H, *J* = 6.8 Hz), 0.95 (d, 3 H, *J* = 6.8 Hz), 1.06 (d, 3 H, *J* = 7.1 Hz), 1.75–1.95 (m, 1 H), 2.05–2.35 (m, 3 H), 2.94 (q, 1 H, *J* = 7.1 Hz), 3.95–4.30 (m, 3 H), 5.96–6.10 (m, 2 H), 6.54–6.62 (m, 1 H).

MS: *m/z* (%) 315 (10), 300 (4), 272 (5), 204 (80), 160 (21), 119 (100), 91 (78), 73 (40), 59 (11).

HR-MS: *m/z* calcd for $C_{19}H_{29}NOSi$: 315.2018. Found: 315.2002.

(-)-(4*S*)-2-[(5*R*,6*S*)-5-Benzyl-6-methyl-cyclohexa-1,3-dienyl]-4-isopropyl-4,5-dihydro-oxazole (16a)

The reaction was carried out as described for **10a** with methyl lithium and benzylbromide on a scale of 1.00 mmol of **3a** in THF. GC analysis (initial T: 150 °C; initial time: 5 min; 25 °C/min; major diastereoisomer **16a** (12.4 min); minor diastereoisomer **16b** (13.0 min)) showed the formation of two products in the ratio of 95:5. Purification by flash chromatography (hexane-Et_2O, 5:1) afforded the mixture of diastereomisomers (150.6 mg, 51%). A sample of pure **16a** was obtained by preparative HPLC (Silica spheri 5 mm, 250 × 10 mm column; hexane−EtOAc, 20:1, 5mL/min).

$[\alpha]^{20}_D$ –440.7 (c 4.19, $CHCl_3$).

IR (CH_2Cl_2): 3085w, 3070w, 3060w, 3055m, 3050m, 3035m, 2965vs, 2930s, 2905s, 2875s, 1052s, 1611vs, 1574w, 1496m, 1481w, 1467m, 1455m, 1407w, 1385w, 1363m, 1348m, 1304w, 1281w, 1274w, 1266w, 1240m, 1048s, 1022s, 974m cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 0.92 (d, 3 H, *J* = 6.8 Hz), 0.97 (d, 3 H, *J* = 7.2 Hz), 0.99 (d, 3 H, *J* = 6.8 Hz), 1.83–1.93 (m, 1 H), 2.27–2.34 (m, 1 H), 2.45 (dd, 1 H, *J* = 9.0, 13.0 Hz), 2.67 (dd, 1 H, *J* = 7.0, 13.0 Hz), 2.81 (bq, 1 H, *J* = 7.2 Hz), 3.98–4.10 and 4.20–4.25 (m, 3 H), 5.92 (dd, 1 H, *J* = 5.6, 9.2Hz), 6.03 (dd, 1 H, *J* = 5.6, 9.2Hz), 6.63 (d, 1 H, *J* = 5.2 Hz), 7.10–7.28 (m, 5 H).

MS: *m/z* (%) 296 (M+1, 3), 252 (1), 204 (31), 160 (26), 119 (90), 91 (100).

HR-MS: *m/z* calcd for $C_{20}H_{25}NO$: 295.1936. Found: 295.1915.

(–)-(4*S*)-2-((5*R*,6*S*)-5-Allyl-6-methyl-cyclohexa-1,3-dienyl)-4-tert-butyl-4,5-dihydro-oxazole (17a)

The reaction was carried out exactly as that described for **10a** using complex **3b** in place of **3a**, MeLi and allylbromide HPLC analysis showed the formation of a single diastereoisomer. Flash chromatography (hexane−Et_2O, 8:1) afforded **17a** (149.4 mg, 58%).

$[\alpha]^{20}_D$ –512.4 (c 0.835, $CHCl_3$).

IR (CH_2Cl_2): 3077w, 3040w, 2960vs, 1947m, 2905m, 2870m, 1650m, 1612vs, 1573w, 1479m, 1403w, 1363m, 1348m, 1334m, 1300m, 1240m, 1210w, 1014m, 981m, 960m, 917m cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 0.89 (s, 9 H), 1.03 (d, 3 H, *J* = 7.3 Hz), 1.89-2.03 (m, 1 H), 2.07-2.17 (m, 2 H), 2.87 (q, 1 H, *J* = 7.3 Hz), 3.91 (dd, 1 H, *J* = 6.7, 10.0 Hz), 4.08–4.18 (m, 2 H), 4.91–5.03 (m, 2 H), 5.69–5.80 (m, 1 H), 5.94 (dd, 1 H, *J* = 5.5, 9.6 Hz), 5.99 (dd, 1 H, *J* = 5.1, 9.6 Hz), 6.56 (d, 1 H, *J* = 5.1 Hz).

MS: *m/z* (%) 259 (20), 218 (100), 202 (68), 160 (40), 146 (20), 119 (50), 110 (20), 91 (30), 86 (65), 84 (100).

HR-MS: *m/z* calcd. for $C_{17}H_{25}NO$: 259.1936. Found: 259.1917.

(–)-(4*S*)-2-[(5*R*,6*S*)-5-Allyl-6-butyl-cyclohexa-1,3-dienyl]-4-tert-butyl-4,5-dihydro-oxazole (18a)

The reaction was carried out in THF (10 mL) with complex **3b** (339.3 mg, 1.0 mmol), BuLi and allylbromide. The procedure used was that described for **11a**. HPLC analysis showed the formation of a single diastereoisomer. Flash chromatography (hexane–Et_2O, 5:1) afforded **18a** (192.9 mg, 62%).

$[\alpha]^{20}_D$ –443.2 (c 1.09, $CHCl_3$).

IR (CH_2Cl_2): 3077w, 3039w, 2958vs, 2931s, 2870m, 1649m, 1613s, 1479m, 1462m, 1442m, 1364m, 1352m, 1354m, 1299m, 1027m, 960m, 917m cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 0.86 (m, 3 H), 0.88 (s, 9 H), 1.18–1.50 (m, 6 H), 1.92–2.02 (m, 1 H), 2.07–2.17 (m, 1 H) 2.23–2.32 (m, 1 H), 2.73–2.80 (m, 1 H), 3.90 (dd, 1 H, *J* = 7.0, 10.0 Hz), 4.07 (dd, 1 H, *J* = 7.0 Hz), 4.15 (dd, 1 H, *J* = 7.0, 10.0 Hz), 4.93–5.04 (m, 2 H), 5.70–5.80 (m, 1 H), 5.91 (dd, 1 H, *J* = 5.5, 9.1 Hz), 5.98 (dd, 1 H, *J* = 5.5, 9.1 Hz), 6.58 (d, 1 H, *J* = 5.5 Hz).

MS: *m/z* (%) 301 (20), 260 (100), 244 (30), 204 (30), 161 (23), 146 (32), 105 (30), 91 (31), 86 (64), 84 (100).

HR-MS: *m/z* calcd for $C_{20}H_{31}NO$ 301.2405. Found: 301.2384.

(–)-(4*S*)-2-[(5*R*,6*S*)-5-Allyl-6-phenyl-cyclohexa-1,3-dienyl]-4-tert-butyl-4,5-dihydro-oxazole (19a) and (4*S*)-2-[(5*S*,6*R*)-5-Allyl-6-phenyl-cyclohexa-1,3-dienyl]-4-tert-butyl-4,5-dihydro-oxazole (19b)

The procedure followed was analogous to that described for **13** using complex **3b** in place of **3a** (1 mmol scale, THF−toluene, 1:5, 48 mL), PhLi and allylbromide. HPLC analysis (hexane–EtOAc, 20:1, 5 mL/min, major 4.6 min, minor 6.0 min) showed two products in the ratio of 92:8. Flash chromatography (hexane−Et_2O, 6:1) afforded **19a** (164 mg, 51%) and **19b** (9.0 mg, 3%).

19a

$[\alpha]^{20}_D$ –484.1 (c 0.755, $CHCl_3$).

IR (CH_2Cl_2): 3080w, 3040w, 3027w, 2960s, 2905m, 2873m, 1650m, 1615vs, 1492m, 1452m, 1403m, 1364m, 1350m, 1300m, 1230m, 1050m, 1030m, 960m, 919m cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): δ = 0.85 (s, 9 H), 2.06–2.35 (m, 2 H), 2.40–2.54 (m, 1 H), 3.80 (dd, 1 H, *J* = 7.5, 10 Hz), 3.98–4.17 (m, 3 H), 5.00–5.16 (m, 2 H), 5.64–5.95 (m, 2 H), 6.11 (dd, 1 H, *J* = 6.0, 10.0 Hz), 6.91 (d, 1 H, *J* = 5.5 Hz), 7.10–7.30 (m, 5 H).

MS: *m/z* (%) 321 (5), 280 (100), 264 (35), 260 (38), 244 (15), 238 (15) 222 (25), 181 (40). HR-MS: *m/z* calcd for $C_{22}H_{27}NO$: 321.2092. Found: 321.2071.

19b

^1H NMR ($CDCl_3$, 200 MHz): δ = 0.56 (s, 9 H), 2.20–2.35 (m, 2 H), 2.46–2.58 (m, 1 H), 3.83 (dd, 1 H, *J* = 6.0,10.0 Hz), 3.96–4.10 (m, 3 H), 5.00–5.12 (m, 2 H), 5.77–6.00 (m, 2 H), 6.12 (dd, 1 H, *J* = 6.0, 10.0 Hz), 6.86 (d, 1 H, *J* = 6.0 Hz), 7.10–7.30 (m, 5 H).

(–)-(4*S*)-2-[(5*R*,6*S*)-6-Methyl-5-propargyl-cyclohexa-1,3-dienyl]-4-*tert*-butyl-4,5-dihydro-oxazole (20a)

MeLi (1.6N in Et_2O, 1.2 mmol, 0.75 mL) was added to a solution of oxazoline complex **3b** (1.0 mmol) in THF (10 mL) at −90 °C. After warming to −78 °C over a period of 4 h, HMPA (1.7 mL) and propargyl bromide (10 mmol, 0.7 mL) were added. The reaction mixture was slowly warmed to r.t. and was stirred overnight. After work-up as described for **10a**, analysis of the crude mixture by GC. showed the formation of a single product. Flash chromatography (hexane−Et_2O, 6:1) yielded **20a** (202.2 mg, 79%).

$[\alpha]^{20}_D$ –406.7 (c 0.595, $CHCl_3$).

IR (CH_2Cl_2): 3303s, 3040w, 2961vs, 2904s, 2870s, 1651m, 1613s, 1574w, 1479w, 1402w, 1364w, 1349m, 1336w, 1299m, 1241m, 1209w, 1113w, 1067m, 1051m, 1036m, 984m, 964m cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.87 (s, 9 H), 1.05 (d, 3 H, *J* = 7.1 Hz), 1.94 (t, 1 H, *J* = 2.6 Hz), 1.95-2.35 (m, 3 H), 2.99 (q, 1 H, *J* = 7.1 Hz), 3.85- 4.20 (m, 3 H), 5.86-6.08 (m, 2 H), 6.55-6.60 (m, 1 H).

MS: *m/z* (%) 258 (22), 257 (10), 218 (15), 200 (100), 161 (18), 160 (26), 146 (29), 119 (56), 118 (27), 117 (10), 115 (10), 108 (13), 105 (20), 91 (70).

HR-MS: *m/z* calcd for $C_{17}H_{23}NO$: 257.1779. Found: 257.1769.

(–)-1-[(1*S*,6*R*)-5-((4*S*)-4-Isopropyl-4,5-dihydro-oxazol-2-yl)-6-methyl-cyclohexa-2,4-dienyl]-ethanone (21a) and 1-[(1*R*,6*S*)-5-((4*S*)-4-Isopropyl-4,5-dihydro-oxazol-2-yl)-6-methyl-cyclohexa-2,4-dienyl]-ethanone (21b)

A pressure resistant Schlenk tube equipped with a pressure gauge was charged with a solution of complex **3a** (678 mg, 2.0 mmol) in THF (20 mL). To this magnetically stirred solution at −90 °C under N_2 was added dropwise MeLi (1.48 mL of a 1.62M Et_2O solution, 2.40 mmol). The reaction was warmed to −78 °C over a period of 3 h and then MeI (1.25 mL, 10 equiv, distilled from P_2O_5) and anhyd MeCN (20 mL) were added. The reaction vessel was placed in a liquid N_2 bath, evacuated, and placed under an atmosphere of CO. The liquid N_2 bath was replaced by a dry ice/acetone bath and pressure of CO was increased to 4 bar. The reaction was left to warm to r.t. and was stirred overnight. CO was vented and the excess MeI and solvents were evaporated. The residue was dissolved in 20 mL of anhyd THF and cannulated into a 60 mL anhyd Schlenk tube containing a dispersion of NaH (240 mg, 3 equiv, 60% oil dispersion, prewashed with anhyd pentane) in anhyd THF (5 mL) at −78 °C. After 15 min HMPA (3.5 mL) and MeI (1.25 mL) were added, the temperature was raised to 20 °C over a period of 4 h, and the solution stirred overnight. Volatiles were evaporated in vacuum, the residue dissolved in Et_2O (30 mL), washed with a sat. NH_4Cl solution (10 mL) and H_2O (2 × 10 mL). The combined aq phases were extracted with Et_2O (3 × 20 mL), and the combined organic phases were dried ($MgSO_4$), filtered and evaporated. The crude product mixture was analyzed by HPLC (hexane–EtOAc, 3:1; 5mL/min) and found to consist of a mixture of products in a 95:5 ratio. Flash chromatography (hexane−Et_2O, 3:1, then 100% Et_2O) afforded **21a** (255 mg, 49%) and **21b** (15 mg, 3% (impure)). A pure sample of **21b** was obtained by preparative HPLC.

21a

Mp = 69–71 °C (MeOH).

$[\alpha]^{20}_D$ –312.8 (c 1.05, $CHCl_3$).

IR (CH_2Cl_2): 3065w, 3050w, 2980vs, 2930s, 2905s, 2970s, 1707vs, 1652s, 1615vs, 1578w, 1466m, 1460m, 1405w, 1385m, 1366s, 13o3w, 1277w, 1270w, 1260w, 1237s, 1226s, 1151w, 1095m, 1007vs, 960m, 911w, 893w cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.86 (d, 3 H, *J* = 6.7Hz), 0.89 (d, 3 H, *J* = 6.8 Hz), 0.96 (d, 6 H, *J* = 6.8 Hz), 1.23 (s, 3 H), 1.80–2.00 (m, 1 H), 3.07 (bq, 1 H, *J* = 6.7Hz), 3.98–4,30 (m, 3 H), 6.01 (dd, 1 H, *J* = 9.8, 5.4 Hz), 6.37 (bd, 1 H, *J* = 9.8 Hz), 6.59 (bd, 1 H, *J* = 5.4 Hz).

MS: m/z (%) 218 (47), 204 (18), 133 (100), 105 (72).

HR-MS: *m/z* calcd for $C_{16}H_{23}NO_2$: 261.1728. Found: 261.1733.

Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.49; H, 8.79; N, 5.36.

21b

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.887 (d, 3 H, *J* = 6.8Hz), 0.892 (d, 3 H, *J* = 6.9Hz), 0.94 (d, 3 H, *J* = 6.8Hz), 1.25 (s, 3 H), 1.82–1.95 (m, 1 H), 2.22 (s, 3 H), 3.08 (dq, 1 H, *J* = 1.0, 6.9 Hz), 4.00–4.30 (m, 3 H), 6.02 (dd, 1 H, *J* = 5.5,10 Hz), 6.39 (bd, 1 H, *J* = 10Hz), 6.60 (bd, 1 H, *J* = 1.0, 5.5 Hz).

(–)-1-[(1*S*,6*R*)-5-((4*S*)-4-*tert*-Butyl-4,5-dihydro-oxazol-2-yl)-6-methyl-cyclohexa-2,4-dienyl]-ethanone (22a)

The reaction was carried out exactly as that described for **21a** but using complex **3b** in place of **3a** on a 1.0 mmol scale. HPLC analysis showed the formation of a single diastereoisomer. Flash chromatography (hexane−Et_2O, 3:1 to 100% Et_2O) afforded **22a** (165 mg, 60%), mp = 79.5–80.5 °C.

$[\alpha]^{20}_D$ –311 (c 1.05, $CHCl_3$).

IR (CH_2Cl_2): 3058w, 2965s, 2933m, 2905m, 2871m, 1703vs, 1651m, 1613s, 1479m, 1456m, 1400m, 1383m, 1364s, 1300m, 1236m, 1153m, 1098m, 1052m, 1007s, 956m, 888m cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.90 (3 H, d, *J* = 7.2Hz), 0.92 (s, 9 H), 1.23 (s, 3 H), 2.23 (s, 3 H), 3.11 (dq, 1 H, *J* = 1.5,7.0 Hz), 3.90–3.98 (m, 1 H), 4.09–4.22 (m, 2 H), 6.03 (dd, 1 H, *J* = 5.5,9.9 Hz), 6.38 (d, 1 H, *J* = 9.9 Hz), 6.60 (d, 1 H, *J* = 5.5Hz).

MS: *m/z* (%) 275 (5), 232 (100), 218 (25), 188 (10), 174 (5), 160 (14), 133 (35), 105 (17). HR-MS: *m/z* calcd for $C_{17}H_{25}NO_2$: 275.1885. Found: 275.1883.

Anal. calcd for $C_{17}H_{25}NO_2$: C, 74.14, H, 9.15, N, 5.08. Found: C, 73.90, H, 9.06, N 4.93.

Sequential Nucleophile/Electrophile Additions to Complex 6 ((2*S*)-2-Methoxymethyl-pyrrolidin-1-yl)-[(5*R*,6*S*)-6-methyl-5-(3-trimethylsilanyl-prop-2-ynyl)-cyclohexa-1,3-dienylmethylene]-amine (23a)

MeLi (1.27 N in Et_2O, 1.2 mmol, 0.945 mL) was added to a solution of hydrazone complex **6** (354 mg, 1.0 mmol) in THF (10 mL) at −78 °C. After warming to −40 °C over a period of 2 h, the solution was stirred at this temperature for an additional 2 h before being recooled to −78 °C. HMPA (1.7 mL) and 3-trimethylsilylpropargyl bromide (5 mmol, 0.7 mL) were added. The stirred reaction mixture was slowly warmed to r.t. overnight. Purification by flash chromatography (hexane−Et_2O, 15:1) afforded **23a** (248 mg, 72%). ^{1}H NMR 400 MHz showed only traces (< 1%) of another diastereoisomer.

$[\alpha]^{20}_D$ –420 (c 0.41, $CHCl_3$).

IR (CH_2Cl_2): 3030w, 2985s, 2961s, 2926m, 2900m, 2876m, 2168m, 1545m, 1458m, 1368m, 1340m, 1114s, 1029w, 972w, 845vs cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.15 (s, 9 H), 1.02 (d, 3 H, *J* = 7.2 Hz), 1.80–2.00 (m, 4 H), 2.00–2.20 (m, 3 H), 2.90–3.00 (m, 2 H), 3.38 (s, 3 H), 3.45–3.55 (m, 4 H), 5.77 (d, 1 H, *J* = 5.5 Hz), 5.83 (dd, 1 H, *J* = 5.5, 9.2 Hz), 6.01 (dd, 1 H, *J* = 5.5, 9.2), 6.89 (s, 1 H).

MS: *m/z* (%) 344 (8), 299 (7), 233 (41), 173 (19), 114 (24), 70 (100).

HR-MS: *m/z* calcd for $C_{20}H_{32}N_2OSi$: 344.2283. Found: 344.2268.

[(5R,6S)-6-Butyl-5-(3-trimethylsilanyl-prop-2-ynyl)-cyclohexa-1,3-dienylmethylene]-((2S)-2-methoxymethyl-pyrrolidin-1-yl)-amine (24a)

The reaction was carried out as described for **23a** using complex **6** (354 mg, 1.0 mmol), 3-trimethylsilyl propargyl bromide and n-BuLi (1.54 N in hexane, 1.2 mmol, 0.714 mL) as nucleophile. Purification by flash chromatography (hexane−Et_2O, 15:1) yielded **24a** (266 mg, 69%). The 400 MHz ^1H NMR spectrum showed traces (<1%) of another diastereoisomer.

$[\alpha]^{20}_D$ –318 (c 0.445, $CHCl_3$).

IR (CH_2Cl_2): 3052w, 3038w, 2959s, 2932s, 2900s, 2863s, 2854s, 2822m, 2169s, 1545m, 1459m, 1368m, 1340m, 1322m, 1305m, 1278m, 1223m, 1198m, 1116s, 1030m, 971m, 900m, 846s cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 0.15 (s, 9 H), 0.91 (br.t, 3 H, *J* = 6.0 Hz), 1.20–1.40 (m, 6 H), 1.80–2.05 (m, 4 H), 2.05–2.12 (m, 1 H, *J* = 8.8, 16.6 Hz, H-C-C(5')), 2.19–2.26 (m, 1 H, *J* = 6.6, 16.6 Hz), 2.24–2.25 (m, 1 H), 2.85–3.00 (m, 2 H), 3.37 (s, 3H), 3.40–3.47 (m, 4 H), 5.73–5.80 (m, 2 H), 5.99 (dd, 1 H, *J* = 5.1, 8.8 Hz), 6.89 (s, 1 H).

MS: *m/z* (%) 386 (10), 341 (5), 275 (27), 173 (21), 114 (26), 70 (100).

HR-MS: *m/z* calcd for $C_{23}H_{38}N_2OSi$: 386.2753. Found: 386.2706.

((2*S*)-2-Methoxymethyl-pyrrolidin-1-yl)-[(5*R*,6*S*)-6-phenyl-5-(3-trimethylsilanyl-prop-2-ynyl)-cyclohexa-1,3-dienylmethylene]-amine (25a)

The reaction was carried out as described for **23a** using complex **6** (354 mg, 1.0 mmol), 3-trimethylsilylpropargyl bromide and PhLi (2 N in cyclohexane−Et_2O, 1.2 mmol, 0.6 mL) as the nucleophile. Purification by flash chromatography (hexane−Et_2O, 20:1 to 10:1) yielded **25a** (297.5 mg, 73%). The 400 MHz ^1H NMR spectrum showed traces (<1%) of another diastereoisomer.

$[\alpha]^{20}_D$ –371.8 (c 0.6, $CHCl_3$).

IR (CH_2Cl_2): 3054w, 3029w, 2961s, 2915m, 2898m, 2818m, 2170s, 1631w, 1599w, 1545s, 1493m, 1452m, 1366m, 1339s, 1322m, 1224m, 1198m, 1121m, 1032m, 1005w, 971w, 908m, 845s cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 0.21 (s, 3 H), 1.80–2.00 (m, 4 H), 2.25–2.41 (m, 2 H), 2.51–2.57 (m, 1 H), 2.93–3.01 (m, 1 H), 3.08 (s, 3 H), 3.16–3.53 (m, 4 H), 4.32 (s, 1 H), 5.76 (dd, 1 H, *J* = 5.9, 9.2 Hz), 6.08–6.16 (m, 2 H), 6.88 (s, 1 H), 7.10–7.30 (m, 5 H).

MS: *m/z* (%) 407 (26), 406 (23), 361 (18), 295 (26), 180 (16), 173 (24), 114 (18), 96 (21), 70 (100).

HR-MS: *m/z* (%) calcd for $C_{25}H_{34}N_2OSi$: 406.2440. Found: 406.2440.

1-{5-[(2*S*)-2-Methoxymethyl-pyrrolidin-1-ylimino)-methyl]-(1*S*,6*R*)-1,6-dimethyl-cyclohexa-2,4-dienyl}-ethanone(26a)

A pressure resistant Schlenk tube equipped with a pressure gauge was charged with a solution of complex **6** (354 mg, 1.0 mmol) in THF (15 mL). To the stirred, cold (−78 °C) solution under N_2 was added dropwise MeLi (0.688 mL of a 1.6 M Et_2O solution, 1.1 mmol). The reaction was warmed to −40 °C over a period of 2 h, stirred at this temperature for 1 h, recooled to −78 °C and then treated with MeI (0.620 mL, 10 equiv) and HMPA (1.7 mL). 4 bar of CO was then pressed onto the solution. The reaction was left to warm slowly to r.t. and stirred overnight. CO was vented and the excess of MeI and solvents were evaporated. The crude red oil was taken up in Et_2O−hexane and filtered through a plug of silica gel. After concentration, the residue was dissolved in THF (15 mL), cooled to −78 °C and reacted with EtONa (0.60 mL of a 2.64 M solution in EtOH) and MeI (0.50 mL, 8 mmol). The temperature was raised slowly to r.t. and was stirred overnight. Volatiles were removed in vacuum and the crude product submitted to flash chromatography (hexane−Et_2O 20:1) to give **26a** (168 mg, 58%). Integration of the CH=N signals in the ^1H NMR spectrum of a sample analyzed before chromatography showed a diastereoisomeric ratio of >98:2.

$[\alpha]^{20}_D$ –434.4 (c 1.44, $CHCl_3$).

IR (CH_2Cl_2): 3070s, 2990s, 2950s, 2850s, 1700s, 1665s, 1550m, 1450m, 1350m, 1110s cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 0.85 (d, 3 H, *J* = 6.8 Hz), 1.20 (s, 3 H), 1.80–2.05 (m, 4 H), 2.24 (s, 3 H), 2.98–3.06 (m, 1 H), 3.13 (dq, 1 H, 1.5, 6.8 Hz), 3.38 (s, 3 H), 3.32–3.40 (m, 1 H), 3.44 (dd, 1 H, *J* = 9.2, 15.8 Hz), 3.60 (dd, 1 H, *J* = 3.7, 9.2 Hz), 3.62–3.69 (m, 1 H), 5.78 (d, 1 H, *J* = 5.5 Hz), 6.00 (dd, 1 H, *J* = 5.5, 10.0 Hz), 6.15 (d, 1 H, *J* = 10.0 Hz), 6.93 (s, 1 H).

MS: *m/z* (%) 290 (59), 247 (100), 215 (9), 187 (31), 114 (35), 70 (98).

HR-MS: *m/z* calcd for $C_{17}H_{26}N_2O_2$: 290.1994. Found 290.1985.

1-{(6*R*)-6-Butyl-5-[(2*S*)-2-methoxymethyl-pyrrolidin-1-ylimino)-methyl]-1(*S*)-methyl-cyclohexa-2,4-dienyl}-ethanone (27a)

The reaction used BuLi as nucleophile and was carried out as described for **26a** to give **27a** (225.9 mg, 68%). ^1H NMR of CH=N (7.03 and 7.06) showed a diastereoisomeric ratio of 99:1.

$[\alpha]^{20}_D$ –99.9 (c 1.33, $CHCl_3$).

IR (CH_2Cl_2): 3045m, 2931s, 2872s, 1699vs, 1642w, 1544m, 1458m, 1354m, 122m, 1198w, 1119s, 909s cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 0.81 (t, 3 H, *J* = 7.0 Hz), 1.19–1.30 (m, 5 H), 1.19 (s, 3 H), 1.40–1.50 (m, 1 H), 1.82–2.10 (m, 4 H), 2.24 (s, 3 H), 2.96–3.03 (m, 1 H), 3.14–3.18 (m, 1 H), 3.38 (s, 3 H), 3.38–3.50 (m, 2 H), 3.59–3.65 (m, 2 H), 5.80 (d, 1 H, *J* = 5.6 Hz), 5.97 (dd, 1 H, *J* = 5.6, 10.1 Hz), 6.20 (d, 1 H, *J* = 10.1 Hz), 7.03 (s, 1 H).

MS: *m/z* (%) 332 (8), 289 (24), 187 (20), 114 (26), 70 (100), 45 (42).

HR-MS: *m/z* calcd for $C_{20}H_{32}N_2O_2$: 332.2464. Found 332.2510.

1-{5-[((*S*)-2-Methoxymethyl-pyrrolidin-1-ylimino)-methyl]-(1*S*,6*R*)-1-methyl-6-vinyl-cyclohexa-2,4-dienyl}-ethanone (28a)

The reaction used vinyllithium as the nucleophile (generated from tetravinyltin/MeLi) and was carried out as described for **26a** to give **28a** (181 mg, 60%). ^1H NMR of the CH=N signals (6.91 and 6.93) showed a diastereoisomeric ratio of 180:1.

$[\alpha]^{20}_D$ –433.6 (c 0.90, $CHCl_3$).

IR (CH_2Cl_2): 3078w, 3039w, 2976s, 2929s, 2880s, 1702vs, 1633m, 1544s, 1452m, 1352s, 1306w, 1224m, 1122s, 1094s, 909s cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 1.24 (s, 3 H), 1.82–2.07 (m, 4 H), 2.20 (s, 3 H), 2.99–3.06 (m, 1 H), 3.32–3.40 (m, 1 H), 3.37 (s, 3 H), 3.43 (dd, 1 H, *J* = 7.0, 9.2 Hz), 3.60 (dd, 1 H, *J* = 3.3, 9.2 Hz), 3.64–3.70 (m, 1 H), 3.73 (d, 1 H, *J* = 9.2 Hz), 4.95 (dd, 1 H, *J* = 2.2, 9.9 Hz), 5.19 (dd, 1 H, *J* = 2.2, 17.0 Hz), 5.66 (ddd, 1 H, *J* = 9.2,9.9,17.0 Hz), 5.83 (d, 1 H, *J* = 5.5 Hz), 6.02 (dd, 1 H, *J* = 5.5, 10.3 Hz), 6.20 (d, 1 H, *J* = 10.3 Hz), 6.93 (s, 1 H).

MS: *m/z* (%) 302 (14), 259 (27), 187 (15), 144 (31), 129 (71), 70 (100), 45 (90).

HR-MS: *m/z* calcd for $C_{18}H_{26}N_2O_2$: 302.1994. Found 302.1965.

1-{5-[((*S*)-2-Methoxymethyl-pyrrolidin-1-ylimino)-methyl]-(1*S*,6*R*)-1-methyl-6-phenyl-cyclohexa-2,4-dienyl}-ethanone 29a

The reaction used PhLi as the nucleophile and was carried out as described for **26a** to give **29a** (214 mg, 61%). ^1H NMR of the CH=N signals (6.84 and 6.86) showed a diastereoisomeric ratio of 140:1.

$[\alpha]^{20}_D$ –712 (c 0.68, $CHCl_3$).

IR (CH_2Cl_2): 3052w, 2976w, 2880m, 1702vs, 1543s, 1452s, 1352s, 1223w, 1121s, 900w cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.38 (s, 3 H), 1.80 (s, 3 H), 1.80-195 (m, 4 H), 3.18–3.30 (m, 1 H), 3.22 (s, 3 H), 3.26 (dd, 1 H, *J* = 6.6, 9.6 Hz), 3.47 (dd, 1 H, *J* = 3.3, 9.6 Hz), 3.58–3.67 (m, 1 H), 4.17 (s, 1 H), 5.98 (dd, 1 H, J = 1.1, 4.8 Hz), 6.15–6.22 (m, 2 H), 6.84 (s, 1 H), 7.10–735 (m, 5 H).

MS: *m/z* (%) 352 (20), 309 (100), 291 (10), 263 (10), 194 (32).

HR-MS: *m/z* calcd for $C_{22}H_{28}N_2O_2$: 352.2151. Found 352.2179.

Removal of the Chiral Auxiliary in 21a and in 26a-29a Adduct 30.

A 100 mL round bottom flask, equipped with a Dean-Stark trap, was charged with ketone **21a** (184.4 mg, 0.705 mmol), *p*-toluensulfonic acid monohydrate (135.4 mg, 0.712 mmol), ethylene glycol (0.250 mL, 6 equiv, 4.23 mmol), and anhyd toluene (45 mL) in an inert atmosphere. The solution was heated at reflux with azeotropic removal of water and the reaction was monitored by TLC. Additional portions of ethylene glycol (0.5+1 mL) were added after 12 h and 24 h. The solution was cooled to r.t. and washed with aq $NaHCO_3$ solution (10 mL). The aqueous phase was washed with Et_2O (3 × 10 mL), and the combined organic phases were dried ($MgSO_4$), filtered and evaporated. Flash chromatography (hexane−Et_2O, 20:1 to 10:1) afforded the ketal 4(S)-4,5-dihydro-4-(1-methylethyl)-2-{(5S,6R)-5,6-dimethyl-5-[2-methyl1,3-dioxolan-2-yl]cyclohexa-1,3-dien-1-yl}oxazole (129.3 mg, 60%) as a white solid, mp = 81–82 °C.

$[\alpha]^{20}_D$ –129.8 (c 1.6, $CHCl_3$).

IR (CH_2Cl_2): 3046w, 2965vs, 2936s, 2888s, 1650s, 1610vs, 1574w, 1481w, 1456m, 1400m, 1380s, 1365s, 1338w, 1301w, 1228s, 1173vs, 1148m, 1104m, 1091m, 1070m, 1046vs, 1020vs, 999s, 952s, 882m cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.84 (d, 3 H, *J* = 6.8 Hz), 0.94 (d, 3 H, *J* = 6.8Hz), 1.06 (d, 3 H, *J* = 6.8 Hz), 1.12 (s, 3 H), 1.33 (s, 3 H), 1.80–2.00 (m, 1 H), 2.77 (bq, 1 H, *J* = 6.8 Hz), 3.90–4.30 (m, 5 H), 5.94–5.97 (m, 2 H), 6.54–6.58 (m,1 H).

MS: *m/z* (%) 304 (10), 303 (50), 290 (30), 260 (100), 246 (25), 231 (20), 219 (61), 204 (80), 188 (30), 87 (100).

Anal. Calcd for $C_{18}H_{27}NO_3$: C, 70.79; H, 8.91; N, 4.58. Found: C, 70.61; H, 8.89; N, 4.57.

To a stirred solution of the above ketal (73.2 mg, 0.239 mmol) in anhyd CH_2Cl_2 (3 mL) was added MeOTf (0.052 mL, 2 equiv, distilled from P_2O_5) at 20 °C under N_2. After 1.5 h TLC indicated that all starting material was converted into a baseline product. $NaBH_4$ (30 mg, 0.789 mmol, 3.3 equiv) in 2 mL of anhyd THF−MeOH, 3:1 was added via cannula transfer. After 15 min. sat. aq NH_4Cl (1 mL) was added. Extraction CH_2Cl_2 (10 mL) and flash chromatography (hexane−Et_2O, 2:1) afforded aldehyde **30**[17](18 mg, 56%).

$[\alpha]^{20}_D$ –594 (c 1.27, $CHCl_3$).

Recovery of Aldehdes 30-33 from SAMP Hydrazone Dienes 26a-29a; General procedure

The hydrazone compound (1 equiv) was dissolved in MeOH (1 mL/mmol hydrazone). Aq H_2SO_4 (50%, 2 mL/mmol hydrazone) was added and the reaction was stirred, until there was no hydrazone detected by TLC (12–20 h). The solution was diluted with H_2O (10 mL). Extraction with Et_2O (3 × 10 mL) and washing of the organic phase with H_2O, aq $NaHCO_3$, brine and dried over $MgSO_4$. Flash chromatography (hexane−Et_2O, 5:1) afforded the aldehydes **26a-29a**.[40]

Adduct 30

Treatment of **26a** (106.5 mg, 0.367 mmol), as described in the general procedure, afforded **30**[17] (52.3 mg, 80%). Transformation to the SAMP hydrazone and intgration of the ^{1}H NMR CH=N resonance showed a de >98%.

$[\alpha]^{20}_D$ –600.3 (c 0.348, $CHCl_3$).

Adduct 31

Treatment of **27a** (154.5 mg, 0.465 mmol), as described in the general procedure, afforded **31** (79.8 mg, 78%). Transformation to the SAMP hydrazone and intgration of the ^{1}H NMR CH=N resonance showed a de >98%.

$[\alpha]^{20}_D$ –452 (c 0.544, $CHCl_3$).

IR (CH_2Cl_2): 2959w, 2935m, 2862w, 1702m, 1672vs, 1567m, 1467w, 1173m cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.79 (t, 3 H, *J* = 8.0 Hz), 1.00–1.50 (m, 6 H,), 1.17 (s, 3 H), 2.23 (s, 3 H), 3.06–3.12 (m, 1 H), 6.18 (dd, 1 H, *J* = 5.2, 9.6 Hz), 6.72–6.77 (m, 2 H), 9.61 (s, 1 H).

MS: *m/z* (%)220 (1), 177 (3), 163 (13), 121 (90), 57 (100).

HR-MS: *m/z* calcd. for $C_{14}H_{20}O_2$: 220.1463. Found 220.1421.

Adduct 32

Treatment of **28a** (120.1 mg, 0.397 mmol), as described in the general procedure, afforded **32**[17] (55.2 mg, 73%). Transformation to the SAMP hydrazone and integration of the ^{1}H NMR CH=N resonance showed a single diastereoisomer.

$[\alpha]^{20}_D$ –531 (c 0.570, $CHCl_3$).

Adduct 33

Treatment of **29a** (62.1 mg, 0.176 mmol), as described in the general procedure, afforded **33**[17] (33.8 mg, 80%). Transformation to the SAMP hydrazone and integration of the ^{1}H NMR CH=N resonance showed a single diastereoisomer.

$[\alpha]^{20}_D$ – 857 (c 0.586, $CHCl_3$).

Sequential Nucleophile/Electrophile Additions to Complexes 8a and 8b

To a stirred solution of complex **8a** or **8b** (1 mmol) in THF or in toluene (5 mL) was added dropwise a solution of PhLi (0.726 mL of a 1.66 M solution in cyclohexane−Et_2O, 1.2 mmol) at –78 °C. The solution was warmed to –50 °C and stirred at this temperature for 2 h. After recooling to −78 °C, the co-solvant (HMPA or DMPU, 5 mmol, see Table 5) and TMS propargyl bromide (2.5 mmol) were added. The solution was left to slowly warm to r.t. and this was stirred for 16 h. Volatiles were removed in vacuum. The crude product was taken up in Et_2O and filtered over silica gel. Flash chromatography (hexane−Et_2O, 19:1) afforded aldehyde **34**. GC: column *OV-1701*; H_2 3 mL/min, 70 °C, 1 min, 10 °C/min, 250 °C: t_R 16.0 min. HPLC: column Chiracel *OD-H*; hexane–*i*PrOH, 99.5:0.5; 1mL/min; λ 254 nm: (−)-(*R*,*R*)-**34** t_R = 13 min, (+)-(*S*,*S*)-**34** t_R = 17 min. A 4:1 mixture of the enantiomers (+)-(*S*,*S*)-**34**:(−)-(*R*,*R*)-**34** showed an $[\alpha]^{20}_D$ = +480.0 (c = 0.46, $CHCl_3$).

IR ($CHCl_3$): 3009w, 2961w, 2819w, 2719w, 2172m, 1676s, 1572m, 1492w, 1453w, 1405w, 1324w, 1251m, 1174m, 1034w, 845s cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.17 (s, 9 H), 2.24 (dd, *J* = 16.7, 8.4, 1 H), 2.38 (dd, *J* = 16.7, 6.4, 1 H), 2.65–2.80 (m, 1 H), 4.11 (s, 1 H), 6.3 (m, 2 H), 6.97 (dd, *J* = 5.1, 1.2 1 H), 7.1–7.3 (m, 5 H), 9.55 (s,1 H).

^{13}C NMR (50 MHz, $CDCl_3$): 0.1 (CH_3), 25.1 (CH_2), 38.9 (CH), 41.9 (CH), 87.1 (C), 103.9 (C), 123.3 (CH), 126.9 (CH), 127.1 (CH), 128.6 (CH), 138.1 (C), 138.2 (CH), 141.0 (CH), 141.9 (C), 192.6 (CHO).

MS: *m/z* (%) 294 (3, M^+), 203 (26), 183 (15), 155 (100).

HR-MS**:** *m/z* calcd for $C_{19}H_{22}SiO$: 294.144. Found: 294.145.

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(25) **Crystal structure determination of 3a**: $Cr(CO)_3(C_{12}H_{15}NO)$, Mr = 325.3; μ = 0.782 mm^{-1}, dx = 1.451 $g.cm^{-3}$, monoclinic, *P*21, Z = 4, a = 11.0923(10), b = 11.2412(7), c = 12.0144(12)Å, β = 96.471(11)°, V = 1488.5(2)$Å^3$, yellow prism 0.10 x 0.20 x 0.26. Cell dimensions and intensities were measured at 200 K on a Stoe IPDS diffractometer with graphite-monochromated Mo Kα radiation (λ = 0.71069 Å). 22868 measured reflections, 7125 unique reflections of which 3728 were observables (|Fo| > 4 σ (Fo)); Rint for equivalent reflections 0.069. Data were corrected for absorption (T min, max = 0.8492, 0.9441). Full-matrix least-squares refinement based on F using weight of $1/[\sigma^2(Fo)+ 0.0003(Fo)^2]$ gave final values R = 0.032, *w*R2 = 0.032 and Flack parameter x = 0.02(5). Hydrogen atoms were placed in calculated positions.
(26) Crystallographic data (excluding structure factors) have been deposited to the *Cambridge Crystallographic Data Base* (deposition No. CCDC163963, CCDC163964 for **3a** and **6** respectively). Copies of the data can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: Int. + 44(1223)336-033; e-mail: deposit@ccdc.cam.ac.uk).
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(29) **Crystal structure determination of 6**: $Cr(CO)_3(C_{13}H_{18}N_2O)$, Mr = 354.3; μ = 0.689 mm^{-1}, dx = 1.415 $g.cm^{-3}$, monoclinic, *P*21, Z = 4, a = 10.229(2), b = 13.276(2), c = 12.267(3)Å, β = 92.973(6)°, V = 1663.6(6)$Å^3$, yellow prism 0.11 × 0.24 × 0.24. Cell dimensions and intensities were measured at room temperature on a Philips PW1100 diffractometer with graphite-monochromated Mo Kα]radiation (λ = 0.71069 Å). Two reference reflections measured every 60 min showed variation of about 10%; all intensities were corrected for this drift. −10 < h <10; 0 < k < 14; 0 < l < 12 and all anti− reflections; 4522 measured reflections, 4194 unique reflections of which 3155 were observables (|Fo| > 4 σ (Fo)); Rint for equivalent reflections 0.031. Data were corrected for absorption (T min, max = 0.8814, 0.9245). Full-matrix least-squares refinement based on F using weight of $1/[\sigma^2(Fo)+ 0.0003(Fo)^2]$ gave final values R = 0.050, *w*R2 = 0.047 and Flack parameter x = 0.02(6). Hydrogen atoms were placed in calculated positions. The methoxymethyl substituant of the anti-conformer is disordered. Two disordered fragments have been refined with population parameters of 0.70 and 0.30 for C12b-O1b-C13b and C12b'-O1b'-C13b' respectively. The partial decomposition of the crystal during data collection and the presence of the disorder, led to relatively large uncertainties in the final coordinates.

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