Ligand-mediated enantioselective addition of lithium carbazolates to aldehydes

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The enantioselective synthesis of acyclic pyrrole, indole and other *N*-carbazole carbinols *via* ligand-mediated addition of lithium carbazolates to aldehydes, together with studies into their catalytic enantioselective synthesis using substoichiometric base and ligand, are reported. The subsequent exploitation of the resulting stereocentre as a controlling element in 1,3-*syn*- and *anti*-selective reduction of *β*-ketones and elaboration to homoallylic alcohols is also described.

Introduction

The ligand-mediated enantioselective addition of organometallics to electrophiles has been, and remains, an area of significant study.[1] One particularly privileged system is the *β*-amino alcohol ligand-mediated addition of dialkylzincs to aldehydes. One aspect is the lack of a background reaction which guarantees that the reaction only takes place within the chiral space of the associated ligands.[2]

In the case of additions of organolithiums to electrophiles,[3] the high reactivity of the organolithiums and the exothermic nature of their reactions leads to potential difficulties in controlling selectivity.[4] The transition states are much earlier, by the Hammond postulate, and thus it is more challenging to attain the energy difference between the diastereomeric transition states required for high selectivity.[4] Regardless of this obstacle, certain ligands and processes have been discovered in which high levels of control are observed.[3]

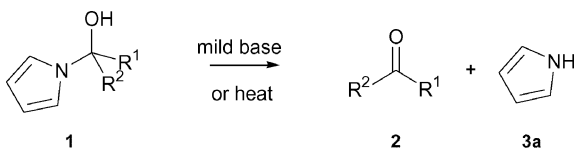
In the addition of organolithiums to aldehydes, it has been possible to attain good to excellent selectivities. However, temperatures below −100 °C are often required.[3c] Additionally, most examples lack substrate generality, in both nucleophilic and electrophilic components, and many use lithium amides/alkoxides as the chiral controller (*via* co-aggregation) resulting in the need for excess quantities of organolithium reagents.[5]

We have been interested in the synthesis and chemistry of *N*-heterocyclic *N*-carbinols, specifically those derived from pyrrole, indole and other carbazoles.[6–8] Having developed the addition of lithium pyrrolate to aldehydes as a method of their protection,[6a] we envisaged that it should be possible to carry out this process in an enantioselective fashion. The generated stereocentre might then be exploited as a controlling element in the synthesis of enantioenriched chiral aldehydes.[9–11] To this end an investigation into the ligand-mediated addition of lithium carbazolates to aldehydes was started and the preliminary findings have been disclosed.[6c] We now present a full account of our investigations into the enantioselective addition of lithium carbazolates to aldehydes, the ability of this functional group to direct 1,3-reductions, and the development of a catalytic enantioselective variant of the addition.

Results and discussion

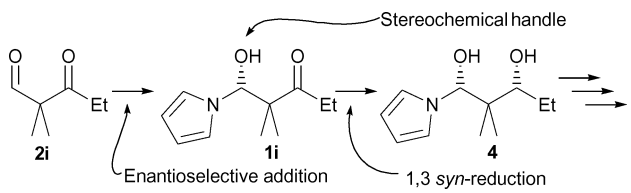
The synthesis of enantioenriched aldehydes is often crucial in the synthetic planning and completion of the total synthesis of natural products.[12] In most cases these aldehydes are accessed by reduction of ester and/or oxidation of alcohol functions.[12]

It had previously been shown that *N*-pyrrole carbinols may function as masked carbonyls from which the carbonyl can be revealed by treatment with mild bases and/or by application of heat,[6a,7] thus avoiding acidic deprotection, oxidation or reduction protocols (Scheme 1).



Scheme 1 Pyrrole carbinols as masked carbonyls.

Our concept required the enantioselective addition of pyrrole to an aldehyde to furnish a new stereocentre (Scheme 2). This new *N*-carbinol stereocentre could then be exploited as a stereodirecting group in the manipulation of a second prochiral group already present in the protected aldehyde. Subsequent elimination of pyrrole would reveal the desymmetrised aldehyde ready for further synthetic transformations.[6,13]



Scheme 2 Pyrrole carbinols as stereochemical tools.

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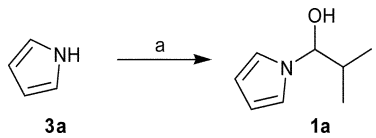
We envisaged that the enantioselective synthesis of pyrrole carbinols could be achieved *via* a ligand-mediated addition of lithium pyrrolate to aldehydes. Research within our group had demonstrated that lithium pyrrolate formed insoluble aggregates in non-coordinating solvents such as toluene and hexane.[14] It was further shown that these aggregates did not react with conjugated acceptors even over prolonged periods of time.

However, under similar conditions, the reaction of lithium pyrrolate with isobutyraldehyde was complete within 15 minutes when performed in toluene and even more rapidly in hexane where the reaction was complete within five minutes (Scheme 3). Thus for our initial investigations it was decided to use one equivalent of ligand with respect to lithium pyrrolate.



Scheme 3 *Reagents and conditions*: (a) i) *n*-BuLi, −78 °C, hexane or toluene; ii) isobutyraldehyde, −78 °C; iii) $NH_4Cl_{(aq)}$.

Identification of a suitable ligand and scope of reaction

A range of ligands and co-salts was selected from the literature that had been previously shown to give good selectivities in the 1,2-addition of organolithiums to electrophiles.[3c,15] The ability of these ligands to influence the addition of lithium pyrrolate to isobutyraldehyde in both hydrocarbon and ethereal solvents was assessed (Table 1).

Attempts to induce selectivity using lithium alkoxide **5** *via* co-aggregation with both a 1 : 1 mixture and a 3 : 1 mixture of **5** to lithium pyrrolate **3b**, in the hope of producing the corresponding tetramers, gave disappointing results.[15,16] Results with sparteine **6** were also disappointing: however it was interesting that when amine **7** was used, the same selectivity was observed with the three non-coordinating solvents indicating that either virtual complete ligation or significant rate acceleration had occurred. The most promising result came when using diether **8** in toluene which provided the pyrrole carbinol in good yield and enantioselectivity. Overall it was observed that, for neutral ligands, toluene gave the greatest selectivity, the coordinating solvent tetrahydrofuran gave the lowest, and diethyl ether and hexane gave similar levels of control, albeit lower than that observed with toluene. Due to the success with ligand **8** and the scope for structural modification it was hoped that further optimization would be possible. To this end a series of diether ligands was synthesised and assessed (Table 2).

The results showed that increasing the steric bulk of the alkyl group on the ether oxygen, by changing the methyl groups to ethyl groups, led to complete loss of selectivity (entry a). A similar result was observed when the methyl was changed to a methoxymethyl group (entry b). BINOL-derived ligands also led to lower selectivities (entries d and e). Replacing the phenyl groups of diether **8** with sterically more demanding cyclohexyl groups had little effect on the stereochemical outcome of the reaction (entry c). Attempts to improve the selectivity by using more equivalents of ligand, a lower temperature, or diisopropylether as the solvent,[3b] had little effect on the asymmetric induction (Table 3).

Of the ligands and conditions studied, the optimal procedure in terms of simplicity and selectivity was that using one equivalent of diether **8** at −78 °C in toluene. The scope of these conditions over a range of aldehydes and heterocycles was examined next (Table 4).

The results of these experiments indicated that the stereoinduction was maintained for a range of branched and unbranched aliphatic aldehydes, whilst for conjugated aldehydes the selectivity was lower. When the nucleophile was changed to simple indoles an increase in selectivity was observed with the highest selectivity observed in the case of the reaction of 3-vinylindole with trimethylacetaldehyde (entry l). Disappointingly, in the case of protected tryptamines much lower selectivities were observed and only poor yields of the carbinols could be isolated (entries m–o). These results indicate that the carbamates are altering the nature of the lithium complexes, perhaps by forming aggregates of lower reactivity.[17] The reaction with carbazole proceeded smoothly: however, the carbinol and residual carbazole were inseparable by chiral HPLC and attempts to purify the product led to decomposition of the carbinol (entry p). An attempt with imidazole was made, but the product was too unstable and not isolable. The absolute stereochemistry of **1b** was determined by the Mosher esterification method and the others by analogy.[6c,18] The stereochemical outcome of these reactions is consistent with the model proposed by Tomioka *et al.* for the addition of organolithiums to imines and *α*,*β*-unsaturated esters mediated by ligand **8** (Fig. 1).[19]

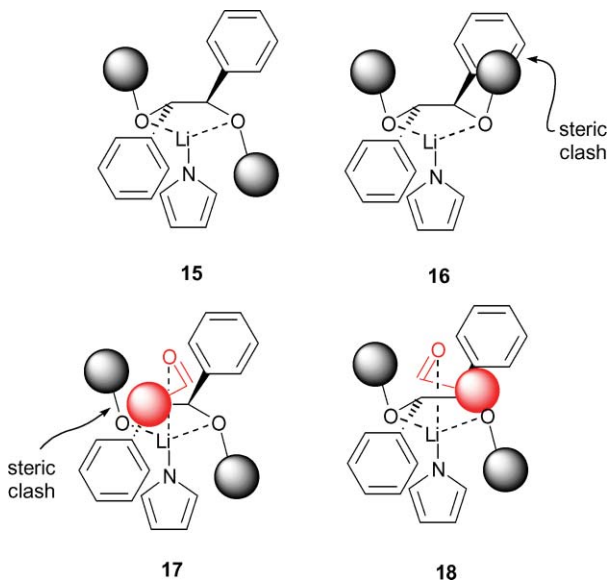
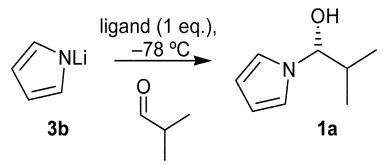


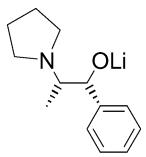
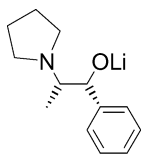
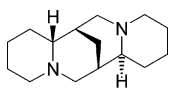
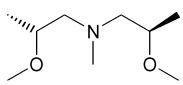
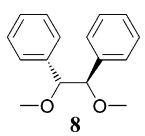
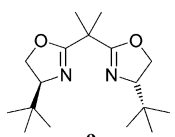
Fig. 1 Stereochemical model.[6c]

It is proposed that the reacting complex is one where the lithium is ligated by the two ethereal oxygen atoms of **8**. The methyl groups adopt a conformation that minimises steric clash with the *vicinal* phenyl groups, shown by **15**. This relays the chirality of the backbone to the ligating ethers generating a chiral space around the bound lithium atom. Two diastereomeric transition states are then possible by attack of either the *re* or *si* face of the aldehyde complexed to the lithium metal.

The unfavourable steric clash between the methyl group and the aldehyde in **17** destabilises this complex with respect to complex **18** leading to the observed stereochemical outcome. In

Table 1 Initial ligand screen



		Tetrahydrofuran		Diethyl ether		Toluene		Hexane	
Entry	Ligand	ee (%)[a]	Yield (%)[b]	ee (%)[a]	Yield (%)[b]	ee (%)[a]	Yield (%)[b]	ee (%)[a]	Yield (%)[b]
a	 **5**	−2	88	−8	92	−20	85	−8	90
b[c]	 **5**	−2	85	16	95	−17	88	−8	89
c	 **6**	7	87	−3	91	14	92	3	92
d	 **7**	19	91	25	89	25	92	25	95
e	 **8**	12	88	60	93	63	90	45	90
f	 **9**	—	—	—	—	16	78	—	—

[a] Determined by chiral HPLC analysis. [b] Determined by ^{1}H NMR integration with respect to an internal standard. [c] 3 equivalents of lithium alkoxide **5** used.

the case of larger ethereal substituents (Table 2), increased steric clash between the ligated pyrrolate and these groups presumably generates complex **16** which is pseudo-achiral in the space directly around the pyrrole unit, thus leading to diminished selectivities.

Application as a stereodirecting group

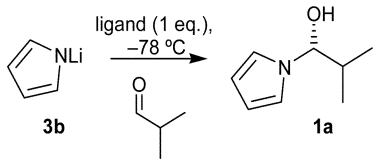
Having identified a ligand which efficiently mediates the enantioselective synthesis of *N*-carbazole carbinols, the ability of the new stereocentre to control a diastereoselective reaction was investigated next. The decision was made to investigate directed *β*-ketone reductions. Due to the speed, simplicity and convenience of synthesising racemic ketone **1i**, initial investigations into 1,3-reductions were made using this material. Samples were subjected to a number of standard reduction conditions (Table 5).

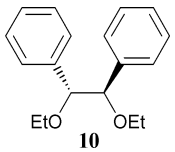
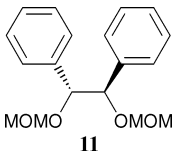
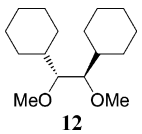
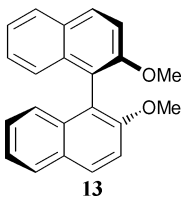
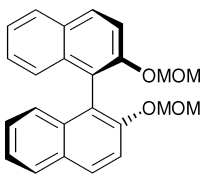
These reactions proved successful allowing access to either diastereomer in high selectivity, with zinc borohydride[20] providing the *syn*-diastereomer and tetramethylammonium triacetoxyborohydride providing the *anti*-diol.[21]

The relative stereochemistry was determined by the method of Rychnovsky *et al*.[22] Acid catalysed ketalisation of diol **4** (4 : 1 dr) in acetone gave *syn*-acetonide **21** and *anti*-acetonide **22** as an inseparable mixture (Scheme 4).

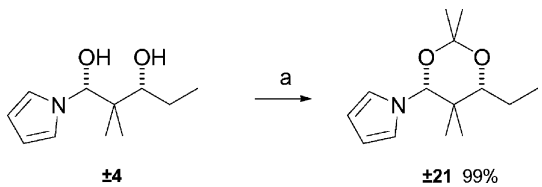
The chemical shifts of the acetonide methyl groups in **21** are consistent with a chair conformation, and hence show the *syn*-relationship of the alcohols in diol **4**. Additional confirmation

Table 2 Study of diether ligands



Entry	Ligand	ee (%)[a]	Yield (%)[b]
a	 **10**	<10	74
b	 **11**	<10	76
c	 **12**	50	82
d	 **13**	<10	84
e	 **14**	26	83

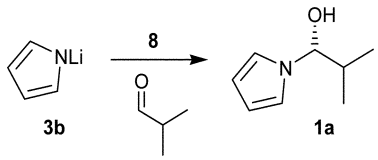
[a] Determined by chiral HPLC analysis. [b] Determined by ^{1}H NMR integration with respect to an internal standard.



Scheme 4 *Reagents and conditions*: (a) *p*-TsOH (cat.), $Me_2C{=}O$, $Me_2C(OMe)_2$, rt.

comes from the chemical shifts observed for the minor diastereomer in the ^{13}C NMR which are diagnostic for the twist-boat conformation that would be expected for the acetonide **22** derived from the *anti*-diol **20** (Fig. 2).

Table 3 Solvent, temperature and stoichiometry study



Entry	Eq. **8**	Solvent	Temperature/°C	ee (%)[a]	Yield (%)[b]
a	2	PhMe	−78	63	85
b	2	Et_2O	−78	56	80
c	1	i-Pr_2O	−78	45	83
d	1	PhMe	−95	66	82
e	1	i-Pr_2O	−95	59	80

[a] Determined by chiral HPLC analysis. [b] Determined by ^{1}H NMR integration with respect to an internal standard.

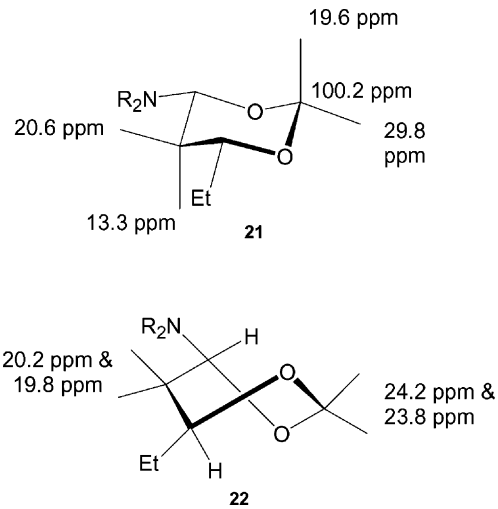


Fig. 2 Determination of relative stereochemistry by ^{13}C NMR analysis.

Stereodivergent synthesis of homoallylic alcohol 23

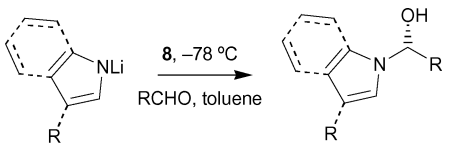
The success of the *syn*- and *anti*-reductions above enabled the stereodivergent synthesis of both enantiomers of homoallylic alcohol **23** to be carried out.

The addition of lithium pyrrolate to aldehyde **2i** mediated by ether **8** on a 10 mmol scale proceeded with 93% isolated yield and 46% ee (*cf.* 50% ee for 1 mmol). Subsequent reduction using the previously optimized conditions gave *syn*- and *anti*-diols (*R*,*R*)-**4** and (*R*,*S*)-**20** which were then subjected to tandem deprotection-HWE conditions to complete the synthesis of both enantiomers of homoallylic alcohol **23** (Scheme 5). Interestingly, when we attempted this reaction using Masamune–Roush conditions[23] a complex mixture of unidentified products resulted, however using either the lithium or sodium salt of *t*-butyldiethylphosphonoacetate gave the desired olefin in excellent yield (Table 6).

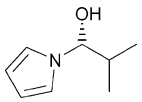
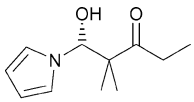
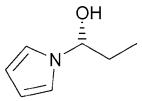
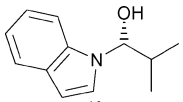
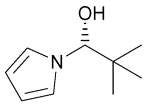
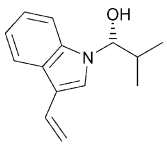
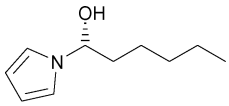
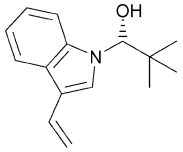
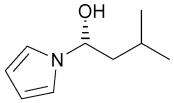
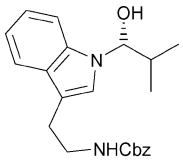
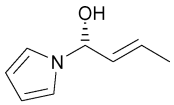
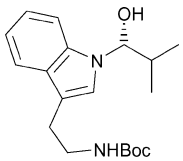
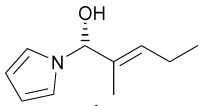
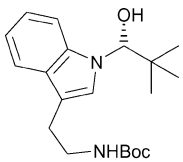
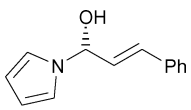
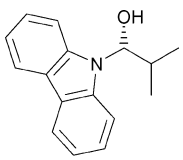
Investigations into amine ligands

One of the drawbacks of ligand **8** was that its separation from the enantiomerically enriched carbinol was often problematic. A potential solution to this problem was to introduce an

Table 4 Scope of the addition

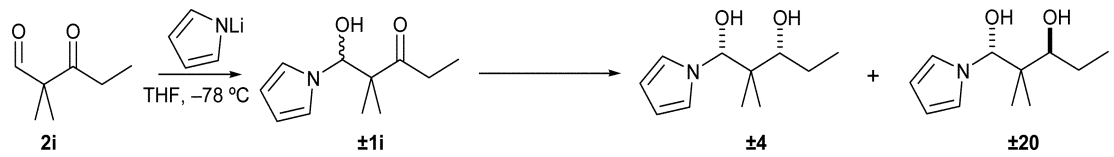


19 **1**

Entry	Adduct **1**	ee (%)[a]	Yield (%)	Entry	Adduct **1**	ee (%)	Yield (%)
a	 **1a**	63	90[b]	i	 **1i**	50	90[e]
b	 **1b**	63	78[b]	j	 **1j**	66	79[d]
c	 **1c**	64	83[b]	k	 **1k**	68	79[d]
d	 **1d**	62	84[b]	l	 **1l**	86	52[e]
e	 **1e**	55	87[b]	m	 **1m**	9	9[e]
f	 **1f**	ND[c]	73[b]	n	 **1n**	17	32[e]
g	 **1g**	29	80[b]	o	 **1o**	28	15[e]
h	 **1h**	34	75[b]	p	 **1p**	—[f]	—[f]

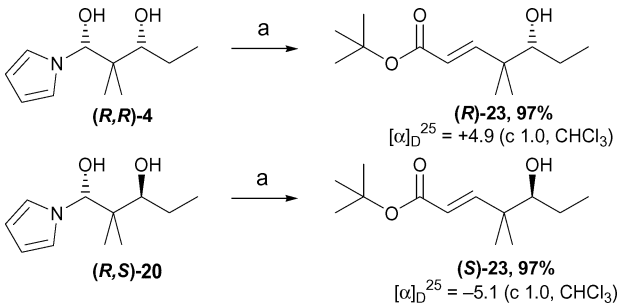
[a] Determined by chiral HPLC analysis. [b] Ligand inseparable from product, yield determined by ^{1}H NMR integration with respect to an internal standard. [c] It was not possible to find conditions to separate the enantiomers. [d] Ligand inseparable from product, yield determined from mass recovery and ^{1}H NMR integration. [e] Isolated yield. [f] See text.

Table 5 Directed diastereoselective ketone reduction



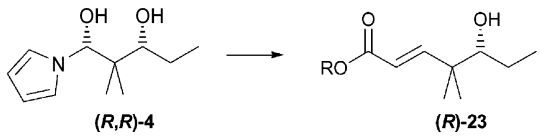
Entry	Conditions	Solvent	Temperature/°C	**4** : **20**[a]	Yield (%)[b]
A	$LiBH_4$	Et_2O	−23	4 : 1	85
B	$LiBH_4$	Et_2O	−78	12 : 1	87
C	$Zn(BH_4)_2$	Et_2O	−23	16 : 1	92
D	$Zn(BH_4)_2$	Et_2O	−35	17 : 1	90
E	Et_2BOMe, $NaBH_4$	THF, MeOH	−78	10 : 1	80
F	$Me_4NBH(OAc)_3$	MeCN, AcOH	−30	1 : 19	84

[a] Determined by ^1H NMR. [b] Isolated yield.



Scheme 5 *Reagents and conditions*: (a) $(EtO)_2P(=O)CH_2CO_2t$-Bu, NaH, THF, 0 °C, 20 minutes.

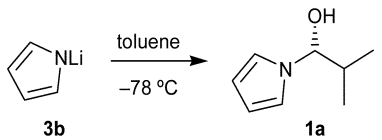
Table 6 Tandem-deprotection-HWE reactions

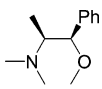
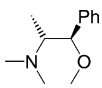
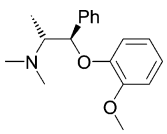
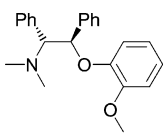


Entry	Conditions	R	Time	Yield (%)[a]
a	DBU, LiCl, MeCN, rt	Et	4 hours	—
b	BuLi, THF, rt	*t*-Bu	6 hours	95
c	NaH, THF, 0 °C	*t*-Bu	20 minutes	98

[a] Isolated yield.

Table 7 Amine-containing ligand screen



Entry	Ligand	ee (%)[a]	Yield (%)[b]
a	 **24**	1	87
b	 **25**	35	90
c	 **26**	53	90
d	 **27**	58	95

[a] Determined by chiral HPLC analysis. [b] Isolated yield.

amine function. To this end ligands **24**–**27**, which are structurally similar to the diether **8** and have had success in other reactions, were synthesised by literature methods.[24–27]

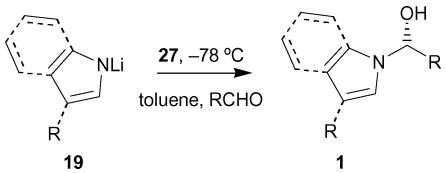
The observed trend in selectivity (Table 7) is in keeping with the addition of alkyllithiums to imines,[28] with amine **24** giving little selectivity and amine **27** giving the highest. When this ligand was applied to a range of nucleophiles and aldehydes the selectivity diminished (Table 8). The increase in yield in the case of carbinol **1n** is consistent with the presumed monomeric nature of the ligand complexes and the previously proposed rationale for the low reactivity of the complexes of **8** with tryptamines.

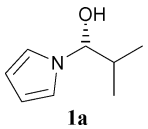
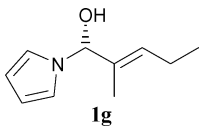
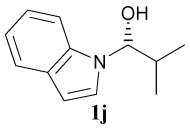
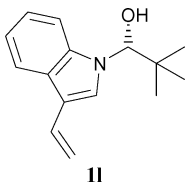
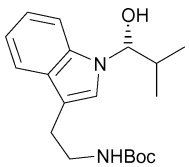
Studies into a catalytic cycle

For a successful ligand-mediated reaction, it is necessary to minimise the background reaction and to have control over the ligated reaction and the degree of ligation (Scheme 6).

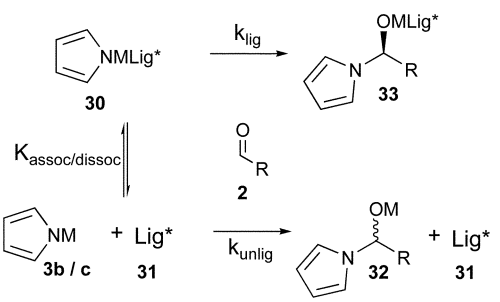
Maturation of the metal pyrrolate/ligand mixture sets up an equilibrium between complex **30** and organometallic **3** and ligand **31**. Each of species **30** and **3b/c** may potentially react with the aldehyde to give the pyrrole carbinol on protic work up. If

Table 8 Amine ligand scope



Entry	Adduct	ee (%)[a]	Yield (%)[b]
a	 **1a**	58	95
b	 **1g**	7	75
c	 **1j**	22	84
d	 **1l**	0	30
e	 **1n**	6	65

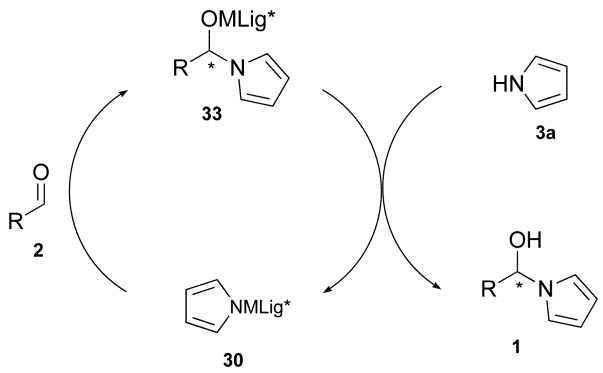
[a] Determined by chiral HPLC analysis. [b] Isolated yield.



Scheme 6 Ligand-mediated additions.

the rate acceleration caused by the ligand is dramatic ($k_{lig} \gg k_{unlig}$) and the equilibrium of **3b/c**, **30** and **31** is fast then the ligated reaction will dominate, irrespective of the position of the equilibrium ($K_{assoc/dissoc}$). If the acceleration is lower, then the position of this equilibrium becomes important. If the rate constants are sufficiently similar then it is essential that all the metal species are ligated. Formally the condition necessary for high asymmetric induction is k_{lig}[**30**] $\gg k_{unlig}$[**3b/c**], assuming that the ligated reaction proceeds in high selectivity.

Having shown that the addition of lithium pyrrolate is fast even in non-polar solvents, it was unlikely that the condition $k_{lig} \gg k_{unlig}$ would be met. The only reasonable way to achieve good asymmetric induction would be to have complete ligation, hence the use of one equivalent of ligand with respect to lithium pyrrolate described above. To reduce the amount of ligand required, we proposed to use a substoichiometric quantity of metal pyrrolate and thus a substoichiometric quantity of chiral ligand with the hope that a catalytic cycle would operate (Scheme 7).



Scheme 7 Proposed catalytic cycle.

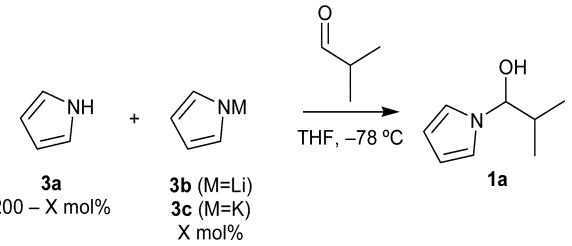
The ligand–metal pyrrolate complex **30** would first react with the aldehyde to generate carbinoxide complex **33**. Crucial to the proposal would be the ability of this complex to deprotonate pyrrole **3a** and thus regenerate **30**.

To test the validity of this proposal, pyrrole (2 eq.) was deprotonated with potassium hexamethyldisilazide or *n*-butyllithium (20 mol%) in THF at −78 °C and then treated with isobutyraldehyde, quenched with aqueous ammonium chloride after 30 minutes and analysed by ^{1}H NMR (Table 9).

In THF at −78 °C no turnover was observed with lithium pyrrolate, but potassium pyrrolate did behave catalytically down to 1 mol% with the best conversions observed for >10 mol%. Based on these partly encouraging preliminary results, a screen of both diether **8** and the more strongly coordinating sparteine **6** was undertaken in the reaction of lithium, sodium and potassium pyrrolates with isobutyraldehyde in toluene at −78 °C. For both ligands and each of metal pyrrolates **3** a stoichiometric and substoichiometric reaction was performed to allow direct comparisons to be made (Table 10).

The results indicate that the only way to achieve a catalytic cycle in non-coordinating solvents was with strongly coordinating ligands (such as sparteine **6**) and potassium counterions. Disappointingly however, with such a metal and ligand combination virtually no enantiocontrol was witnessed in the reaction. A trial reaction employing 18-crown-6 with potassium pyrrolate produced no turnover hence these studies were not pursued further. The results also show that hexamethyldisilylamine has a detrimental effect on the enantioselectivity of the addition

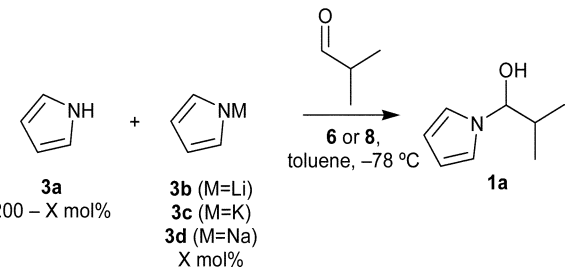
Table 9 Catalytic synthesis of pyrrole carbinols



Entry	Base[a]	X	Conv. (%)[b]
a	*n*-BuLi	20	15
b	KHMDS	20	86
c	KHMDS	10	84
d	KHMDS	5	25
e	KHMDS	2.5	12.5
f	KHMDS	1	7.5

[a] Used to generate metal pyrrolate. [b] Determined by ^{1}H NMR integration with respect to an internal standard.

Table 10 Enantioselective catalytic synthesis



Entry	Base[a]	X	Ligand	Eq.	Conv. (%)[b]	ee (%)[c]
a	LiHMDS	100	**8**	1	70 (20)	30
b	NaHMDS	100	**8**	1	25	2
c	KHMDS	100	**8**	1	17	2
d	LiHMDS	20	**8**	0.4	15	ND
e	NaHMDS	20	**8**	0.4	10	ND
f	KHMDS	20	**8**	0.4	<10	ND
g	LiHMDS	100	**6**	1	50 (45)	23
h	NaHMDS	100	**6**	1	75 (13)	2
i	KHMDS	100	**6**	1	98	2
j	LiHMDS	20	**6**	0.4	15	8
k	NaHMDS	20	**6**	0.4	11	2
l	KHMDS	20	**6**	0.4	60	4
m	KHMDS	20	18-C-6[d]	0.4	17	N/A

[a] Used to generate metal pyrrolate. [b] Determined by ^{1}H NMR with respect to an internal standard, number in parentheses indicates the amount of a compound tentatively assigned to be the TMS ether of **1a**. [c] Determined by chiral HPLC analysis. [d] 18-crown-6 was used as a dry solution in toluene (2.41 M).

of lithium pyrrolate to isobutyraldehyde mediated by ligand **8** (entry a).

Conclusions

The ligand-mediated addition of lithium indolate and lithium pyrrolate to aldehydes has been shown to proceed in moderate to good enantioselectivity. The pyrrole carbinol function has been utilised as an efficient stereodirecting group in the synthesis of homoallylic alcohols. Finally it has been shown that it is possible to synthesise pyrrole carbinols using catalytic potassium pyrrolate in THF or in an enantioselective fashion using potassium pyrrolate in combination with sparteine in toluene.

We are currently investigating other methods for the enantioselective synthesis of pyrrole carbinols and the results will be published in due course.

Experimental

General methods

^{1}H NMR spectra were recorded on Bruker DPX 400 or AMX 500 spectrometers in deuterochloroform operating at 400 MHz or 500 MHz respectively with digital deuterium lock. ^{13}C NMR spectra were recorded on a Bruker DPX 400 or AMX 500 in deuterochloroform at 100 MHz or 125 MHz respectively with a digital deuterium lock. Chemical shifts are quoted in parts per million (ppm) downfield of tetramethylsilane relative to the solvent (7.26 ppm for $CHCl_3$ and 77.0 ppm for ^{13}C of $CDCl_3$) and coupling constants (J) are given in Hz. NMR spectra were acquired at 300 K. High resolution mass spectrometric (HRMS) analyses were measured on a Micromass Q-TOF or a Micromass LCT Premier spectrometer at the Department of Chemistry, University of Cambridge or on a Finnigan MAT 900 XLT or a Finnigan MAT 95 XP spectrometer at the EPSRC National Mass Spectrometry Service Centre, Swansea. Elemental analyses (EA) were performed by the Microanalysis department, Department of Chemistry, University of Cambridge using an Exeter Analytical, Inc. CE-440 Elemental Analyzer. Infrared spectra were recorded on a Perkin Elmer 1 FT-IR Spectrometer fitted with an Attenuated Total Reflectance (ATR) sampling accessory as thin films or flattened solids. Absorption maxima (ν_{max}) are reported in wavenumbers (cm^{-1}). Optical rotations were recorded on a Perkin Elmer 343 polarimeter and are reported in 10^{-1} deg cm^2 g^{-1} at 589 nm, concentration (c) is given in g (100 mL)$^{-1}$. Enantiomeric excesses were measured using a HP1090 with diode array detection and the following columns: Chiralcel® OD, 250 mm × ø 4.6 mm; Chiralcel® OB, 250 mm × ø 4.6 mm; and Chiralpak® AD, 250 mm × ø 4.6 mm, all manufactured by Daicel Chemical Industries Ltd. Authentic racemic samples were prepared by the method previously reported.[6a] Melting points were determined on a Gallenkamp apparatus and are uncorrected. Reactions involving moisture and/or air sensitive reagents were carried out in oven-dried glassware under an atmosphere of argon. Except as otherwise indicated all reactions were continually agitated with magnetic stirring. All flash column chromatography was carried out using slurry-packed Merck 9385 Kieselgel 60 silica gel or on prepacked Biotage columns. Solvents used for chromatography were distilled from glass prior to use. Petroleum ether refers to the fraction boiling between 40–60 °C unless otherwise stated. Hexane refers to hexanes fraction unless otherwise stated.

Materials

Tetrahydrofuran and diethyl ether were distilled from a mixture of lithium aluminium hydride and calcium hydride with triphenylmethane as an indicator for tetrahydrofuran dryness; toluene

and hexane were distilled from calcium hydride; diisopropyl ether was distilled from sodium. Methanol was distilled from calcium methoxide. Pyrrole was distilled from calcium hydride, degassed and stored under argon. Acetic acid was distilled from chromium trioxide and acetic anhydride. All aqueous solutions were saturated unless otherwise stated. All aldehydes were purified by standard methods before use.[29] Tetramethylammonium triacetoxyborohydride,[21b] zinc borohydride,[30] amines **7**,[31] **24**,[24] **25**,[24] **26**,[25,26] **27**,[26,27] (*R*,*R*)-hydrobenzoin,[32] diether **8**,[19b] methyl ether **13**,[33] MOM-ether **14**,[34] Cbz-protected tryptamine,[35] Boc-protected tryptamine[36] and aldehyde **2i**[37] were prepared by the literature methods.

General procedure one A—Table 1–4 (entries a–i), 7 and 8 (entries a and b)

n-Butyllithium (0.40 mL, 1.0 mmol, 2.5 M in hexane) was added to a solution of pyrrole (1.1 mmol) in solvent (10 mL) at 0 °C. The solution was allowed to warm to room temperature over 5 minutes before the ligand (1.0 mmol) was added in one portion. After 25 minutes, the mixture was cooled to −78 °C and aldehyde (1.0 mmol) was added. After a further 30 minutes, a pre-cooled (−78 °C) solution of acetic acid (1.5 mL, 1.5 mmol, 1.0 M in THF) was added, and the reaction was allowed to warm to 0 °C over 30 minutes before being filtered though a plug of silica (25 mm × ø 25 mm) eluting with ethyl acetate and concentrated under reduced pressure. When the ligand and the products were inseparable yields were determined by ^{1}H NMR integration with respect to an internal standard, methyl 3,4,5-trimethoxybenzoate or DCM as appropriate.

General procedure one B—Table 4 (entries j–p) and 8 (entries c and d)

n-Butyllithium (1.5 mmol) was added to a solution of *N*-heterocycle (1.5 mmol) and ligand (1.5 mmol) in toluene (15 mL). The mixture was stirred at room temperature for 30 minutes and then cooled to −78 °C. After being stirred for a further 10 minutes, aldehyde (1.75 mmol) was added. The reaction mixture was stirred for 15 minutes and then quenched by the addition of a −78 °C solution of acetic acid in THF (2.25 mmol, 1.0 M). Saturated ammonium chloride (5 mL) and ethyl acetate (10 mL) were added and the mixture was warmed to room temperature. The aqueous phase was extracted with ethyl acetate (2 × 10 mL) and the combined organic extracts were washed with brine (5 mL), concentrated under reduced pressure and purified by flash column chromatography.

(1*R*,2*R*)-1,2-Diethoxy-1,2-diphenylethane 10

A solution of (*R*,*R*)-(+)-hydrobenzoin (2.0 g, 9.3 mmol) in THF (10 mL) was added dropwise to a suspension of sodium hydride (0.96 g, 24 mmol, 60% in mineral oil, washed with hexane) in THF (20 mL). The mixture was heated to reflux for 30 minutes, before cooling to 0 °C. Ethyl iodide (2.0 mL, 25 mmol) was added dropwise. After 15 hours at room temperature, potassium hydroxide (25 mL, 50% w/v in water) was added. After a further hour, the mixture was extracted with diethyl ether (50 mL and 20 mL), the combined organics were washed with aqueous sodium hydrogen carbonate (5 mL), brine (5 mL) and dried ($MgSO_4$). Concentration under reduced pressure gave a yellow oil. Purification by flash column chromatography eluting with petroleum ether : diethyl ether (20 : 1 to 1 : 1) gave diether **10** (1.9 g, 75%) as an oil. $[\alpha]_D = -22.9$ (*c* 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, lit[38]): δ_H 7.17–7.15 (6H, m, Ar*H*), 7.07–7.05 (4H, m, Ar*H*), 4.42 (2H, s, 2 × PhC*H*), 3.49–3.37 (4H, m, 2 × CH_2), 1.17 (6H, t, *J* 7.0, 2 × CH_3); ^{13}C NMR (100 MHz, lit[38]): δ_C 139.5 (C), 127.7 (CH), 127.6 (CH), 121.2 (CH), 85.8 (CH), 65.0 (CH_2), 15.3 (CH_3).

(1*R*,2*R*)-1,2-Dimethoxymethoxy-1,2-diphenylethane 11

A solution of (*R*,*R*)-(+)-hydrobenzoin (2.0 g, 9.3 mmol) in THF (10 mL) was added dropwise to a suspension of sodium hydride (0.96 g, 24 mmol, 60% in mineral oil, washed with hexane) in THF (20 mL). The mixture was heated to reflux for 30 minutes, before cooling to 0 °C. Chloromethoxymethyl ether (2.3 mL, 30 mmol) was added dropwise. After 15 hours at room temperature, potassium hydroxide (30 mL, 50% w/v in water) was added. After a further hour, the mixture was extracted with diethyl ether (60 mL and 20 mL), and the combined organics were washed with aqueous sodium hydrogen carbonate (5 mL), brine (5 mL) and dried ($MgSO_4$). Concentration under reduced pressure followed by purification by flash column chromatography eluting with hexane : ethyl acetate (20 : 1 to 1 : 1) gave a white solid which was recrystallised from hexane to give diether **11** (2.2 g, 78%) as prisms. Mp 37–38 °C; $[\alpha]_D = -161.2$ (*c* 1.6, $CHCl_3$); IR (film)/cm^{-1} ν_{max} = 1093 (C–O); ^{1}H NMR (400 MHz): δ_H 7.26–7.19 (10H, m, Ar*H*), 4.82 (2H, s, 2 × PhC*H*), 4.56 (2H, d, *J* 6.7, 2 × CH_aH_b), 4.54 (2H, d, *J* 6.7, 2 × CH_aH_b), 3.06 (6H, s, CH_3); ^{13}C NMR (100 MHz): δ_C 138.8 (C), 127.9 (CH), 127.7 (CH), 127.5 (CH), 94.6 (CH_2), 81.2 (CH), 55.3 (CH_3); *m*/*z* (ESI) MNH_4^+ 320.1856, $C_{18}H_{26}N_1O_4^+$ requires 320.1856; EA anal. calcd for $C_{18}H_{25}O_4$: C 71.50, H 7.33, found: C 71.52, H 7.30%.

(1*R*,2*R*)-1,2-Dicyclohexyl-1,2-dimethoxyethane 12

Rhodium (0.3 g, 5% w/w on alumina) was added to a solution of (*R*,*R*)-(+)-hydrobenzoin (5.0 g, 23 mmol) in methanol (25 mL). The mixture was placed under an atmosphere of hydrogen (50 bar) at 50 °C until the consumption of hydrogen ceased (~18 hours), at which point the reaction was diluted with diethyl ether (100 mL), filtered though Celite® and concentrated under reduced pressure. The resultant solid was recrystallised from petroleum ether (60–80 °C) : chloroform (4 : 1) to give (1*R*,2*R*)-1,2-dicyclohexyl-1,2-ethanediol (5.2 g, 98%) as needles. Mp 137–138 °C [lit[39] 136–137 °C]; IR (film)/cm^{-1} ν_{max} = 3269 (br, O–H); $[\alpha]_D = -2.7$ (*c* 0.80, $CHCl_3$) [lit[39] $[\alpha]_D = -2.6$ (*c* 0.78, $CHCl_3$)]; ^{1}H NMR (400 MHz, lit[39]): δ_H 3.34 (2H, br, 2 × C*H*OH), 1.88–1.43 and 1.32–1.00 (22H, m, 10 × CH_2 and 2 × C*H*CHOH); ^{13}C NMR (100 MHz, lit[39]): δ_C 75.1 (CH), 40.4 (CH), 29.6 (CH_2), 28.2 (CH_2), 26.4 (CH_2), 26.2 (CH_2), 26.0 (CH_2). A solution of (*R*,*R*)-1,2-dicyclohexyl-1,2-ethanediol (2.0 g, 8.8 mmol) in THF (10 mL) was added dropwise to a suspension of sodium hydride (0.96 g, 24 mmol, 60% in mineral oil, washed with hexane) in THF (20 mL). The mixture was heated to reflux for 30 minutes, before cooling to 0 °C. Dimethylsulfate (2.5 mL, 26 mmol) was added dropwise. After 15 hours at room temperature, potassium hydroxide (20 mL, 50% w/v in water) was carefully added. After a further hour the reaction was extracted

with diethyl ether (50 mL, 20 mL), the combined organics were washed with aqueous sodium hydrogen carbonate (5 mL), brine (5 mL) and dried ($MgSO_4$). Concentration under reduced pressure followed by recrystallisation from hexane gave diether **12** (2.1 g, 94%) as prisms. Mp 53–54 °C; $[\alpha]_D = -4.8$ (c 1.0, $CHCl_3$); IR (film)/cm^{-1} $\nu_{max} = 1095$ (C–O); ^{1}H NMR (400 MHz): δ_H 3.44 (6H, s, 2 × CH_3O), 2.95 (1H, t, J 4.6, CH_3OCH), 2.94 (1H, t, J 4.6, CH_3OCH), 1.74–1.72 (4H, m, 4 × CH_{eq}), 1.66–1.62 (6H, m, 6 × CH_{eq}), 1.49–1.43 (2H, m, 2 × CH_3OCHCH), 1.25–1.13 (10H, m, 10 × CH_{ax}); ^{13}C NMR (100 MHz): δ_C 86.8 (CH), 60.9 (CH_3), 39.9 (CH), 30.4 (CH_2), 27.3 (CH_2), 26.6 (CH_2), 26.5 (CH_2), 26.3 (CH_2); m/z (ESI) MH$^+$ 255.2319, $C_{16}H_{31}O_2^+$ requires 255.2320; EA anal. calcd for $C_{16}H_{30}O_2$: C 75.54, H 11.89, found: C 75.56, H 11.68%.

(*R*)-2-Methyl-1-pyrrol-1-ylpropan-1-ol 1a

Prepared using general procedure one A in toluene. It was not possible to separate the ligand and the product by flash column chromatography. Chiral HPLC conditions Chiralcel® OD, 1 mL min^{-1}, hexane : IPA (98 : 2) τ_R 11.2 minutes (*S*), τ_R 13.5 minutes (*R*). IR (film)/cm^{-1} $\nu_{max} = 3433$ (br, O–H); ^{1}H NMR (400 MHz): δ_H 6.80 (2H, t, J 2.2, N(CH=CH)$_2$), 6.18 (2H, t, J 2.2, N(CH=CH)$_2$), 4.98 (1H, dd, J 8.1 and 3.5, NCHOH), 2.72 (1H, d, J 3.5, OH), 2.20 (1H, m, CH(CH$_3$)$_2$), 1.09 (3H, d, J 6.7, CH(CH_3)$_a$(CH$_3$)$_b$), 0.71 (3H, d, J 6.8, CH(CH$_3$)$_a$(CH_3)$_b$); ^{13}C NMR (100 MHz): δ_C 118.2 (CH), 108.3 (CH), 87.9 (CH), 35.2 (CH), 18.6 (CH_3), 17.7 (CH_3); m/z (ESI) MH$^+$ 140.1069, $C_8H_{14}NO^+$ requires 140.1070.

(*R*)-1-Pyrrol-1-ylpropan-1-ol 1b

Prepared using general procedure one A in toluene. It was not possible to separate the ligand and the product by flash column chromatography. Chiral HPLC conditions Chiralcel® OD, 1 mL min^{-1}, hexane : IPA : methanol (99.4 : 0.5 : 0.1) τ_R 32.8 minutes (*S*), τ_R 36.1 minutes (*R*). IR (film)/cm^{-1} $\nu_{max} =$ 3406 (br, O–H); ^{1}H NMR (400 MHz): δ_H 6.82 (2H, t, J 2.2, N(CH=CH)$_2$), 6.19 (2H, t, J 2.2, N(CH=CH)$_2$), 5.29 (1H, t, J 6.6, NCHOH), 2.75 (1H, s, OH), 2.01 (1H, doublet quintet, J 14.0 and 6.6, CH_aH$_b$CH$_3$), 1.92 (1H, doublet quintet, J 14.0 and 6.6, CH$_a$$H_bCH_3$), 0.88 (3H, t, J 6.6, CH$_3$); ^{13}C NMR (100 MHz): δ_C 118.0 (CH), 108.7 (CH), 84.0 (CH), 30.2 (CH_2), 9.4 (CH_3); m/z (ESI) MH$^+$ 126.0915, $C_7H_{12}NO^+$ requires 126.0913.

(*R*)-2,2-Dimethyl-1-pyrrol-1-ylpropan-1-ol 1c

Prepared using general procedure one A in toluene. It was not possible to separate the ligand and the product by flash column chromatography. Chiral HPLC conditions Chiralcel® OD, 1 mL min^{-1}, hexane : IPA (98 : 2) τ_R 11.5 minutes (*S*), τ_R 13.5 minutes (*R*). IR (film)/cm^{-1} $\nu_{max} = 3473$ (O–H); ^{1}H NMR (400 MHz): δ_H 6.80 (2H, t, J 2.1, N(CH=CH)$_2$), 6.16 (2H, t, J 2.1, N(CH=CH)$_2$), 5.09 (1H, d, J 2.9, NCHOH), 2.65 (1H, br, OH), 0.96 (9H, s, C(CH$_3$)$_3$); ^{13}C NMR (100 MHz): δ_C 119.3 (CH), 107.5 (CH), 89.9 (CH), 35.2 (C), 25.3 (CH_3); m/z (ESI) MH$^+$ 154.1228, $C_9H_{16}NO^+$ requires 154.1226.

(*R*)-1-Pyrrol-1-ylhexan-1-ol 1d

Prepared using general procedure one A in toluene. It was not possible to separate the ligand and the product by flash column chromatography. Chiral HPLC conditions Chiralcel® OD, 1 mL min^{-1}, hexane : IPA : methanol (99.4 : 0.5 : 0.1) τ_R 30.9 minutes (*S*), τ_R 34.8 minutes (*R*). IR (film)/cm^{-1} $\nu_{max} =$ 3407 (br, O–H); ^{1}H NMR (400 MHz): δ_H 6.83 (2H, t, J 2.1, N(CH=CH)$_2$), 6.19 (2H, t, J 2.1, N(CH=CH)$_2$), 5.38 (1H, m, NCHOH), 2.68 (1H, br, OH), 1.98 (2H, m, CHCH_2), 1.38–1.22 (6H, m, 3 × CH_2), 0.92 (3H, m, CH_3); ^{13}C NMR (100 MHz): δ_C 118.0 (CH), 108.7 (CH), 82.7 (CH), 37.0 (CH_2), 31.3 (CH_2), 24.7 (CH_2), 22.5 (CH_2), 13.9 (CH_3); m/z (ESI) MH$^+$ 168.1382, $C_{10}H_{18}NO^+$ requires 168.1383.

(*R*)-3-Methyl-1-pyrrol-1-ylbutan-1-ol 1e

Prepared using general procedure one A in toluene. It was not possible to separate the ligand and the product by flash column chromatography. Chiral HPLC conditions Chiralcel® OD, 1 mL min^{-1}, hexane : IPA (98 : 2) τ_R 11.8 minutes (*S*), τ_R 13.2 minutes (*R*). IR (film)/cm^{-1} $\nu_{max} = 3415$ (br, O–H); ^{1}H NMR (400 MHz): δ_H 6.80 (2H, t, J 2.2, N(CH=CH)$_2$), 6.21 (2H, t, J 2.2, N(CH=CH)$_2$), 5.37 (1H, t, J 6.7, NCHOH), 1.84 (1H, dt, J 13.4 and 6.7, CH_aH$_b$), 1.75 (1H, dt, J 13.4 and 6.7, CH$_a$$H_b$), 1.54 (1H, nonet, J 6.7, CH$_2$CH), 0.97 (3H, d, J 6.7, CH(CH_3)$_a$(CH$_3$)$_b$), 0.93 (3H, d, J 6.7, CH(CH$_3$)$_a$(CH_3)$_b$); ^{13}C NMR (100 MHz): δ_C 118.2 (CH), 108.6 (CH), 81.1 (CH), 45.7 (CH_2), 24.5 (CH), 22.6 (CH_3), 22.4 (CH_3); m/z (EI) M$^{\bullet+}$ 153.1148, $C_8H_{14}NO^{\bullet+}$ requires 153.1148.

(*E*)-(*R*)-1-Pyrrol-1-ylbut-2-en-1-ol 1f

Prepared using general procedure one A in toluene. It was not possible to separate the ligand and the product by flash column chromatography. All attempts to separate the enantiomers by chiral HPLC were unsuccessful. IR (film)/cm^{-1} $\nu_{max} = 3391$ (br, O–H), 1673 (C=C); ^{1}H NMR (400 MHz): δ_H 6.85 (2H, t, J 2.1, N(CH=CH)$_2$), 6.21 (2H, t, J 2.1, N(CH=CH)$_2$), 5.93 (2H, m, NCHOH and CH=CHCH$_3$), 5.81 (1H, m, CH=CHCH$_3$), 2.57 (1H, d, J 5.3, OH), 1.79 (3H, dt, J 6.3 and 1.2, CH$_3$); ^{13}C NMR (100 MHz): δ_C 129.9 (CH), 129.1 (CH), 118.4 (CH), 108.9 (CH), 81.7 (CH), 17.5 (CH_3); m/z (EI) M$^{\bullet+}$ 137.0838, $C_8H_{11}NO^{\bullet+}$ requires 137.0841.

(*E*)-(*R*)-2-Methyl-1-pyrrol-1-ylpent-2-en-1-ol 1g

Prepared using general procedure one A in toluene. It was not possible to separate the ligand and the product by flash column chromatography. Chiral HPLC conditions Chiralcel® OD, 1 mL min^{-1}, hexane : IPA (98 : 2) τ_R 11.1 minutes (*S*), τ_R 13.1 minutes (*R*). IR (film)/cm^{-1} $\nu_{max} = 3406$ (br, O–H), 1676 (C=C); ^{1}H NMR (400 MHz): δ_H 6.79 (2H, t, J 2.2, N(CH=CH)$_2$), 6.20 (2H, t, J 2.2, N(CH=CH)$_2$), 5.74 (1H, t, J 7.5, CHCH$_2$), 5.64 (1H, s, NCHOH), 3.85 (1H, br, OH), 2.14 (2H, quintet, J 7.5, CH$_2$), 1.55 (3H, s, CCH$_3$), 1.06 (3H, t, J 7.5, CH$_2$CH_3); ^{13}C NMR (100 MHz): δ_C 132.3 (C), 129.9 (CH), 118.7 (CH), 108.5 (CH), 84.9 (CH), 20.9 (CH_2), 13.8 (CH_3), 12.1 (CH_3); m/z (EI) M$^{\bullet+}$ 165.1147, $C_{10}H_{15}NO^{\bullet+}$ requires 165.1148.

(*R*)-3-Phenyl-1-pyrrol-1-ylprop-2-en-1-ol 1h

Prepared using general procedure one A in toluene. It was not possible to separate the ligand and the product by flash column chromatography. Chiral HPLC conditions Chiralcel® OD, 1 mL min^{-1}, hexane : IPA (90 : 10) τ_R 15.0 minutes (*S*), τ_R 18.2 minutes (*R*). IR (film)/cm^{-1} ν_{max} = 3405 (br, O–H), 1661 (C=C); ^{1}H NMR (400 MHz, lit[7f]): δ_H 7.46–7.26 (5H, m, Ph), 6.93 (2H, t, *J* 2.2, N(C*H*=CH)$_2$), 6.81 (1H, dd, *J* 16.0 and 1.3, CH(OH)CH=C*H*), 6.43 (1H, dd, *J* 16.0 and 4.7, CH(OH)C*H*=CH), 6.29 (2H, t, *J* 2.2, N(CH=C*H*)$_2$), 6.04 (1H, m, NC*H*OH), 3.33 (1H, br, OH); ^{13}C NMR (100 MHz, lit[7f]): δ_C 135.7 (C), 132.8 (CH), 128.7 (CH), 128.5 (CH), 127.0 (CH), 126.7 (CH), 118.7 (CH), 109.2 (CH), 81.4 (CH); *m*/*z* (EI) $M^{\bullet+}$ 199.0998, $C_{13}H_{13}NO^{\bullet+}$ requires 199.0997.

(*R*)-1-Hydroxy-2,2-dimethyl-1-pyrrol-1-ylpentan-3-one 1i

Prepared using general procedure one A in toluene to give carbinol **1i** (176 mg, 90%) as an oil. Chiral HPLC conditions Chiralcel® OD, 1 mL min^{-1}, hexane : IPA (98 : 2) τ_R 15.2 minutes (*S*), τ_R 17.8 minutes (*R*). IR (film)/cm^{-1} ν_{max} = 3445 (br, O–H), 1698 (C=O); ^{1}H NMR (400 MHz): δ_H 6.71 (2H, t, *J* 2.2, N(C*H*=CH)$_2$), 6.13 (2H, t, *J* 2.2, N(CH=C*H*)$_2$), 5.43 (1H, d, *J* 3.9, NC*H*OH), 4.36 (1H, br, OH), 2.52–2.41 (2H, m, CH_2), 1.80 (3H, s, C(C*H*$_3$)$_a$(CH$_3$)$_b$), 1.13 (3H, s, C(CH$_3$)$_a$(C*H*$_3$)$_b$), 1.02 (3H, t, *J* 7.1, CH_2CH_3); ^{13}C NMR (100 MHz): δ_C 217.8 (C), 120.3 (CH), 108.2 (CH), 87.8 (CH), 52.4 (CH_3), 32.4 (CH_2), 22.9 (CH_3), 19.5 (CH_3), 7.5 (CH_3); *m*/*z* (ESI) MH^+ 196.1335, $C_{11}H_{18}NO_2^+$ requires 196.1332.

(*R*)-Indol-1-yl-2-methylpropan-1-ol 1j

Preparation using general procedure one B in toluene gave carbinol **1j** [*ca.* 0.225 g, 1.19 mmol, 79% (contaminated with ligand)] as an oil. Chiral HPLC conditions Chiralcel® OD, 1 mL min^{-1}, hexane : IPA (95 : 5) τ_R 16.1 minutes (*S*), τ_R 29.6 minutes (*R*). IR (film)/cm^{-1} ν_{max} = 3413 (br, O–H), 1611 (C=C); ^{1}H NMR (400 MHz): δ_H 7.63 (1H, d, *J* 8.0, Ar*H*), 7.48 (1H, d, *J* 8.5, Ar*H*), 7.28 (1H, d, *J* 3.5, NCH=C*H*), 7.21 (1H, td, *J* 7.5 and 1.0, Ar*H*), 7.13 (1H, td, *J* 7.5 and 1.0, Ar*H*), 6.55 (1H, d, *J* 3.5, NC*H*=CH), 5.47 (1H, dd, *J* 8.5 and 3.5, NC*H*OH), 2.57 (1H, d, *J* 3.5, OH), 2.44–2.35 (1H, m, (CH$_3$)$_2$C*H*), 1.18 (3H, d, *J* 6.5, (C*H*$_3$)$_a$(CH$_3$)$_b$CH), 0.70 (3H, d, *J* 7.0, (CH$_3$)$_a$(C*H*$_3$)$_b$CH); ^{13}C NMR (100 MHz): δ_C 135.5 (C), 129.0 (C), 124.6 (CH), 121.7 (CH), 121.1 (CH), 119.9 (CH), 110.1 (CH), 102.5 (CH), 85.3 (CH), 34.5 (CH), 18.9 (CH_3), 18.1 (CH_3). *m*/*z* (ESI) MH^+ 190.1229, $C_{12}H_{16}NO^+$ requires 190.1226.

3-Vinylindole

n-Butyllithium (12.5 mL, 2.5 M in hexanes, 31.3 mmol) was added dropwise to a stirred solution of methyltriphenylphosphonium iodide (14.6 g, 36.0 mmol) in THF (90 mL) at −50 °C. The reaction mixture was warmed to 0 °C over 30 minutes, then cooled to −30 °C. A pre-mixed solution of indole-3-carboxaldehyde (4.56 g, 31.3 mmol) and LHMDS (31.3 mL, 1.0 M in THF, 31.3 mmol) in THF (36 mL) was added. The reaction mixture was stirred for 30 minutes at room temperature, then poured onto ice-cold water (200 mL) and extracted with ethyl acetate (2 × 100 mL). The organic extracts were concentrated under reduced pressure and purified by flash column chromatography (2 : 1 hexanes : ethyl acetate) to give 3-vinylindole (3.87 g, 27.1 mmol, 87%) as a yellow powder. IR (film)/cm^{-1} ν_{max} = 3390 (N–H), 1632 (C=C), 1568 (C=C), 1527 (C=C); ^{1}H NMR (400 MHz, lit[40]): δ_H 8.07 (1H, br s, NH), 7.90 (1H, dd, *J* 8.5 and 0.5, Ar*H*), 7.37 (1H, d, *J* 7.5, Ar*H*), 7.26–7.18 (3H, m, Ar*H*), 6.92 (1H, dd, *J* 18.0 and 11.5, C*H*=CH$_2$), 5.73 (1H, dd, *J* 18.0 and 1.5, CH$_a$H$_b$), 5.20 (1H, dd, *J* 11.5 and 1.5, CH$_a$H$_b$); ^{13}C NMR (100 MHz, lit[40]): δ_C 136.7 (C), 129.4 (CH), 125.6 (C), 123.4 (CH), 122.5 (CH), 120.4 (CH), 120.1 (CH), 115.9 (C), 111.3 (CH), 110.8 (CH_2); *m*/*z* (EI) $M^{\bullet+}$ 143.0733, $C_{10}H_9N^{\bullet+}$ requires 143.0735.

(*R*)-3-Vinylindol-1-yl-2-methylpropan-1-ol 1k

Preparation using general procedure one B in toluene gave carbinol **1k** [0.256 g, 1.19 mmol, 79% (contaminated with ligand)] as an oil. Chiral HPLC conditions Chiralpak® AD, 1 mL min^{-1}, hexane : IPA (95 : 5) τ_R 8.8 minutes (*R*), τ_R 10.1 minutes (*S*). IR (film)/cm^{-1} ν_{max} = 3362 (br, O–H), 1629 (C=C); ^{1}H NMR (400 MHz): δ_H 7.90 (1H, dd, *J* 6.5 and 2.0, Ar*H*), 7.40 (1H, dd, *J* 7.0 and 2.0, Ar*H*), 7.27 (1H, s, NC*H*=C), 7.26–7.19 (2H, m, 2 × Ar*H*), 6.90 (1H, dd, *J* 18.0 and 11.5, C*H*=CH$_a$H$_b$), 5.74 (1H, dd, *J* 18.0 and 1.5, CH=C*H*$_a$H$_b$), 5.31 (1H, dd, *J* 8.5 and 3.5, NC*H*OH), 5.22 (1H, dd, *J* 11.5 and 1.5, CH=CH$_a$*H*$_b$), 2.93 (1H, d, *J* 3.5, OH), 2.35–2.26 (1H, m, (CH$_3$)$_2$C*H*), 1.13 (3H, d, *J* 6.5, (C*H*$_3$)$_a$(CH$_3$)$_b$CH), 0.70 (3H, d, *J* 6.5, (CH$_3$)$_a$(C*H*$_3$)$_b$CH); ^{13}C NMR (100 MHz): δ_C 136.4 (C), 129.3 (CH), 126.6 (C), 123.9 (CH), 122.3 (CH), 120.5 (CH), 120.3 (CH), 115.3 (C), 110.8 (CH_2), 110.4 (CH), 85.1 (CH), 34.4 (CH), 18.8 (CH_3), 18.1 (CH_3); *m*/*z* (EI) $M^{\bullet+}$ 215.1308, $C_{14}H_{17}NO^{\bullet+}$ requires 215.1310.

(*R*)-3-Vinylindol-1-yl-2,2-dimethylpropan-1-ol 1l

Preparation using general procedure one B in toluene gave carbinol **1l** (0.177 g, 0.774 mmol, 52%) as an oil. Chiral HPLC conditions Chiralcel® OD, 1 mL min^{-1}, hexane : IPA (98 : 2) τ_R 33.6 minutes (*S*), τ_R 49.1 minutes (*R*). $[\alpha]_D$ = +13.3 (*c* 0.975, $CHCl_3$, 86% ee); IR (film)/cm^{-1} ν_{max} = 3524 (O–H), 1630 (C=C), 1609 (C=C); ^{1}H NMR (400 MHz): δ_H 7.87 (1H, d, *J* 7.0, Ar*H*), 7.42 (1H, s, NCH=C), 7.38 (1H, d, *J* 8.0, Ar*H*), 7.24–7.15 (2H, m, 2 × Ar*H*), 6.90 (1H, dd, *J* 18.0 and 11.5, C*H*=CH$_2$), 5.71 (1H, dd, *J* 18.0 and 1.5, CH=C*H*$_a$H$_b$), 5.63 (1H, d, *J* 3.5, NC*H*OH), 5.19 (1H, dd, *J* 11.5 and 1.5, CH=CH$_a$*H*$_b$), 2.57 (1H, d, *J* 3.5, OH), 1.04 (9H, s, (C*H*$_3$)$_3$C); ^{13}C NMR (100 MHz): δ_C 137.2 (C), 129.4 (CH), 126.0 (C), 124.8 (CH), 122.1 (CH), 120.2 (CH), 120.1 (CH), 114.9 (C), 110.6 (CH), 110.5 (CH_2), 85.9 (CH), 38.0 (C), 25.6 (CH_3); no HRMS due to sample instability.

(*R*)-(1-Hydroxy-2-methylpropyl)-1*H*-indol-3-ylethylcarbamic acid benzylester 1m

Preparation using general procedure one B in toluene gave carbinol **1m** (0.0305 g, 0.0833 mmol, 9%) as an oil on a 0.926 mmol scale. Chiral HPLC conditions Chiralcel® OD, 1 mL min^{-1}, hexane : IPA (90 : 10) τ_R 31.8 minutes (*R*), τ_R 61.7 minutes (*S*). $[\alpha]_D$ = 0.00 (*c* 1.53, $CHCl_3$, 9% ee); IR (film)/cm^{-1} ν_{max} = 3291 (br, O–H), 1679 (N=O), 1613 (C=C); ^{1}H NMR (400 MHz): δ_H 7.57 (1H, d, *J* 8.0, Ar*H*), 7.45 (1H, d, *J* 8.5, Ar*H*), 7.37–7.29 (5H, m, Ph), 7.21 (1H, td, *J* 7.5 and 1.0, Ar*H*), 7.11 (1H, t, *J* 7.5, Ar*H*), 7.09 (1H, s, NCH=C), 5.42 (1H, dd, *J* 8.5 and 3.5, NC*H*OH), 5.08 (2H, s, OCH_2Ph), 4.79 (1H, br, NH), 3.51 (2H, q, *J* 6.5, NCH_2), 2.95 (2H, t, *J* 6.5, NCH_2CH_2), 2.61 (1H, s, OH), 2.41–2.31 (1H, m,

$(CH_3)_2CH$), 1.17 (3H, d, *J* 6.5, $(CH_3)_a(CH_3)_bCH$), 0.68 (3H, d, *J* 7.0, $(CH_3)_a(CH_3)_bCH$); ^{13}C NMR (100 MHz): δ_C 156.5 (C), 136.5 (C), 136.0 (C), 128.5 (CH), 128.2 (C), 128.1 (CH), 122.6 (CH), 121.9 (CH), 119.6 (CH), 119.0 (CH), 112.5 (CH), 110.3 (CH), 85.1 (CH), 66.6 (CH_2), 41.2 (CH_2), 34.5 (CH), 25.7 (CH_2), 19.0 (CH_3), 18.2 (CH_3); *m*/*z* (ESI) MNa^+ 389.1853, $C_{22}H_{26}N_2O_3Na^+$ requires 389.1841.

(*R*)-(1-Hydroxy-2-methylpropyl)-1*H*-indol-3-ylethylcarbamic acid *tert*-butylester 1n

Preparation using general procedure one B in toluene gave carbinol **1n** (0.158 g, 0.476 mmol, 32%) as an oil. Chiral HPLC conditions Chiralcel® OD, 1 mL min^{-1}, hexane : IPA (90 : 10) τ_R 9.8 minutes (*R*), τ_R 11.5 minutes (*S*). $[a]_D = 0.00$ (*c* 1.00, $CHCl_3$, 17% ee); IR (film)/cm^{-1} $\nu_{max} = 3375$ (br, O–H), 1687 (C=O), 1613 (C=C); ^{1}H NMR (400 MHz): δ_H 7.56 (1H, d, *J* 7.5, Ar*H*), 7.44 (1H, d, *J* 8.0, Ar*H*), 7.19 (1H, td, *J* 7.5 and 1.0, Ar*H*), 7.11 (1H, td, *J* 8.0 and 1.0, Ar*H*), 7.07 (1H, br s, NCH=C), 5.40 (1H, dd, *J* 8.5 and 4.0, NC*H*OH), 4.61 (1H, br, NH), 3.39–3.29 (2H, m, NCH_2), 3.29 (1H, br, OH), 2.88 (2H, br, NCH_2CH_2), 2.39–2.30 (1H, m, $(CH_3)_2CH$), 1.41 (9H, s, $OC(CH_3)_3$), 1.16 (3H, d, *J* 6.5, $(CH_3)_a(CH_3)_bCH$), 0.69 (3H, d, *J* 7.0, $(CH_3)_a(CH_3)_bCH$); ^{13}C NMR (100 MHz): δ_C 156.0 (C), 136.0 (C), 128.3 (C), 122.5 (CH), 121.8 (CH), 119.4 (CH), 119.1 (CH), 112.8 (C), 110.2 (CH), 85.1 (CH), 79.2 (C), 40.8 (CH_2), 34.5 (CH), 28.4 (CH_3), 25.7 (CH_2), 19.0 (CH_3), 18.2 (CH_3); *m*/*z* (ESI) MNa^+ 355.2009, $C_{19}H_{28}N_2O_3Na^+$ requires 355.1998.

(*R*)-(1-Hydroxy-2,2-dimethylpropyl)-1*H*-indol-3-ylethylcarbamic acid *tert*-butylester 1o

Preparation using general procedure one B in toluene gave carbinol **1o** (0.0788 g, 0.227 mmol, 15%) as an oil. Chiral HPLC conditions Chiralcel® OD, 1 mL min^{-1}, hexane : IPA (90 : 10) τ_R 8.9 minutes (*R*), τ_R 12.5 minutes (*S*). $[a]_D = +4.09$ (*c* 0.635, $CHCl_3$, 28% ee); IR (film)/cm^{-1} ν_{max} = 3402 (O–H), 1689 (C=O), 1612 (C=C); ^{1}H NMR (400 MHz): δ_H 7.56 (1H, d, *J* 8.0, Ar*H*), 7.37 (1H, *J* 8.5, Ar*H*), 7.20–7.14 (2H, m, 2 × Ar*H*), 7.10 (1H, td, *J* 7.5 and 1.0, Ar*H*), 5.62 (1H, d, *J* 3.0, NC*H*O), 4.59 (1H, br, NH), 3.41 (2H, br, NCH_2), 2.92 (2H, t, *J* 6.5, NCH_2CH_2), 2.83 (1H, s, OH), 1.42 (3H, s, $OC(CH_3)_3$), 1.02 (3H, s, $CHC(CH_3)_3$); ^{13}C NMR (100 MHz): δ_C 156.0 (C), 136.8 (C), 127.7 (C), 123.4 (CH), 121.7 (CH), 119.2 (CH), 118.9 (CH), 112.4 (C), 110.4 (CH), 86.0 (CH), 79.1 (C), 57.1 (CH_2), 40.9 (CH_2), 38.1 (C), 28.4 (CH_3), 25.7 (CH_3); no HRMS due to sample instability.

(*R*)-Carbazol-9-yl-2-methylpropan-1-ol 1p

Prepared by the method previously reported.[6a] IR (film)/cm^{-1} ν_{max} = 3421 (br, O–H), 1625 (C=C), 1597 (C=C); ^{1}H NMR (400 MHz): δ_H 8.08 (2H, d, *J* 7.5, 2 × Ar*H*), 7.64 (2H, d, *J* 8.0, 2 × Ar*H*), 7.43 (2H, t, *J* 8.0, 2 × Ar*H*), 7.24 (2H, t, *J* 7.5, 2 × Ar*H*), 5.77 (1H, d, *J* 9.0, NC*H*OH), 2.82 (1H, octet, *J* 7.0, $(CH_3)_2CH$), 2.63 (1H, s, OH), 1.29 (3H, d, *J* 6.5, $(CH_3)_a(CH_3)_bCH$), 0.59 (3H, d, *J* 6.5, $(CH_3)_a(CH_3)_bCH$); ^{13}C NMR (100 MHz): δ_C (100 MHz, $CDCl_3$) 139.3 (C), 125.6 (CH), 123.5 (CH), 120.2 (CH), 119.4 (CH), 111.0 (C), 85.4 (CH), 33.0 (CH), 19.6 (CH_3), 18.4 (CH_3); no HRMS due to sample instability.

(*R*)-1-Hydroxy-2,2-dimethyl-1-pyrrol-1-ylpentan-3-one 1i

n-Butyllithium (4.0 mL, 10 mmol, 2.5 M in hexane) was added to a solution of pyrrole (0.73 mL, 11 mmol) in toluene (100 mL) at 0 °C. The solution was allowed to warm to room temperature over 5 minutes before diether **8** (2.42 g, 10.0 mmol) was added in one portion. After 25 minutes, the mixture was cooled to −78 °C and the aldehyde **2i** (1.28 g, 10 mmol) was added over 5 seconds. After 30 minutes at this temperature, the reaction was quenched by the addition of a pre-cooled (−78 °C) solution of acetic acid (15 mL, 15 mmol, 1.0 M in THF). After a further 30 minutes, the reaction was allowed to warm to 0 °C over 15 minutes before being filtered though a plug of silica (60 mm × ø 60 mm) eluting with ethyl acetate and concentrated under reduced pressure to give the crude product. The enantiomeric excess was determined as 46% by chiral HPLC. Purification by flash column chromatography eluting with hexane : ethyl acetate (20 : 1 to 1 : 5) gave carbinol **1i** (1.8 g, 93%) as a pale brown oil together with ether **8** (2.3 g, 95%) as a white solid. Chiral HPLC analysis indicated no change in enantiomeric excess. $[a]_D = +18.2$ (*c* 1.10, $CHCl_3$, 46% ee). All spectroscopic and chromatographic data was consistent with that previously recorded.

2,2-Dimethyl-1-pyrrol-1-ylpentane-1,3-diol 4

Lithium borohydride reduction. Lithium borohydride (0.77 mL, 1.5 mmol, 2.0 M in THF) was added to a solution of racemic carbinol **1i** (271 mg, 1.38 mmol) in diethyl ether (10 mL) at −78 °C. After 2 hours, the reaction was quenched with methanol (2 mL) followed by the addition of pH 7 phosphate buffer (10 mL) and ethyl acetate (25 mL). The layers were separated and the organics washed with brine (5 mL), dried ($MgSO_4$) and the solvent removed under reduced pressure. Analysis by ^{1}H NMR gave a crude diastereomeric ratio of 12 : 1 *syn* : *anti*. Purification by flash column chromatography eluting with hexane : ethyl acetate (20 : 1 to 1 : 5) gave diol **4** (237 mg, 87%, 12.1 : 1 dr) as an oil. IR (film)/cm^{-1} ν_{max} = 3399 (br, O–H); ^{1}H NMR (400 MHz): δ_H 6.81 (2H, t, *J* 2.0, $N(CH=CH)_2$), 6.14 (2H, t, *J* 2.0, $N(CH=CH)_2$), 5.33 (1H, s, NC*H*OH), 4.26 (1H, br, OH), 3.26 (1H, dd, *J* 10.5 and 1.9, C*H*CH_2), 2.69 (1H, br, OH), 1.55 (1H, dqd, *J* 14.1, 7.1 and 1.8, $CH_aH_bCH_3$), 1.40–1.28 (1H, ddq, *J* 14.1, 10.5 and 7.1, $CH_aH_bCH_3$), 1.00 (3H, s, $C(CH_3)_a(CH_3)_b$), 0.98 (3H, t, *J* 7.1, CH_2CH_3), 0.67 (3H, s, $C(CH_3)_a(CH_3)_b$); ^{13}C NMR (100 MHz): δ_C 119.7 (CH), 107.5 (CH), 89.2 (CH), 79.3 (CH), 43.6 (C), 24.2 (CH_2), 20.5 (CH_3), 14.3 (CH_3), 11.0 (CH_3); *m*/*z* (ESI) MH^+ 198.1492, $C_{11}H_{20}NO_2^+$ requires 198.1489.

Zinc borohydride reduction. Freshly prepared zinc borohydride (24 mL, 3.6 mmol, ~0.15 M in diethyl ether) was added to a solution of carbinol (*R*)-**1i** (231 mg, 1.18 mmol, 46% ee) in diethyl ether (6 mL) at −35 °C. After 8 hours, the reaction was quenched with methanol (5 mL) followed by the addition of aqueous sodium potassium tartrate (15 mL) and ethyl acetate (25 mL). After 10 minutes, the layers were separated and the aqueous phase further extracted with ethyl acetate (2 × 50 mL). The combined organics were washed with brine (15 mL), dried ($MgSO_4$) and the solvent removed under reduced pressure. Analysis by ^{1}H NMR indicated a diastereomeric ratio of 16.6 : 1 *syn* : *anti*. The crude product was purified by flash column chromatography eluting

with hexane : ethyl acetate (20 : 1 to 1 : 5) to give (*R*,*R*)-diol **4** (209 mg, 90%, 46% ee, 16.6 : 1 dr) as an oil. $[a]_D = +5.2$ (*c* 1.1, $CHCl_3$, 46% ee).

Diethylmethoxyborane and sodium borohydride reduction. A solution of diethylmethoxyborane (1.35 mL, 1.35 mmol, 1.0 M in THF) was added to a solution of racemic carbinol **1i** (195 mg, 1.00 mmol) in THF (10 mL) and methanol (3 mL). The mixture was slowly cooled to −78 °C and, after 1.5 hours, sodium borohydride (76 mg, 2.0 mmol) was added in one portion. After 18 hours the reaction was quenched by the addition of acetic acid (5 mL) and allowed to warm to 0 °C. The reaction was diluted with ethyl acetate (100 mL), washed with aqueous sodium hydrogen carbonate (30 mL) and brine (5 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Analysis by ^{1}H NMR indicated a diastereomeric ratio of 12.0 : 1 *syn* : *anti.* The crude product was purified by flash column chromatography eluting with hexane : ethyl acetate (20 : 1 to 1 : 5) to give diol **4** (158 mg, 80%, 10 : 1 dr) as an oil.

(1*R*,2*S*)-2,2-Dimethyl-1-pyrrol-1-ylpentane-1,3-diol 20

Distilled acetic acid (5 mL) was added to a solution of tetramethylammonium triacetoxyborohydride (1.3 g, 5.0 mmol) in acetonitrile (5 mL) at room temperature. After 25 minutes, the mixture was cooled to −25 °C and a solution of carbinol (*R*)-**1i** (195 mg, 1.00 mmol, 46% ee) in acetonitrile (2.5 mL) added. After 18 hours, the mixture was poured into aqueous sodium potassium tartrate (25 mL), aqueous sodium hydrogen carbonate (25 mL) and ethyl acetate (50 mL). After 10 minutes the layers were separated and the aqueous layer further extracted with ethyl acetate (2 × 50 mL), the combined organics were washed with brine (15 mL), dried ($MgSO_4$) and the solvent removed under reduced pressure. Analysis by ^{1}H NMR indicated a diastereomeric ratio of 19.0 : 1 *anti* : *syn.* The crude product was purified by flash column chromatography eluting with hexane : ethyl acetate (20 : 1 to 1 : 5) to give diol **20** (166 mg, 84%, 46% ee, 19.2 : 1 dr) as an oil. IR (film)/cm^{-1} $\nu_{max} = 3320$ (br, O–H); $[a]_D = +0.5$ (*c* 0.9, $CHCl_3$, 46% ee); ^{1}H NMR (400 MHz): δ_H 6.82 (2H, t, *J* 2.2, N(C*H*=CH)$_2$), 6.16 (2H, t, *J* 2.2, N(CH=C*H*)$_2$), 5.32 (1H, s, NC*H*OH), 4.81 (1H, br, OH), 3.53 (1H, dd, *J* 10.6 and 1.9, C*H*(OH)CH$_2$), 2.66 (1H, br, O*H*), 1.58 (1H, dqd, *J* 14.7, 7.4 and 1.9, CH_aH$_b$CH$_3$), 1.41 (1H, ddq, *J* 14.7, 10.6 and 7.4, CH$_a$$H_bCH_3$), 1.01 (3H, t, *J* 7.4, CH$_2$CH_3), 0.94 (3H, s, C(CH_3)$_a$(CH$_3$)$_b$), 0.87 (3H, *s*, C(CH$_3$)$_a$(CH_3)$_b$); ^{13}C NMR (100 MHz): δ_C 119.5 (CH), 107.6 (CH), 90.0 (CH), 78.9 (CH), 42.6 (CH), 24.4 (CH$_2$), 21.3 (CH$_3$), 19.8 (CH$_3$), 11.0 (CH$_3$); *m*/*z* (ESI) MH$^+$ 198.1487, $C_{11}H_{20}NO_2^+$ requires 198.1489.

1-(6-Ethyl-2,2,5,5-tetramethyl-[1,3]dioxan-4-yl)-1*H*-pyrrole 21

p-Toluenesulfonic acid (4 mg) was added to a solution of racemic diol **4** (49 mg, 0.24 mmol) in acetone (1.2 mL) and 2,2-dimethoxypropane (0.70 mL). After 3 minutes at room temperature, sodium hydrogen carbonate (20 mg) was added in one portion. The reaction was filtered though a plug of silica (25 mm × ø 25 mm) eluting with ethyl acetate and the solvent was removed under reduced pressure to give acetonide **21** (56 mg, 99%) as a pale yellow solid. Mp 55–57 °C; IR (film)/cm^{-1} $\nu_{max} = 1066$ (C–O); ^{1}H NMR (400 MHz): δ_H 6.79 (2H, t, *J* 2.0, N(C*H*=CH)$_2$), 6.15 (2H, t, *J* 2.0, N(CH=C*H*)$_2$), 5.27 (1H, s, NC*H*C), 3.49 (1H, dd, *J* 10.0 and 1.8, C*H*CH$_2$), 1.57–1.36 (2H, m, CH_2CH$_3$), 1.54 (3H, s, OC(CH_3)$_{eq}$(CH$_3$)$_{ax}$O), 1.53 (3H, s, OC(CH$_3$)$_{eq}$(CH_3)$_{ax}$O), 0.99 (3H, t, *J* 7.3, CH$_2$CH_3), 0.91 (3H, s, NCHC(CH$_3$)$_{eq}$(CH_3)$_{ax}$), 0.77 (3H, s, NCHC(CH_3)$_{eq}$(CH$_3$)$_{ax}$); ^{13}C NMR (100 MHz): δ_C 120.2 (CH), 107.4 (CH), 100.2 (C), 89.1 (CH), 79.4 (CH), 39.5 (C), 29.8 (CH$_3$), 22.0 (CH$_2$), 20.6 (CH$_3$), 19.6 (CH$_3$), 13.3 (CH$_3$), 11.3 (CH$_3$); *m*/*z* (ESI) MH$^+$ 238.1802, $C_{14}H_{24}NO_2^+$ requires 238.1802. The following peaks were observed in the ^{13}C NMR and assigned to the minor (anti) diastereomer **22**: ^{13}C NMR (100 MHz): δ_C 119.6 (CH), 107.5 (CH), 102.1 (C), 87.8 (CH), 78.8 (CH), 43.1 (C), 24.2 (CH$_3$), 23.8 (CH$_3$), 20.2 (CH$_3$), 19.8 (CH$_3$).

(*R*)-5-Hydroxy-4,4-dimethylhept-2-enoic acid *tert*-butyl ester 23

t-Butyldiethylphosphonoacetate (0.12 mL, 0.50 mmol) was added to a suspension of sodium hydride (17 mg, 0.42 mmol, 60% in mineral oils) in THF (1 mL) at 0 °C. After 5 minutes, a solution of (*R*,*R*)-**4** (55 mg, 0.28 mmol, 46% ee, 16.6 : 1 dr) in THF (1 mL) was added. After a further 20 minutes, the reaction was then filtered through a plug of silica (40 mm × ø 40 mm) eluting with diethyl ether. Concentration under reduced pressure followed by flash column chromatography eluting with hexane : diethyl ether (20 : 1 to 1 : 5) gave alcohol **23** (61 mg, 97%) as an oil. IR (film)/cm^{-1} $\nu_{max} = 3418$ (br, O–H), 1715 (C=O), 1696 (C=C); $[a]_D = +4.9$ (*c* 1.0, $CHCl_3$, 40% ee); ^{1}H NMR (400 MHz): δ_H 6.87 (1H, d, *J* 16.0, CH=C*H*C(CH$_3$)$_2$), 5.72 (1H, d, *J* 16.0, C*H*=CHC(CH$_3$)$_2$), 3.24 (1H, dd, *J* 10.4 and 2.0, C*H*OH), 1.55 (1H, m, CHCH_aH$_b$), 1.48 (9H, s, C(CH$_3$)$_3$), 1.24 (1H, m, CHCH$_a$$H_b$), 1.05 (6H, s, C(CH$_3$)$_2$), 0.98 (3H, t, *J* 7.3, CH$_2$CH$_3$); ^{13}C NMR (100 MHz): δ_C 166.3 (C), 154.1 (CH), 121.3 (CH), 80.3 (C), 80.0 (CH), 41.7 (C), 28.1 (CH$_3$), 24.7 (CH$_2$), 22.8 (CH$_3$), 22.4 (CH$_3$), 11.2 (CH$_3$); *m*/*z* (ESI) MH$^+$ 246.2063, $C_{13}H_{25}NO_3^+$ requires 246.2064.

(*S*)-5-Hydroxy-4,4-dimethylhept-2-enoic acid *tert*-butyl ester 23

(*S*)-**23** was prepared in an analogous fashion and yield to (*R*)-**23**. $[a]_D = -5.1$ (*c* 1.1, $CHCl_3$, 41% ee). All spectroscopic data were consistent with those previously recorded.

General procedure two—Table 9

Base was added to a solution of pyrrole (0.70 mL, 10 mmol) in THF (20 mL) at −78 °C. After 15 minutes, isobutyraldehyde (0.450 mL, 5.0 mmol) in THF (2 mL) was added dropwise over 3 minutes. After the specified length of time at this temperature, the reaction was quenched with aqueous ammonium chloride (2 mL) and allowed to warm to room temperature. The mixture was diluted with water (5 mL) and extracted with diethyl ether (40 mL). The organic layer was washed with brine (4 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give **1a** as an oil. The yield was determined by ^{1}H NMR integration with 1,2,3-trimethoxybenzene as internal standard.

General procedure three—Table 10, entries a–c and g–i

Base (1.0 mmol) was added to a solution of pyrrole (0.080 mL, 1.1 mmol) in toluene (10 mL) at 0 °C. The solution was allowed to warm to room temperature over 5 minutes before the ligand

(1 mmol) was added in one portion. After a further 25 minutes, the reaction was cooled to −78 °C and isobutyraldehyde (0.09 mL, 1 mmol) was added. After a further 30 minutes, the reaction was quenched by the addition of a pre-cooled (−78 °C) solution of acetic acid (1.5 mL, 1.5 mmol, 1.0 M in THF). After a further 30 minutes, the reaction was allowed to warm to 0 °C over 15 minutes before being filtered though a plug of silica (25 mm × ø 25 mm) eluting with ethyl acetate and concentrated under reduced pressure to give the crude product. The yield and enantiomeric excess were determined by ^{1}H NMR with DCM as an internal standard and chiral HPLC respectively. All spectroscopic data were consistent with those previously recorded.

General procedure four—Table 10, entries d–f and j–m

Base (0.2 mmol) was added to a stirred solution of pyrrole (0.150 mL, 2.0 mmol) in toluene (10 mL) at 0 °C. The solution was allowed to warm to room temperature over 5 minutes before the ligand (0.4 mmol) was added in one portion. After a further 25 minutes, the reaction was cooled to −78 °C and aldehyde (1.0 mmol) was added dropwise over 1 minute. After 30 minutes, the reaction was quenched by the addition of a pre-cooled (−78 °C) solution of acetic acid (1.0 mL, 1.0 mmol, 1.0 M in THF). After a further 30 minutes, the reaction was allowed to warm to 0 °C over 15 minutes before being filtered though a plug of silica (25 mm × ø 25 mm) eluting with ethyl acetate and concentrated under reduced pressure to give the crude product. The yield and enantiomeric excess were determined by ^{1}H NMR with DCM as an internal standard and chiral HPLC respectively. All spectroscopic data were consistent with those previously recorded.

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References

1 (*a*) E. N. Jacobsen, A. Pfaltz and H. Yamamoto, *Comprehensive asymmetric catalysis*, Springer Verlag, Berlin, 1999; (*b*) R. Noyori, *Asymmetric catalysis in organic synthesis*, Wiley, New York, 1994.
2 (*a*) R. Noyori and M. Kitamura, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 49; (*b*) K. Soai and S. Niwa, *Chem. Rev.*, 1992, **92**, 833.
3 (*a*) K. Tomioka, *Synthesis*, 1990, 541; (*b*) S. E. Denmark and O. J. C. Nicaise, *Chem. Commun.*, 1996, 999; (*c*) *Organolithiums in enantioselective synthesis*, ed. D. M. Hodgson, Springer Verlag, Heidelberg, 2003.
4 P. Muller, Y. F. Allenbach and G. Bernardinelli, *Helv. Chim. Acta*, 2003, **86**, 3164.
5 See J. Granander, R. Sott and G. Hilmersson, *Tetrahedron: Asymmetry*, 2003, **14**, 439, and refs cited therein.
6 (*a*) D. J. Dixon, M. S. Scott and C. A. Luckhurst, *Synlett*, 2003, 2317; (*b*) D. J. Dixon and A. C. Lucas, *Synlett*, 2004, 1092; (*c*) D. J. Dixon, M. S. Scott and C. A. Luckhurst, *Synlett*, 2005, 2420; (*d*) M. S. Scott, C. A. Luckhurst and D. J. Dixon, *Org. Lett.*, 2005, **7**, 5813.
7 (*a*) M. S. Taggart and G. H. Richter, *J. Am. Chem. Soc.*, 1934, **56**, 1385; (*b*) S. D. Lee, M. A. Brook and T. H. Chan, *Tetrahedron Lett.*, 1983, **24**, 1569; (*c*) S. Brandänge and B. Rodriguez, *Acta Chem. Scand. Ser. B*, 1987, **41**, 740; (*d*) S. Brandänge, E. Holmgren, H. Leijonmarck and B. Rodriguez, *Acta Chem. Scand.*, 1995, **49**, 922; (*e*) E. Arai, H. Tokuyama, M. S. Linsell and T. Fukuyama, *Tetrahedron Lett.*, 1998, **39**, 71; (*f*) D. A. Evans, G. Borg and K. A. Scheidt, *Angew. Chem., Int. Ed.*, 2002, **41**, 3188.
8 For reports on oxazolidin-2-one-derived *N*-carbinols see: (*a*) J. Bach, S. D. Bull, S. G. Davies, R. L. Nicholson, H. J. Sanganee and A. D. Smith, *Tetrahedron Lett.*, 1999, **40**, 6677; (*b*) S. D. Bull, S. G. Davies, R. L. Nicholson, H. J. Sanganee and A. D. Smith, *Tetrahedron: Asymmetry*, 2000, **11**, 3475; (*c*) J. Bach, C. Blachere, S. D. Bull, S. G. Davies, R. L. Nicholson, P. D. Price, H. J. Sanganee and A. D. Smith, *Org. Biomol. Chem.*, 2003, **1**, 2001; (*d*) S. G. Davies, I. A. Hunter, R. L. Nicholson, P. M. Roberts, E. D. Savory and A. D. Smith, *Tetrahedron*, 2004, **60**, 7553; (*e*) S. G. Davies, R. L. Nicholson and A. D. Smith, *Org. Biomol. Chem.*, 2005, **3**, 348; (*f*) C. Gaul and D. Seebach, *Org. Lett.*, 2000, **2**, 1501; (*g*) C. Gaul, K. Scharer and D. Seebach, *J. Org. Chem.*, 2001, **66**, 3059; (*h*) C. Gaul and D. Seebach, *Helv. Chim. Acta*, 2002, **85**, 772.
9 A. H. Hoveyda, D. A. Evans and G. C. Fu, *Chem. Rev.*, 1993, **93**, 1307.
10 The one-pot enantioselective synthesis of aldehydes *via* addition of chiral lithium amides followed by *ortho*-lithiation or directed organolithium addition has been reported: (*a*) A. Alexakis, T. Kanger, P. Mangeney, F. Rosemunch, A. Perrotey and E. Rose, *Tetrahedron: Asymmetry*, 1995, **6**, 2135; (*b*) A. Alexakis, T. Kanger, P. Mangeney, F. Rosemunch, A. Perrotey and E. Rose, *Tetrahedron: Asymmetry*, 1995, **6**, 47; (*c*) G. G. A. Balavoine, J. C. Daran, G. Iftime, E. Manoury and C. J. Moreau-Bossuet, *J. Organomet. Chem.*, 1998, **567**, 191; (*d*) G. Iftime, J. C. Daran, E. Manoury and G. G. A. Balavoine, *Angew. Chem., Int. Ed.*, 1998, **37**, 1698; (*e*) N. Brémand, P. Mangeney and J. F. Normant, *Tetrahedron Lett.*, 2001, **42**, 1883.
11 A similar approach using a reversible diastereoselective aldol addition has recently been reported: M. Cheeseman, F. J. P. Feuillet, A. L. Johnson and S. D. Bull, *Chem. Commun.*, 2005, 2374.
12 (*a*) K. C. Nicolaou and E. J. Sorensen, *Classics in total synthesis: targets, strategies, methods*, Wiley-VCH, Weinheim, 1996; (*b*) K. C. Nicolaou and S. A. Snyder, *Classics in total synthesis II: more targets, strategies, methods*, Wiley-VCH, Weinheim, 2003.
13 (*a*) S. Matsunaga, T. Kinoshita, S. Okada, S. Harada and M. Shibasaki, *J. Am. Chem. Soc.*, 2004, **126**, 7559; (*b*) S. Harada, S. Handa, S. Matsunaga and M. Shibasaki, *Angew. Chem., Int. Ed.*, 2005, **44**, 4365.
14 R. D. Richardson, F. A. Hernandez Juan and D. J. Dixon, *Synlett*, 2006, 77.
15 A. Thompson, E. G. Corley, M. F. Huntington, E. J. J. Grabowski, J. F. Remenar and D. B. Collum, *J. Am. Chem. Soc.*, 1998, **120**, 2028.
16 (1*R*,2*S*)-2-Pyrrolidine-1-phenylpropan-1-ol was kindly donated by Dr J. W. Burton: D. Zhao, C. Chen, F. Xu, L. Tan, R. Tillyer, M. E. Pierce and J. R. Moore, *Org. Synth.*, 1999, **77**, 12.
17 M. A. Beswick and D. S. Wright, in *Comprehensive Organometallic Chemistry II*, ed. E. W. Abel, F. G. A. Stone and G. Wilkinson, Pergmamon Press, Oxford, 1995, ch. 1.
18 (*a*) G. R. Sullivan, J. A. Dale and H. S. Mosher, *J. Org. Chem.*, 1973, **38**, 2143, for a recent review see: (*b*) J. M. Seco, E. Quiñoá and R. Riguera, *Chem. Rev.*, 2004, **104**, 17.
19 (*a*) M. Hasegawa, D. Taniyama and K. Tomioka, *Tetrahedron*, 2000, **56**, 10153; (*b*) M. Shindo, K. Koga and K. Tomioka, *J. Org. Chem.*, 1998, **63**, 9351.
20 T. Oishi and T. Nakata, *Acc. Chem. Res.*, 1984, **17**, 338.
21 (*a*) D. A. Evans and K. T. Chapman, *Tetrahedron Lett.*, 1986, **27**, 5939; (*b*) D. A. Evans, K. T. Chapman and E. M. Carreira, *J. Am. Chem. Soc.*, 1988, **110**, 3560–3578.
22 S. D. Rychnovsky, B. N. Rogers and T. I. Richardson, *Acc. Chem. Res.*, 1998, **31**, 9–17.
23 M. A. Blanchette, W. Choy, J. T. Davis, A. P. Essenfeld, S. Masamune, W. R. Roush and T. Sakai, *Tetrahedron Lett.*, 1984, **25**, 2183.
24 S. J. Coote, S. G. Davies, C. L. Goodfellow, K. H. Sutton, D. Middlemiss and A. Naylor, *Tetrahedron: Asymmetry*, 1990, **1**, 817.
25 (*a*) M. E. Vandort, Y. W. Jung, P. S. Sherman, M. R. Kilbourn and D. M. Wieland, *J. Med. Chem.*, 1995, **38**, 810; (*b*) S. Manabe, *Chem. Commun.*, 1997, 737.
26 M. Okuda and K. Tomioka, *Tetrahedron Lett.*, 1994, **35**, 4585.
27 K. Nishimura and K. Tomioka, *J. Org. Chem.*, 2002, **67**, 431.
28 I. Inoue, M. Shindo, K. Koga, M. Kanai and K. Tomioka, *Tetrahedron: Asymmetry*, 1995, **6**, 2527.
29 W. L. F. Armarego and D. D. Perrin, *Purification of laboratory chemicals*, Butterworth-Heinemann, Oxford, 1997.
30 W. J. Gensler, F. Johnson and D. B. Sloan, *J. Am. Chem. Soc.*, 1960, **82**, 6074.
31 Kindly donated by R. D. Richardson: T. Perrault, *Can. J. Chem.*, 1968, **46**, 3762.

32 Z. M. Wang and K. B. Sharpless, *J. Org. Chem.*, 1994, **59**, 8302.
33 L. Goobi, P. Seiler, F. Diederich and V. Gramlich, *Helv. Chim. Acta*, 200, **83**, 1711.
34 X.-W. Yang, J.-J. Sheng, C.-S. Da, H.-S. Wang, W. Su, R. Wang and A. S. C. Chan, *J. Org. Chem.*, 2000, **65**, 295.
35 D. H. R. Barton, Y. Hervé, P. Potier and J. Thierry, *Tetrahedron*, 1988, **44**, 5479.
36 H. Droste and T. Wieland, *Liebigs Ann. Chem.*, 1987, 901.
37 (*a*) E. Benzing, *Angew. Chem.*, 1959, **71**, 521; (*b*) K. H. Altmann, G. Bold, G. Caravatti, D. Denni, A. Florsheimer, A. Schmidt, G. Rihs and M. Wartmann, *Helv. Chim. Acta*, 2002, **85**, 4086.
38 K. Ishimaru, K. Monda, Y. Yamamoto and K. Akiba, *Tetradedron*, 1998, **54**, 727.
39 R. W. Hoffmann, K. Ditrich, G. Koster and R. Sturmer, *Chem. Ber.*, 1989, **122**, 1783.
40 W. E. Noland, *J. Org. Chem.*, 1963, **28**, 884.