Atroposelectivity in the electrophilic substitution reactions of laterally lithiated and silylated tertiary amides

Jonathan Clayden,*[a] Jennifer H. Pink,[a] Neil Westlund[a] and Christopher S. Frampton[b]

[a] *Department of Chemistry, University of Manchester, Oxford Rd., Manchester, UK M13 9PL*
[b] *Roche Discovery Welwyn, Broadwater Road, Welwyn Garden City, Herts, UK AL7 3AY*

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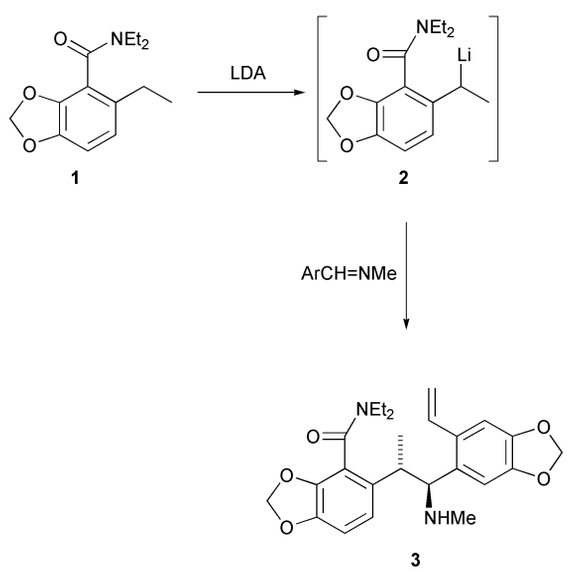
Lateral lithiation–electrophilic quench of 2-alkyl-1-naphthamides and 2,6-dialkylbenzamides yields products containing an atropisomeric Ar–CO axis and a new stereogenic centre with high (generally >95 : 5) diastereoselectivity. With imines as electrophiles, single diastereoisomers containing an atropisomeric axis and two new stereogenic centres are formed. 2,6-Dialkylbenzamides may be functionalised stereoselectively at both the 2- and 6-positions, leading (with imines) to symmetrical compounds bearing 1,7-related stereogenic centres. 2-Alkylbenzamides with only one *ortho* alkyl group are not atropisomeric at ambient temperature but are functionalised diastereoselectively by lateral lithiation–electrophilic quench at −78 °C. Stabilisation of the atropisomeric products by further lithiation and alkylation proves their diastereoselective formation. The lack of stereospecificity in the fluoride-promoted reaction of a laterally silylated 1-naphthamide with an aldehyde suggests that reported reactions of laterally silylated benzamides may also be controlled by the rotationally restricted amide group.

Introduction

Tertiary aromatic amides are among the most reliable directors of regioselective deprotonation,[1] and the ortholithiation of tertiary amides is a very fruitful source of polycyclic aromatic compounds.[2–5] The amides' ability to direct ortholithiation is outclassed only by their ability to direct lateral lithiation—that is, deprotonation at the more acidic benzylic sites of alkyl groups located *ortho* to the amide[6]—and in general a tertiary amide with acidic hydrogen atoms in both the *ortho* and lateral positions is lithiated at the lateral site.[7,8] The efficiency of both reactions derives from the complex-induced proximity effect[9] (initial complexation of the butyllithium to the electron-rich oxygen atom of the amide[10–15]) working in concert with the acidification of *ortho* and lateral hydrogen atoms by the electron-withdrawing carbonyl group.

During the last few years, interest in the *regio*selectivity of these lithiation reactions has stimulated an interest in their *stereo*selectivity.[16] For example, lateral lithiation of amide **1** gives organolithium **2** which generates only a single diastereoisomer of the amine **3** (an intermediate in a synthesis of corydalic acid methyl ester) on addition to an imine (Scheme 1).[17] Similar reactions lead to enantiomerically enriched products in the presence of sparteine.[18] Also in the enantiomerically pure series, lateral lithiation of **4** gives organolithium **5** which is configurationally labile at the lithium-bearing centre but which reacts enantioselectively in the presence of (−)-sparteine and produces laterally functionalised products **6** in up to 92% ee (Scheme 2).[19,20] Chiral lithium amide bases govern the selective lateral lithiation of one of the pair of enantiotopic methyl groups of **7**, leading to enantiomerically enriched atropisomers of **8** (Scheme 3).[21] †

Amide **8** is chiral because of restricted rotation about the Ar–CO bond,[24–29] ‡ and we have previously shown (Scheme 4) that a rotationally restricted amide can be a stereocontrolling influence in the formation of atropisomeric diastereoisomers (that is, diastereoisomers which arise from restricted rotation) *syn*- and *anti*-**10** by the addition of ortholithiated 1-naphthamide **9** to aldehydes.[30–32] We have now investigated the role of a rotationally restricted amide group in the construction of stereogenic centres by lateral lithiation, and in this paper we report our results in full.[33–35] Notably, in nearly every case we have examined, one atropisomeric diastereoisomer is formed with >95 : 5 diastereoselectivity: the amide group imposes not only complete regioselectivity but also complete stereoselectivity on the reaction.



Scheme 1 Lateral lithiation and relative stereochemical control.

† In related reactions, Staunton and Regan[22,23] obtained high levels of asymmetric induction when they employed a chiral lithium amide base in the lithiation–electrophilic quench of 2-methyl substituted aromatic esters, and asymmetric benzylic lithiation of biaryls with *s*-BuLi–(−)-sparteine affords axially chiral biaryls in moderate ee.

‡ In general, tertiary aromatic amides exhibit atropisomerism about their Ar–CO bond if they carry a substituent in both the 2- and the 6-positions.

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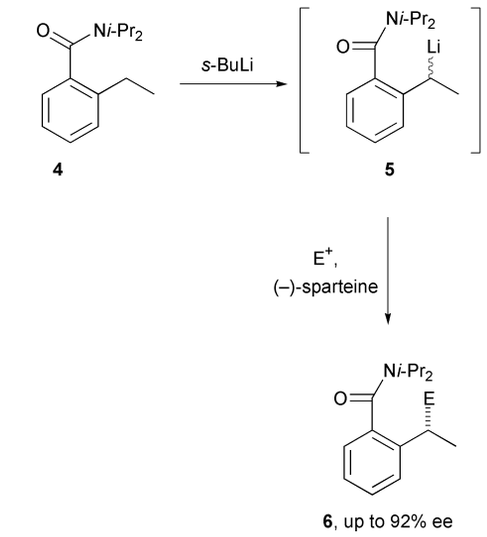
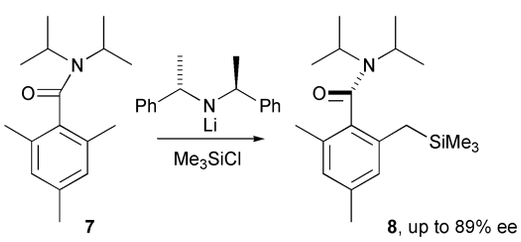
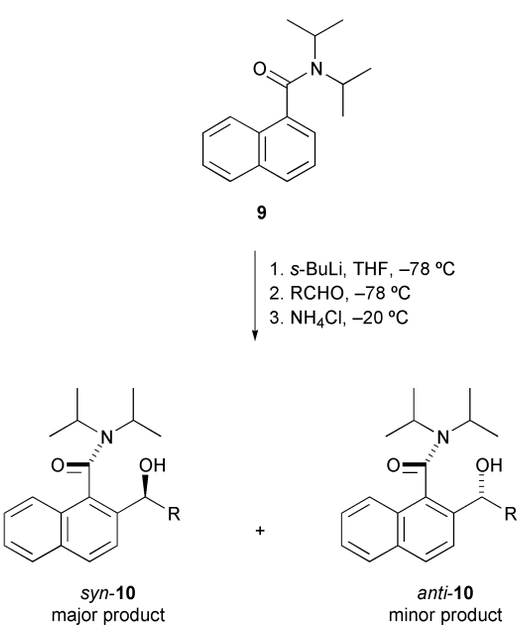


Scheme 2 Lateral lithiation and absolute stereochemical control.



Scheme 3 Desymmetrising lateral lithiation.



Scheme 4 Ortholithiation and stereochemical control.

Results and discussion

Atroposelective lateral lithiation–electrophilic quench of 2-alkyl-1-naphthamides

The 2-alkylnaphthamides **11**,[31] **12**[29] and **13**,[36] starting materials for our lateral lithiation reactions, were made by reacting ortholithiated *N*,*N*-diisopropyl-1-naphthamide **9**[31] with MeI, EtI and PrI respectively. Amide **11** was laterally lithiated and treated with Me_3SiCl to give **14**.

These four amides were then laterally lithiated using *s*-BuLi in THF at −78 °C,§ and the resulting coloured organolithiums were quenched with electrophiles to give one or both of two diastereoisomeric atropisomers of general structure **15**, as shown in Scheme 5 and Table 1.

As far as the stereogenic centre adjacent to the ring was concerned, almost every electrophile (alkylating agents, silylating agents, an aldehyde, a ketone and an imine) reacted with a high level of stereoselectivity: the only exceptions were stannylation (entries 11 and 12) and deuteration (entry 13), which both gave about 10 : 1 stereoselectivity. The alkylated compounds **16a** and **16b** are related to one another by epimerisation (atropisomerisation) about the Ar–CO bond, and indeed heating either **16a** or **16b** to 65 °C in toluene for 48 h gave an equilibrated 59 : 41 mixture of **16a** : **16b** (Scheme 6).[29,36] The silylated compounds **17a** and **17b** could be interconverted by heating to give an equilibrium mixture of the two atropisomers biased heavily in favour of **17a**, containing only 6% **17b**.[29] Stannanes **25a/b** and **26a/b** behaved similarly to silanes **17**.[29,36]

Identification of the stereochemistry of the atropisomeric products turned out to be straightforward with the alkylated and stannylated pairs of diastereoisomers **16** and **24** and with the imine **22a** because **16a**, **24b** and **22a** were crystalline: X-ray crystal structures (shown for **22a** in Fig. 1¶) confirmed their

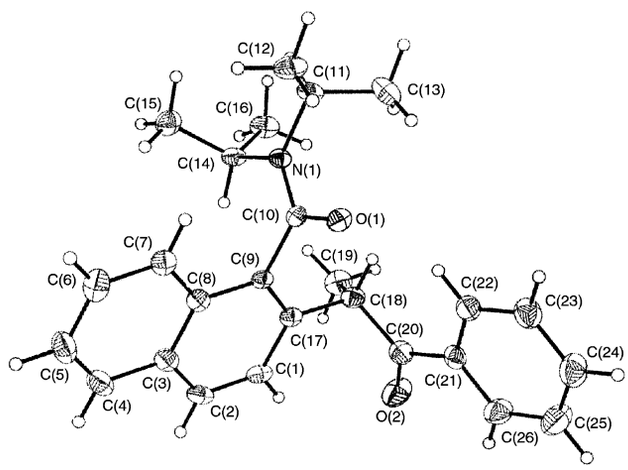


Fig. 1 X-Ray crystal structure of **22a**.

stereochemistry and hence that of their diastereoisomers. The *anti* relative stereochemistry of the stereogenic centres of **22a** is in keeping with precedent (see, for example, Scheme 1).[17] By analogy (see also compound **45a** below), we therefore assign the stereochemistry shown to the other imine **23a** and the other stannanes **25**. The stereochemistry of the silylated compound **18a** was assigned by its stereospecific Fleming–Tamao oxidation[37,38] to the known[31] alcohol **31** (Scheme 7); by analogy we assign the stereochemistry shown to the pair of silylated diastereoisomers **17**. The stereochemistry of the deuterated compound **26a** has previously been determined by NOE studies.[36]

Oxidation of a mixture of the alcohols **20a** and **20b** gave a ketone **28a**, with only a trace (10%) of its diastereoisomer **28b**, proving that the two diastereoisomers **20** differed in stereochemistry only at the hydroxy-bearing centre (Scheme 8). An X-ray crystal structure (Fig. 2) of ketone **28a** proved its stereochemistry, and therefore the stereochemistry at the benzylic stereogenic centre of **20a** and **20b**.

A similar oxidation of **21a** and **21b** gave the racemic ketone **29**. This ketone was enolised stereoselectively by KHMDS: a single, *cis*, silyl enol ether **30** was formed with Me_3SiCl. Alkylation of the same potassium enolate (MeI) gave, with moderate (3 : 1) stereoselectivity, a mixture of diastereoisomers in which **28a** was the minor component, presumably because electrophiles approach the amide-substituted enolate from the less

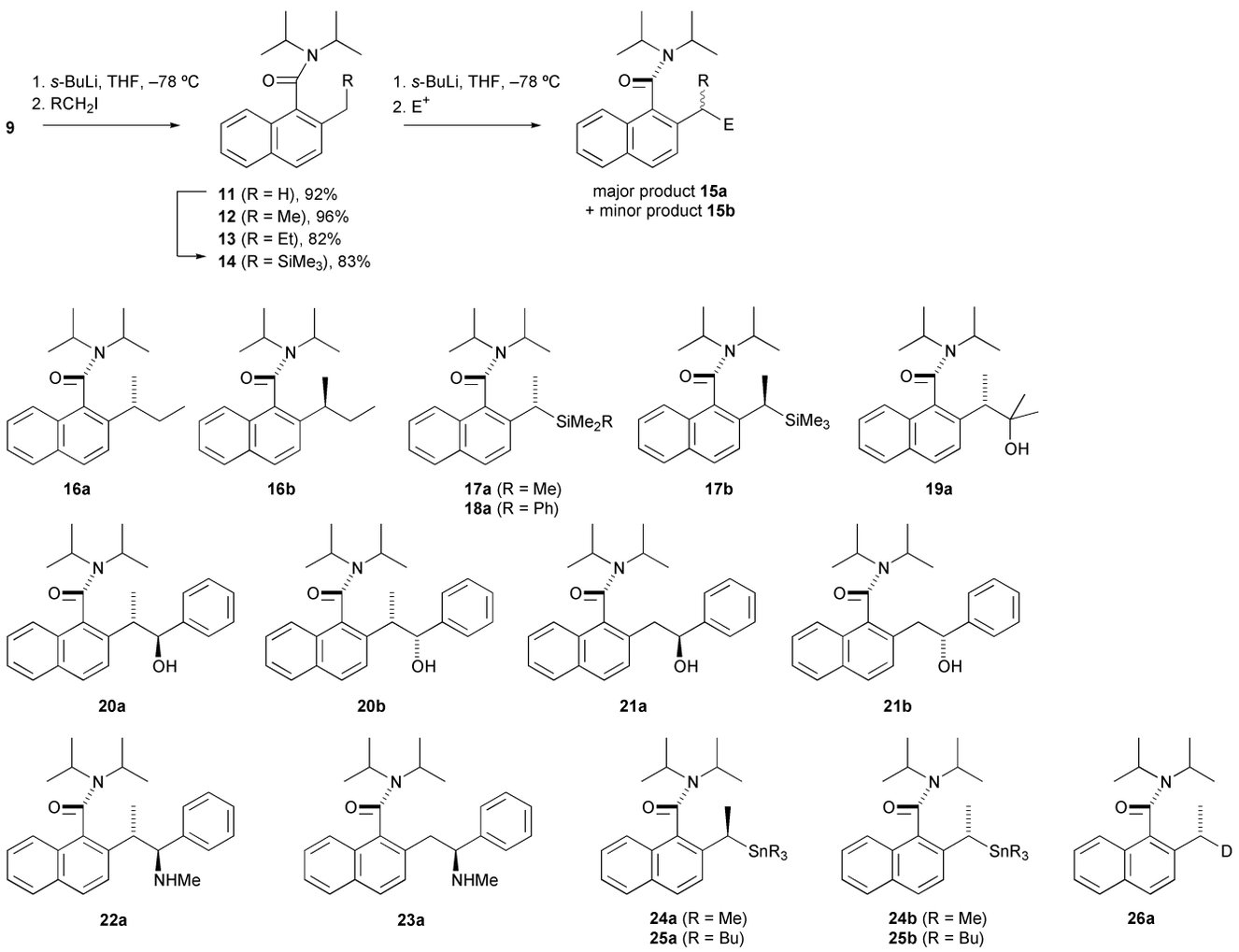
§ Typical procedures for similar lithiations employ TMEDA as a co-solvent.[5,6] We found TMEDA to be unnecessary for high yields in our reactions.

¶ The X-ray crystal structures of **16a** and **24b** have been published.[36]

Table 1 Atroposelective reactions of 2-alkyl-1-naphthamides

Entry	Starting material	Electrophile	Major product	Minor product	Stereoselectivity	Isolated yield (%)
1 [a]	**12**	EtI	**16a**	**16b**	97 : 3	71
2 [a]	**13**	MeI	**16b**	**16a**	99 : 1	84
3	**12**	Me_3SiCl	**17a**	**17b**	98 : 2	76
4	**14**	MeI	**17b**	**17a**	98.5 : 1.5	80
5	**12**	$PhMe_2SiCl$	**18a**	—	97 : 3	85
6	**12**	Acetone	**19a**	—	98 : 2	94
7	**12**	PhCHO	**20a**	**20b**	50 : 50 [b]	58 [c]
8	**11**	PhCHO	**21a**	**21b**	56 : 44	51
9	**12**	PhCH=NMe	**22a**	—	>95 : 5	64
10	**11**	PhCH=NMe	**23a**	—	>95 : 5	71
11 [a]	**12**	Me_3SnBr	**24a**	**24b**	93 : 7	94
12 [a]	**12**	Bu_3SnCl	**25a**	**25b**	89 : 11	78
13 [a]	**12**	CD_3OD	**26a**	—	91 : 9	100

[a] See ref. 36. [b] Single stereoisomer with regard to the benzylic stereogenic centre. [c] Isolated as a mixture of diastereoisomers.



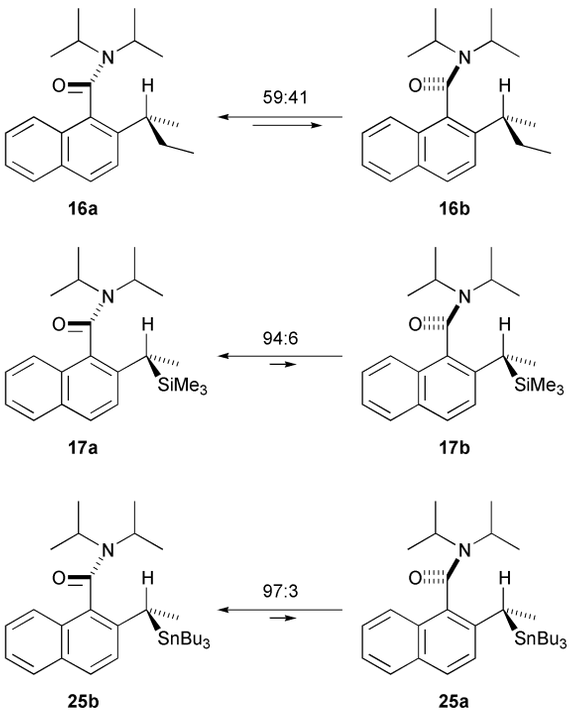
Scheme 5 Atroposelective lateral lithiation.

hindered face.[39] The stereochemistry at the hydroxy-bearing centres of **20** and **21** has been assigned arbitrarily. We assign the stereochemistry of **19a** on the assumption that aldehydes and ketones react with the same stereochemical sense.

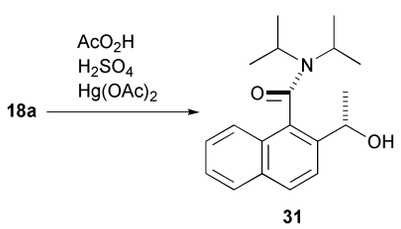
With all electrophiles except tin halides it therefore appears that the major products have stereochemistry at the new benzylic centre as shown in Scheme 9. We recently proved that the lithiation step in such lateral lithiations is atroposelective and generates a single configurationally stable diastereoisomer of the intermediate organolithium shown in Scheme 9.[36] The stereochemical outcome of these reactions must therefore be a result of stereospecific electrophilic substitution of this organolithium. Apparently, all electrophiles react with the organolithium intermediate with retention except tin halides, which react with inversion. Such capricious stereospecificity is far from unknown in the reactions of benzylic organolithiums,[40–43] and it is apparent that soft electrophiles which are reluctant to coordinate to Li—such as tin halides—have a tendency to react with inversion. When the amide carries a planar, non-stereogenic nucleophilic centre, as in the enolate derived from **29**, stereoselectivity is much lower—further evidence that the high levels of stereocontrol in the reactions of laterally lithiated naphthamides arise from stereospecificity, and not simply stereoselectivity, in the electrophilic quench step.

Additions to imines potentially display stereoselectivity in the formation of the new, nitrogen-bearing centre in addition to any stereospecificity at the new benzylic centre. A direct influence from the atropisomeric amide group is clearly behind

this stereoselectivity, because even **23a** is formed as a single diastereoisomer. This remarkable (1,5)-stereocontrol is not matched by additions to aldehydes, maybe as a consequence of the more permissive stereochemical environment around the aldehyde oxygen than around the geometrically defined imine nitrogen. Reversibility is also a feature of the addition to imines: it is important to quench them at low temperature, since warming to room temperature causes reversion to lithiated starting material and imine. Thermodynamic control may therefore be behind the good stereoselectivity observed in these reactions.[17]



Scheme 6 Equilibration of the atropisomers.



Scheme 7 Stereochemistry of **18a**.

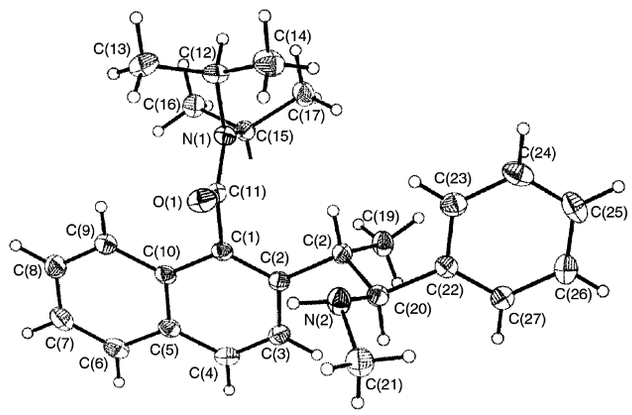
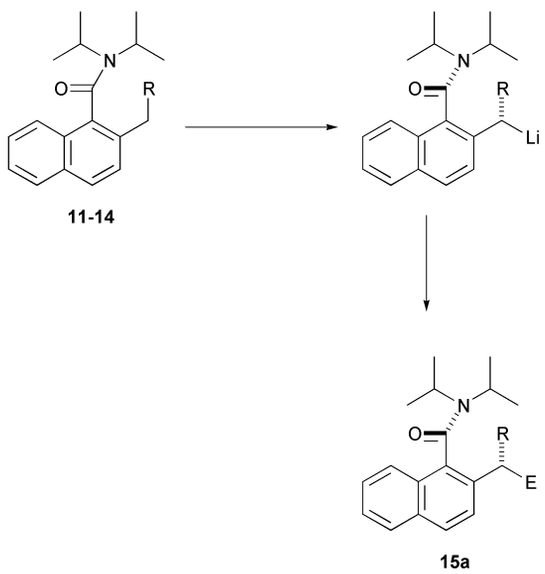
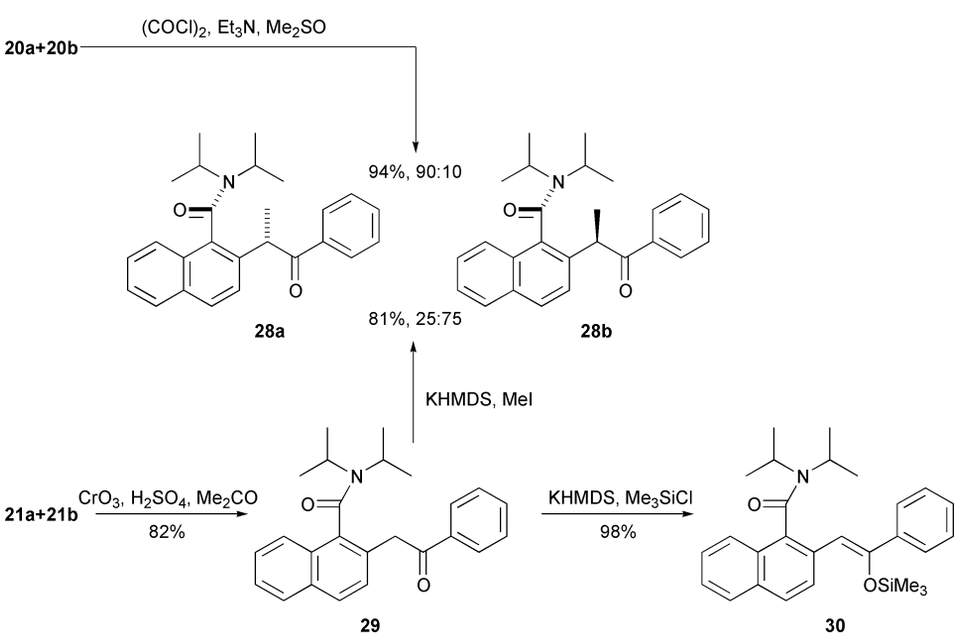


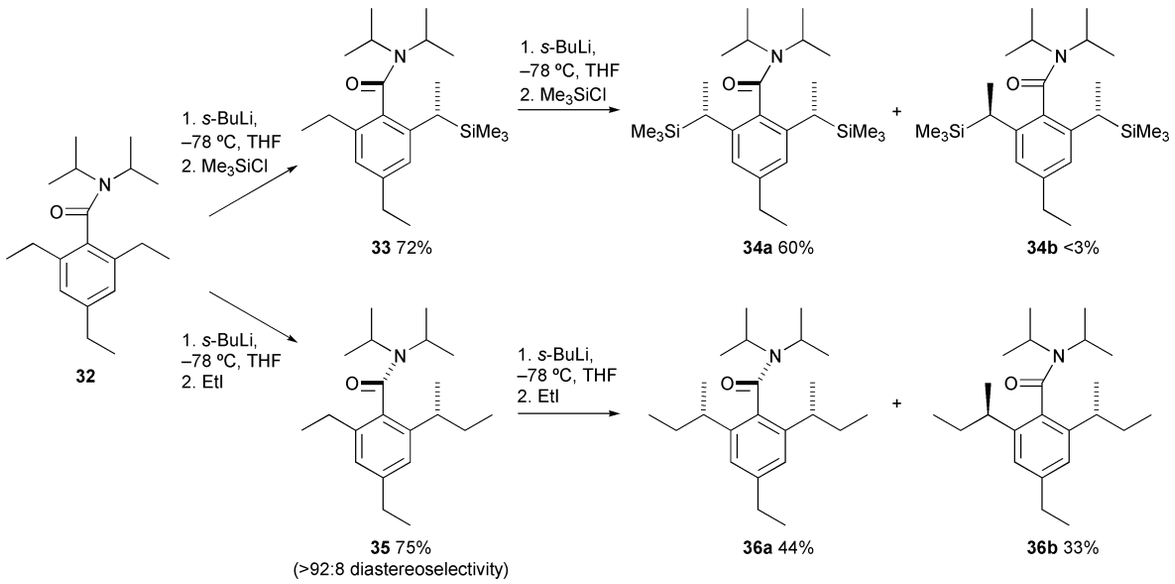
Fig. 2 X-Ray crystal structure of **28a**.



Scheme 9 Stereoselective lithiation; stereospecific quench.



Scheme 8 Stereochemistry of **20** and **21**.



Scheme 10 1,5-Stereocontrol by double lateral lithiation.

Atroposelective lateral lithiation–quench of 2,6-dialkybenzamides

Tertiary 2,6-dialkylbenzamides may possess a stereogenic Ar–CO axis like that of the 2-alkyl-1-naphthamides,[29,44] but offer additional possibilities for stereocontrol *via* double lateral lithiation–electrophilic quench reactions. In order to study these reactions, we made the amides **32** and **7**[21] from the respective acyl chlorides. Mesitoyl chloride is commercially available; **32** was made from 1,3,5-triethylbenzene by bromination (92%),[45] halogen–lithium exchange, and carbonation (60%)–amide coupling (21%) or aminocarbonylation (24%).

The triethylbenzamide **32** was lithiated and then silylated or methylated to give, as expected, single diastereoisomers of the products **33** and **35** (Scheme 10). A second lithiation and silylation returned **34a** with >97 : 3 stereoselectivity (there was no trace of the diastereoisomer **34b** by NMR). The NMR spectral data of **34a** clearly showed it to be *meso*, and we assign it *syn*,*syn* stereochemistry by analogy with the *syn*-selective silylation of the corresponding 1-naphthamide **12**. A second lithiation–methylation of **35** was, surprisingly, not stereoselective, and gave a mixture of two diastereoisomers **36a** and **36b**.‖

The trimethylbenzamide **7**,[21] in line with the precedent set by the 1-naphthamide **11**, gave excellent stereoselectivity in its lithiation–quench reaction with the *N*-methylbenzaldimine but poor selectivity in its reaction with benzaldehyde (Scheme 11). Alcohol **37** was formed as a 65 : 35 mixture of diastereoisomers on addition of PhCHO to lithiated **7**,** but amine **38a** was isolated from the reaction of lithiated **7** with *N*-methylbenzaldimine almost stereochemically pure. Amine **38a** was resistant to further lateral lithiation, but could be lithiated successfully if protected by *N*-benzylation. Some epimerisation about the Ar–CO axis was observed on benzylation of **38a**, and we found that the most diastereoselective way to synthesise **39a** was to trap the lithioamine product of the imine addition reaction directly with benzyl bromide. The best selectivities in subsequent reactions of **39a** were obtained if it was freshly made and used *in situ* for each reaction.

‖ The reason for the lack of stereoselectivity in the second lithiation–quench step is not clear: maybe the barrier to epimerisation in the laterally lithiated benzamides is low, and epimerisation in **35** but not **33** is related to the contrasting thermodynamic bias shown in Scheme 6.

** Assignment of stereochemistry to the major and minor products of this reaction is arbitrary.

Evidence that treatment of **39a** with *s*-BuLi led to lateral lithiation was provided by quenching the lithiated compound **40** with D_2O to give **41**. However, **40** would react with *N*-methylbenzaldimine only in the presence of HMPA or DMPU. Warming the lithioamine product **42** to ambient temperature gave a low (6%) yield of the isoquinolone **43** as a single diastereoisomer. Alternatively, **42** (formed in one pot from **7**) could be benzylated and gave a mixture of compounds in which one symmetrical diastereoisomer, presumably **45a**, predominated. The crystalline diamine **45a** was isolated from a double lateral lithiation–imine addition to **7** in 74% yield as almost a single diastereoisomer: >92% was the *meso* compound shown, whose stereochemistry was confirmed by an X-ray crystal structure (Fig. 3).

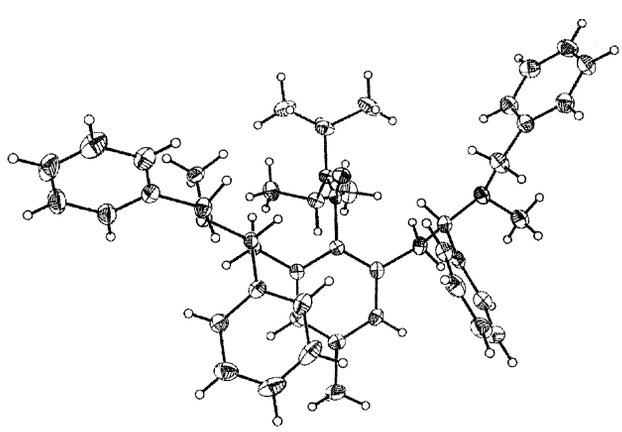
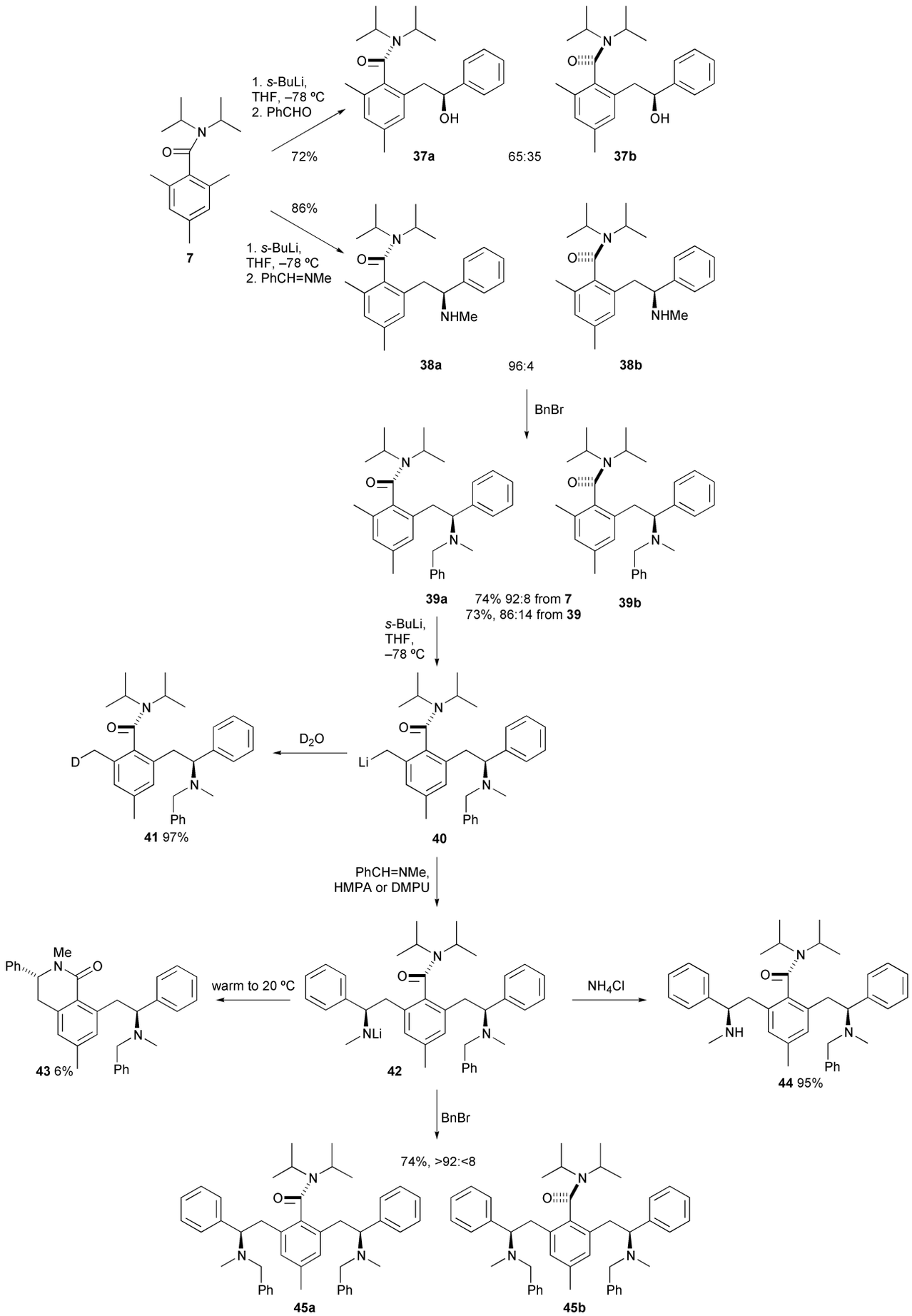


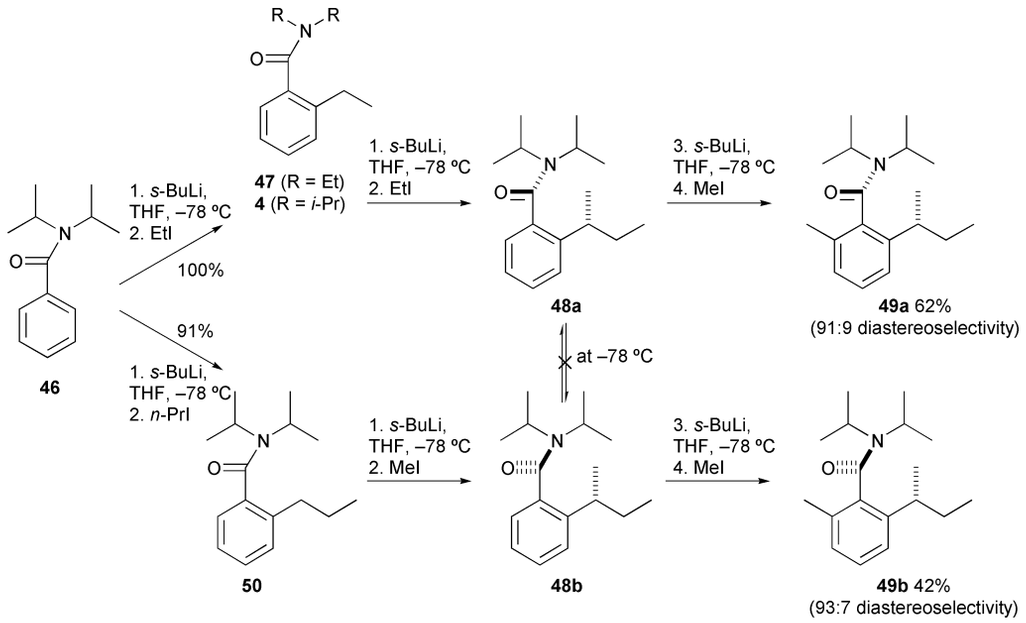
Fig. 3 X-Ray crystal structure of **45a**.

Atroposelective lateral lithiation–quench of 2-alkylbenzamides

Tertiary benzamides bearing a single *ortho* substituent are not usually[46] configurationally stable about the Ar–CO bond and cannot therefore exist as separable atropisomers at ambient temperature.[29] The barrier to rotation about Ar–CO in **47** is 59.4 kJ mol^{-1},[47] making its half-life for enantiomerisation at room temperature less than 0.01 s. However, assuming constancy of $\Delta G^{\ddagger}$ with temperature, this half-life extends to 10 min or more at −78 °C. We therefore expect **47**, **4**, and other 2-substituted tertiary benzamides, to be chiral, racemic atropisomers at temperatures typical of those used for lithiation



Scheme 11 Stereoselective lithiation–quench of a mesitamide.



Scheme 12 Trapping low temperature atropisomers.

chemistry.†† For instance, we might expect **4** to be lithiated diastereoselectively at −78 °C much like **12**.

The problem with testing this hypothesis is the fact that even if the lithiation–quench of **4** is diastereoselective, giving for example **48a**, rapid epimerisation to a mixture of **48a** and **48b** is to be expected on warming the products to room temperature, destroying all evidence of the stereoselectivity.

We solved this problem in the following way. Compounds **4** and **50** were made from **46** by lithiation and alkylation. Compound **4** was lithiated with *s*-BuLi at −78 °C and treated with EtI, presumably giving **48a**. This compound was not isolated: instead, a further equivalent of *s*-BuLi was added, leading to ortholithiation.[7,8] Reaction with methyl iodide introduces a second *ortho* substituent, fixing the conformation of the amide Ar–CO bond and preventing interconversion of the diastereoisomeric atropisomers of **49**. Warming and isolation of the product **49** returned a 91 : 9 mixture of diastereoisomers in which we assume **49a** predominates (Scheme 12).

In order to verify that this diastereoisomeric ratio is under kinetic and not thermodynamic control,[44] we repeated the sequence of reactions with **50** as the starting material. Lateral lithiation, methylation, ortholithiation, and a second methylation gave again a mixture of **49a** and **49b**, this time with **49b** predominating in a 93 : 7 ratio, *via* a compound **48b** which evidently exhibits conformational stability at the temperature of the reaction. Clearly, at −78 °C, **4** and **50** are chiral and can undergo diastereoselective reactions. The lower levels of stereoselectivity in their reactions when compared with the reactions of the naphthamide analogues **12** or **13** must be due either to erosion of kinetic stereoselectivity between the lateral lithiation and ortholithiation steps, or to a lower level of initial stereoselectivity ascribable to the lack of configurational stability[19,20,48] in lithiated **4** (= **5**) or **50**.

The role of atroposelectivity in the fluoride-promoted addition of benzylsilanes to aldehydes

Beak *et al.* have reported the stereospecific transfer of information from an enantiomerically enriched benzylsilane **6** (E = $SiMe_3$) to products **6** with varying degrees of stereospecificity at the stereogenic centre (Scheme 13).[49] There are two possible mechanisms by which the silane might communicate its absolute stereochemistry to the product: an intermediate silicon ate complex may undergo a stereospecific electrophilic substitution, or the rotationally restricted amide axis might provide a mechanism for conformational "chiral memory" of the starting material's configuration. Given the results presented above, and the probable rapidity of an addition reaction of an *in situ* electrophile to a fluoride-generated anion, we feel that the second explanation is very plausible, even though stereospecificity is maintained even when the reaction is carried out at ambient temperature.

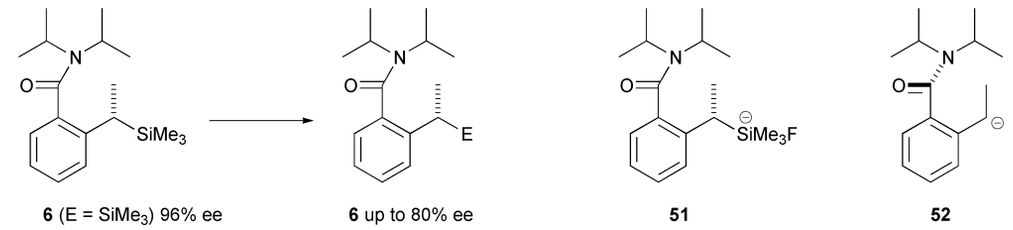
To test this hypothesis, we took the two diastereoisomeric silanes **17a** and **17b** and treated them with TBAF and benzaldehyde under Beak's conditions (Scheme 14).[49] Each reaction gave four diastereoisomers of **20** as shown—two of them (**20a** and **20b**) identical with the compounds obtained from reaction of laterally lithiated **12** with PhCHO. The product mixture from each of the two reactions was essentially identical, so the reactions are stereoselective and not stereospecific.[50] Oxidation of one of the two sets of products gave essentially a single ketone **28a**, showing that the major pair of compounds differed in stereochemistry only at the hydroxy-bearing centre.

Scheme 15 shows the expected outcome from **17a** or **17b** under each of the two mechanisms proposed to account for stereochemical control in Beak's reaction. If the reaction were a stereospecific electrophilic substitution of a silicon ate complex, the ate complexes from **17a** and **17b** would be diastereoisomeric and are therefore expected to give diastereoisomeric products. The fact that the product mixtures from both **17a** and **17b** are essentially identical suggests that this is not the case but that instead the two diastereoisomeric silanes generate a common intermediate, represented by the notional anion **54**, which reacts stereoselectively with electrophiles. Stereoselectivity must presumably arise from the influence of the rotationally restricted amide bond of **54**, which, as with the organolithiums, directs formation of **15a** rather than **15b**.‡‡

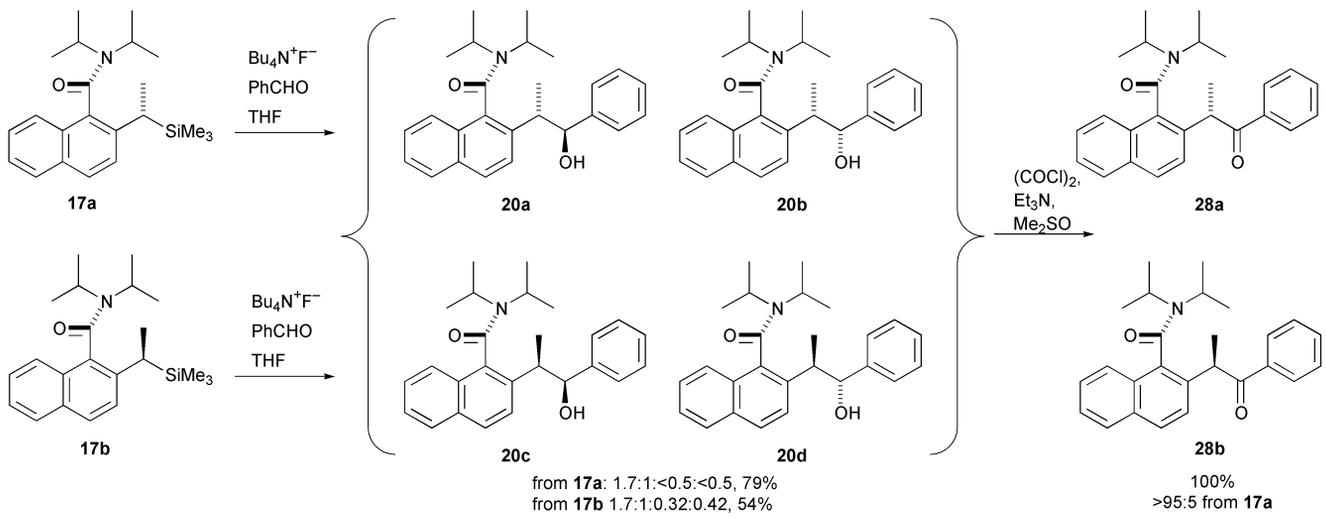
By analogy, stereospecificity in Beak's original reaction is unlikely therefore to be due to the stereospecificity of the electrophilic substitution reaction itself. A more reasonable

†† Amide **4** is expected to be chiral under the conditions used to carry out its asymmetric functionalisation in the presence of (−)-sparteine (ref. 20). However, the consequences of this—such as relative rates of lithiation of the two enantiomers of **4**, or whether complexes of **5** with (−)-sparteine can exist as pairs of atropisomeric diastereoisomers—have not been investigated.

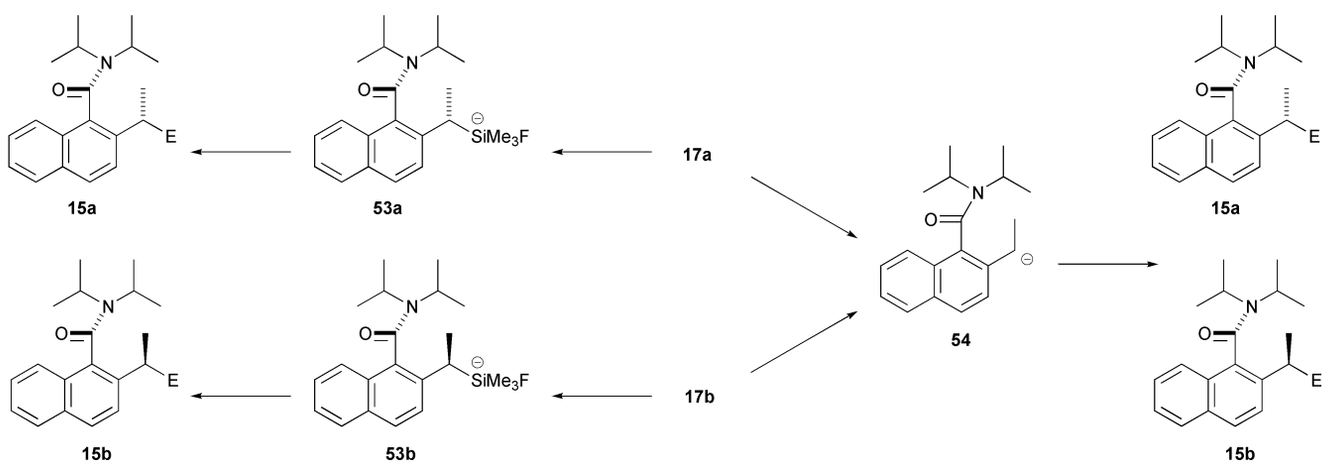
‡‡ The precise nature of **54** is not clear: all that is required of it is that any stereochemistry associated with the anionic centre has no bearing on the stereochemistry of its reactions.



Scheme 13 Stereospecific fluoride-induced substitution of a silyl benzamide.



Scheme 14 Stereoselective fluoride-induced substitution of a silylnaphthamide.



Scheme 15 Mechanisms of fluoride-induced electrophilic substitution.

explanation is that the reaction is an instance of chiral memory:[51] the stereochemistry of the starting silane governs the conformation of the Ar–CO bond, which retains that conformation for long enough to govern the direction of attack of the aldehyde on the 2-ethyl amide anion **52**. A number of stereospecific reactions are known in which stereochemical control is mediated by transient lack of conformational mobility in an otherwise planar intermediate.[52–57]

In this paper we have proposed mechanisms by which atropisomeric amide groups may direct the stereoselectivity of formation and reaction of adjacent benzylic organolithiums and anions. Some features of the compound we have described suggest the ability of a stereogenic centre to control the stereochemistry of the axis (the ability of **52** to "memorise" the chirality of **6** (E = $SiMe_3$), and also the relative stabilities of the diastereoisomers of **16**, **17** and **25**), a phenomenon we have discussed before[44] and to which we shall return in more detail in a future publication.

Experimental

Amides **11**,[31] **12**[29] and **13**[36] were made by literature methods from amide **9** in 92, 96 and 82% yield respectively.

N,*N*-Diisopropyl-2-trimethylsilylmethyl-1-naphthamide 14

sec-Butyllithium (0.94 ml, 1.3 M in cyclohexane, 1.22 mmol) was added dropwise to a solution of *N*,*N*-diisopropyl-2-methyl-1-naphthamide **11**[31] (300 mg, 1.11 mmol) in THF (80 ml) at −78 °C under nitrogen. The purple solution was stirred for 1 h and trimethylsilyl chloride (0.21 ml, 1.67 mmol) was added. After 20 min the mixture was allowed to warm to room temperature. Water (40 ml) was added and the THF was removed under reduced pressure. The aqueous phase was extracted with dichloromethane (3 × 20 ml) and the combined extracts were washed with water (20 ml), dried over magnesium sulfate, filtered and concentrated. Purification by flash chromatography[58] [5% ethyl acetate in light petroleum] gave the silane as a white

crystalline solid (313 mg, 83%), mp 102–103 °C; R_f [10% ethyl acetate in light petroleum] 0.39; ν_{max} (Nujol mull)/cm^{-1} 1626; δ_H (300 MHz; $CDCl_3$) 7.84–7.67 (3H, m, ArH), 7.51–7.27 (2H, m, ArH), 7.21 (1H, d, J = 8.4 Hz, ArH), 3.68–3.48 (2H, m, 2 × NCH), 2.32–2.16 (2H, AB, J = 13.3, $ArCH_AH_B$), 1.79 (3H, d, J = 6.7, NCHCH_3), 1.71 (3H, d, J = 6.9, NCHCH_3), 1.13 (3H, d, J = 6.7, NCHCH_3), 0.98 (3H, d, J = 6.7, NCHCH_3), 0.10 (9H, s, $Si(CH_3)_3$); δ_C (75 MHz; $CDCl_3$) 169.6 (s, CO), 134.0 (s, Ar), 132.4 (s, Ar), 130.9 (s, Ar), 130.1 (s, Ar), 127.8 (d, Ar), 127.5 (d, Ar), 127.2 (d, Ar), 126.4 (d, Ar), 124.7 (d, Ar), 124.5 (d, Ar), 50.8 (d, NCH), 45.8 (d, NCH), 24.4 (t, CH_2), 21.2 (q, NCHCH_3), 20.9 (q, NCHCH_3), 20.6 (q, NCHCH_3), 20.5 (q, NCHCH_3), 1.00 (q, $Si(CH_3)_3$); *m/z* (CI) 344 (7%), 343 (16), 342 (100), 326 (5), 298 (5), 241 (3), 169 (7) (Found: M^+, 341.2170. $C_{21}H_{31}NOSi$ requires *M*, 341.2175).

(R_a*,*S**)-*N*,*N*-Diisopropyl-2-(1-trimethylsilylethyl)-1-naphthamide 17a

sec-Butyllithium (2.98 ml, 1.3 M solution in cyclohexane, 3.88 mmol) was added dropwise to a solution of *N*,*N*-diisopropyl-2-ethyl-1-naphthamide[29] **12** (1.00 g, 3.53 mmol) in THF (70 ml) at −78 °C under nitrogen. The resultant dark green solution was stirred for 1 h and trimethylsilyl chloride (0.67 ml, 5.30 mmol) was added. After 10 min the mixture was allowed to warm to 0 °C. Water (30 ml) was added and the THF was removed under reduced pressure. The aqueous phase was extracted with dichloromethane (3 × 25 ml) and the combined extracts were washed with water (30 ml), dried over magnesium sulfate, filtered and the solvent was evaporated. Purification by flash chromatography[58] [5% ethyl acetate in light petroleum] gave the *silane* **17a** (0.958 g, 76%) as a white crystalline solid, mp 124–125 °C; R_f [10% EtOAc in petrol] 0.44; ν_{max} (Nujol mull)/cm^{-1} 1623; δ_H (300 MHz; $CDCl_3$) 7.82–7.74 (3H, m, ArH), 7.51–7.38 (2H, m, ArH), 7.32 (1H, d, J = 8.5, ArH), 3.72–3.54 (2H, m, 2 × NCH), 2.40 (1H, q, J = 7.4, ArCH), 1.81 (3H, d, J = 6.7, NCHCH_3), 1.70 (3H, d, J = 6.7, NCHCH_3), 1.46 (3H, d, J = 7.4, SiCHCH_3), 1.13 (3H, d, J = 6.7, NCHCH_3), 0.98 (3H, d, J = 6.7, NCHCH_3), 0.06 (9H, s, $Si(CH_3)_3$); δ_C (75 MHz; $CDCl_3$) 169.5 (s, CO), 139.4 (s, Ar), 132.3 (s, Ar), 131.1 (s, Ar), 129.9 (s, Ar), 127.7 (d, Ar), 127.5 (d, Ar), 126.3 (d, Ar), 124.8 (d, Ar), 124.7 (d, Ar), 50.6 (d, NCH), 46.0 (d, NCH), 26.3 (d, ArCH), 21.3 (q, NCHCH_3), 21.0 (q, NCHCH_3), 20.7 (q, NCHCH_3), 20.5 (q, NCHCH_3), 16.2 (q, ArCHCH_3), −2.5 (q, $Si(CH_3)_3$); *m/z* (CI) 357 (28%), 356 (100), 195 (8), 178 (13), 148 (6) (Found: C, 74.53; H, 9.39; N, 4.07%, M^+, 355.2325. $C_{22}H_{33}NOSi$ requires C, 74.31; H, 9.35; N, 3.94%, *M* 355.2331).

HPLC analysis of the crude product mixture was carried out on a phenosphere 100 × 8.00 mm 5 μ silica column, 80 Å, Perkin Elmer LC-480 Diode Array System, eluant 0.5% ethanol in hexane, flow rate 2 ml min^{-1}, UV at 280 nm, t_R 4.34 min (**17a**, 98%), 8.30 (**17b**, 2%).

(R_a*,*R**)-*N*,*N*-Diisopropyl-2-(1-trimethylsilylethyl)-1-naphthamide 17b

sec-Butyllithium (0.61 ml, 1.3 M solution in cyclohexane, 0.789 mmol) was added dropwise to a solution of naphthamide **14** (245 mg, 0.717 mmol) in THF (60 ml) at −78 °C under nitrogen. The dark green solution was stirred at −78 °C for 1 h. Methyl iodide (67 μl, 1.075 mmol) was added. The solution was allowed to warm to 0 °C, water (30 ml) was added and the THF was removed under reduced pressure. The aqueous phase was extracted with dichloromethane (3 × 20 ml), the combined extracts were washed with water (25 ml), dried over magnesium sulfate, filtered and the solvent was evaporated. Purification by flash chromatography[58] [7% ethyl acetate in light petroleum] gave the *silane* **17b** (205 mg, 80%) as a white crystalline solid, mp 123–124 °C; R_f [10% EtOAc–petrol] 0.32; ν_{max} (Nujol mull)/cm^{-1} 1617; δ_H (300 MHz; $CDCl_3$) 7.85–7.73 (3H, m, ArH), 7.50–7.39 (2H, m, ArH), 7.34 (1H, d, J = 8.6, ArH), 3.80–3.55 (2H, m, 2 × NCH), 2.29 (1H, q, J = 7.4, ArCH), 1.82 (3H, d, J = 6.9, NCHCH_3), 1.71 (3H, d, J = 6.7, NCHCH_3), 1.44 (3H, d, J = 7.4, SiCHCH_3), 1.16 (3H, d, J = 6.6, NCHCH_3), 1.07 (3H, d, J = 6.6, NCHCH_3), 0.16 (9H, s, $Si(CH_3)_3$); δ_C (75 MHz; $CDCl_3$) 169.5 (s, CO), 140.3 (s, Ar), 134.2 (s, Ar), 131.4 (s, Ar), 130.1 (s, Ar), 128.0 (d, Ar), 127.8 (d, Ar), 126.7 (d, Ar), 126.1 (d, Ar), 125.0 (d, Ar), 124.8 (d, Ar), 50.7 (d, NCH), 46.0 (d, NCH), 26.9 (d, ArCH), 21.8 (q, NCHCH_3), 21.0 (q, NCHCH_3), 20.6 (q, NCHCH_3), 20.4 (q, NCHCH_3), 18.9 (q, ArCHCH_3), −1.7 (q, $Si(CH_3)_3$); *m/z* (CI) 357 (22%), 356 (100), 284 (5), 255 (5), 183 (3) (Found: C, 74.50; H, 9.45; N, 4.0%, M^+, 355.2327. $C_{22}H_{33}NOSi$ requires C, 74.31; H, 9.35; N, 3.94%, *M* 355.2331).

HPLC analysis of the crude product mixture was carried out on a phenosphere 100 × 8.00 mm 5 μ silica column, 80 Å, Perkin Elmer LC-480 Diode Array System, eluant 0.5% ethanol in hexane, flow rate 2 ml min^{-1}, UV at 280 nm, t_R 4.34 min (**17a**, 1.5%), 8.30 (**17b**, 98.5%).

The rate of interconversion of the atropisomers has been published.[29]

(R_a*,*S**)-*N*,*N*-Diisopropyl-2-(1-dimethylphenylsilylethyl)-1-naphthamide 18a

sec-Butyllithium (0.90 ml, 1.3 M solution in cyclohexane, 1.16 mmol) was added dropwise to a solution of *N*,*N*-diisopropyl-2-ethyl-1-naphthamide[29] **12** (300 mg, 1.06 mmol) in THF (60 ml) at −78 °C under nitrogen. The dark green solution was stirred for 1 h and chlorodimethylphenylsilane (0.356 ml, 2.12 mmol) was added. After 10 min the mixture was allowed to warm to 0 °C. Water (40 ml) was added and the THF was removed under reduced pressure. The aqueous phase was extracted with dichloromethane (3 × 20 ml) and the combined extracts were washed with water (20 ml), dried over magnesium sulfate, filtered and the solvent was evaporated. Purification by flash chromatography[58] [5% ethyl acetate in light petroleum] gave the *silane* **18a** (376 mg, 85%) as a white crystalline solid, R_f [10% EtOAc–petrol] 0.46; δ_H (300 MHz; $CDCl_3$) 7.84–7.77 (2H, m, ArH), 7.74 (1H, d, J = 8.6, ArH), 7.66–7.38 (7H, m, ArH), 7.18 (1H, d, J = 8.6, ArH), 3.71–3.53 (2H, m, 2 × NCH), 2.60 (1H, 1, J = 7.4, ArCH), 1.83 (3H, d, J = 6.9, NCHCH_3), 1.72 (3H, d, J = 6.9, NCHCH_3), 1.37 (3H, d, J = 7.3, ArCHCH_3), 1.09 (3H, d, J = 6.6, NCHCH_3), 0.98 (3H, d, J = 6.7, NCHCH_3), 0.39 (3H, s, $SiCH_3$), 0.24 (3H, s, $SiCH_3$); δ_C (75 MHz; $CDCl_3$); *m/z* (CI) 419 (21%), 418 (100), 340 (30), 183 (18), 152 (11), 135 (11) (Found (EI): M^+, 417.2495. $C_{27}H_{35}NOSi$ requires *M*, 417.2488).

HPLC analysis of the crude product (phenosphere 100 × 8.00 mm 5 μ silica column, 80 Å, Perkin Elmer LC-480 Diode Array System, eluant 0.5% ethanol in hexane, flow rate 2 ml min^{-1}, UV at 280 nm) showed peaks at t_R 4.68 (**18a**, 97%), 11.16 (tentatively identified as **18b**, 3%).

(R_a*,*S**)-*N*,*N*-Diisopropyl-2-[(1,2-dimethyl-2-hydroxy)propyl]-naphthamide 19a

sec-Butyllithium (0.89 ml, 1.3 M solution in cyclohexane, 1.16 mmol) was added dropwise to a solution of *N*,*N*-diisopropyl-2-ethyl-1-naphthamide[29] **12** (300 mg, 1.059 mmol) in dry THF (100 ml) at −78 °C under nitrogen. After 1 h, acetone (0.16 ml, 2.12 mmol) was added. The solution was allowed to warm to 0 °C, water (30 ml) was added and the THF was removed under reduced pressure. The aqueous phase was extracted with dichloromethane (3 × 20 ml) and the combined extracts were washed with water (25 ml), dried over magnesium sulfate, filtered and the solvent was evaporated. Purification by flash chromatography[58] [4 : 1 light petroleum–ethyl acetate] gave the *alcohol* **19a** (339 mg, 94%) as a white crystalline solid, mp 113–116 °C; R_f [EtOAc–petrol, 1 : 4] 0.25; ν_{max} (film)/cm^{-1} 1625; δ_H (300 MHz; $CDCl_3$) 7.89–7.74 (2H, m, 2 × ArH), 7.86 (1H, d, J = 8.7, ArH), 7.57 (1H, d, J = 8.7, ArH), 7.55–7.45 (2H, m, ArH), 4.38 (1H, s, OH), 3.67 (1H, sept, J = 6.7, NCHCH$_3$), 3.55 (1H, sept, J = 6.7, NCHCH$_3$), 3.11 (1H, q, J = 7.1, ArCH), 1.80

(3H, d, J = 6.7, NCHCH_3), 1.75 (3H, d, J = 6.7, NCHCH_3), 1.44 (3H, d, J = 7.1, ArCHCH_3), 1.38 (3H, s, C(OH)CH_3), 1.26 (3H, s, C(OH)CH_3), 1.09 (3H, d, J = 6.7, NCHCH_3), 1.06 (3H, d, J = 6.7, NCHCH_3); δ_C (75 MHz; $CDCl_3$) 171.6 (s, CO), 137.1 (s, Ar), 134.3 (s, Ar), 132.1 (s, Ar), 129.2 (s, Ar), 128.0 (s, Ar), 127.9 (s, Ar), 126.5 (d, Ar), 125.7 (s, Ar), 124.9 (d, Ar), 124.7, (d. Ar), 72.5 (s, COH), 51.2 (d, NCH), 46.8 (d, CH), 46.3 (d, CH), 31.1 (q, CH$_3$CH), 23.6 (q, NCHCH$_3$), 21.0 (q, NCHCH$_3$), 20.5 (q, NCHCH$_3$), 20.5 (q, NCHCH$_3$), 17.1 (q, 2 × C(OH)CH$_3$); *m*/*z* (CI) 343 (22%), 342 (100), 283 (5), 183 (5) (Found: C, 77.17; H, 9.19; N, 4.09%, M + H$^+$, 342.2431. $C_{22}H_{31}NO_2$ requires C, 77.38; H, 9.15; N, 4.10%).

HPLC analysis of the crude product was performed on a phenosphere 100 × 8.00 mm 5 μ silica column, 80 Å, Perkin Elmer LC-480 Diode Array System, eluant 2% ethanol in hexane, flow rate 2 ml min^{-1}, UV at 280 nm), t_R 9.36 (**19a**, 98%), 14.10 (tentatively identified as **19b**, 2%).

(*R*$_a$*,1′*R**,2′*R**)-*N*,*N*-Diisopropyl-2-(2′-hydroxy-1′-methyl-2′-phenylethyl)naphthamide 20a and 20b from 12

sec-Butyllithium (0.88 ml, 1.14 mmol) was added to a solution of naphthamide[29] **12** (269 mg, 0.95 mmol) in THF (14 ml) at −78 °C under nitrogen. After 45 minutes, benzaldehyde (0.18 ml, 1.71 mmol) was added and after a further 30 minutes saturated aqueous ammonium chloride (10 ml). After work-up in the manner described for **19a**, ^{1}H NMR of the crude product showed two diastereoisomers **20a** and **20b** in a ratio of 1 : 1. Purification by flash chromatography[58] eluting with 2 : 1 petrol (bp 40–60 °C)–EtOAc afforded a 50 : 50 mixture (by ^{1}H NMR) of diastereoisomers **20a** and **20b** as a white solid (215 mg, 58%).

N,*N*-Diisopropyl-2-(2′-hydroxy-1′-methyl-2′-phenylethyl)-naphthamide 20 from 17a

Tetra-*n*-butylammonium fluoride (0.422 ml, 1 M solution in THF, dried over molecular sieves, 0.422 mmol) was added to a solution of **17a** (150 mg, 0.281 mmol) and freshly distilled benzaldehyde (0.143 ml, 1.405 mmol) in dry THF (5 ml), in an ice-bath and under nitrogen. The solution was stirred at 0 °C for 4 h and saturated aqueous ammonium chloride solution (10 ml) was added. The aqueous phase was extracted with dichloromethane (3 × 10 ml) and the combined extracts were washed with brine (15 ml), dried over magnesium sulfate, filtered and the solvent was evaporated. Purification by flash chromatography[58] eluting with 7 : 3 petrol (bp 40–60 °C)–EtOAc afforded a mixture of diastereoisomers of the alcohol **20** as a white solid (131 mg, 79%) and *N*,*N*-diisopropyl-2-ethyl-1-naphthamide **12**[29] (18 mg, 21%). HPLC analysis of the alcohol was carried out [phenosphere 100 × 8.00 mm 5 μ silica column, 80 Å, Perkin Elmer LC-480 Diode Array System, eluant 5% ethanol in hexane, flow rate 2 ml min^{-1}, UV at 280 nm, t_R 2.79 (**20a**, 58.0%), 4.18 (**20b**, 33.7%), 6.14 (**20c** or **20d**, 8.35%)]; ratio = 1.7 : 1 : 0.25.

N,*N*-Diisopropyl-2-(2′-hydroxy-1′-methyl-2′-phenylethyl)-naphthamide 20 from 17b

In the same way, tetra-*n*-butyl ammonium fluoride (0.21 ml, 0.211 mmol of a 1 M solution in THF, dried over molecular sieves), **17b** (50 mg, 0.141 mmol) and freshly distilled benzaldehyde (72 μl, 0.705 mmol) in anhydrous THF (5 ml) afforded a mixture of diastereoisomers of the alcohol **20** (20 mg, 37%) in addition to the starting silane **17b** (27 mg, 54%) and a small amount of *N*,*N*-diisopropyl-2-ethyl-1-naphthamide **12** (4 mg, 10%), R_f [EtOAc–petrol, 1 : 4] 0.32 and 0.26, δ_H (300 MHz; $CDCl_3$) (major diastereoisomer) 7.82–7.75 (2H, m, ArH), 7.63 (1H, d, J = 8.8, ArH), 7.53–7.19 (7H, m, ArH), 6.93 (1H, d, J = 8.6, ArH), 5.05 (1H, t, J = 3.4, CH(OH)), 3.97 (1H, d, J = 3.4, OH), 3.64 (1H, sept, J = 6.9, NCH), 3.50 (1H, sept, J = 6.7, NCH), 3.49–3.37 (1H, m, ArCHCH$_3$), 1.79 (3H, d, J = 6.9, NCHCH_3), 1.76 (3H, d, J = 6.7, NCHCH_3), 1.29 (3H, d, J = 7.1, ArCHCH_3), 1.01 (3H, d, J = 6.7, NCHCH_3), 1.00 (3H, d, J = 6.7, NCHCH_3); *m*/*z* (CI) 391 (29%), 390 (100), (364 (62), 362 (40), 360 (22), 306 (76), 304 (56), 302 (35), 284 (29) (Found: M + H 390.2427. $C_{26}H_{31}NO_2$ requires 390.2433).

HPLC analysis of the alcohol was carried out [phenosphere 100 × 8.00 mm 5 μ silica column, 80 Å, Perkin Elmer LC-480 Diode Array System, eluant 5% ethanol in hexane, flow rate 2 ml min^{-1}, UV at 280 nm, t_R 2.88 (**20a**, 49.3%), 4.20 (**20b**, 28.6%), 6.36 (**20c**, 9.10%) and 6.55 min (**20d**, 12.11%)]; ratio = 1.7 : 1 : 0.32 : 0.42.

(*R*$_a$*,2′*R**)- and (*R*$_a$*,2′*S**)-*N*,*N*-Diisopropyl-2-(2′-hydroxy-2′-phenylethyl)-1-naphthamide 21a and 21b

sec-Butyllithium (1.57 ml, 2.04 mmol; 1.3 M solution in hexanes) was added to a solution of naphthamide[31] **11** (457 mg, 1.70 mmol) in THF (25 ml) at −78 °C under nitrogen. After 80 minutes, the purple solution was treated with benzaldehyde (0.50 ml, 5.00 mmol), stirred for 45 minutes, warmed to ambient temperature and quenched with saturated aqueous ammonium chloride (10 ml). The THF was removed under reduced pressure and the residue was extracted with dichloromethane (4 × 15 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the crude product. Purification by flash chromatography[58] [2 : 1 petrol (bp 40–60 °C)–EtOAc] afforded a mixture of the *alcohols* **21a** and **21b** (327 mg, 51%).

Analytical HPLC (6 : 1 hexane–EtOAc) of the crude product showed two atropisomers to be present in a ratio of 56 : 44 (t_R 6.2 and 6.6 minutes).

(*R*$_a$*,1′*R**,2′*R**)-*N*,*N*-Diisopropyl-2-[1′-methyl-2′-(methylamino)-2′-phenylethyl]-1-naphthamide 22a

sec-Butyllithium (0.78 ml, 1.02 mmol; 1.3 M in hexanes) was added dropwise to a solution of naphthamide[29] **12** (239 mg, 0.85 mmol) in THF (2 ml) at −78 °C under nitrogen. After 30 minutes the dark green–blue solution was treated with *N*-benzylidenemethylamine (0.11 ml, 0.93 mmol) and stirred for 3 hours to give a dark pink–red solution. The reaction was quenched at −78 °C (raising to ambient temperature causes reversion to starting material) with saturated aqueous ammonium chloride (5 ml) and allowed to warmed to ambient temperature, diluted with water (10 ml) and the THF was removed under reduced pressure at ambient temperature. The aqueous residue was extracted with dichloromethane (4 × 7 ml) and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the crude product as a single atropisomer (by ^{1}H NMR). Purification by flash chromatography[58] [4 : 1 petrol (bp 40–60 °C)–EtOAc + 1% triethylamine] yielded *amine* **22a** (216 mg, 64%) as a white solid, mp 163–166 °C (EtOAc); ν_{max} (film)/cm^{-1} 3330, 1621; δ_H (300 MHz; $CDCl_3$) 7.78 (3H, m, ArH), 7.45–7.12 (8H, m, ArH), 3.54 (2H, m, 2 × NCH), 3.49 (1H, d, J = 9.5, CH-(CH$_3$)CHNHCH$_3$), 3.05 (1H, m, CH(CH$_3$)CHNHCH$_3$), 2.02 (1H, br s, NH), 1.93 (3H, s, NHCH_3), 1.74 (3H, d, J = 6.9, NCHCH_3), 1.70 (3H, d, J = 6.7, NCHCH_3), 0.99–0.90 (9H, m, 2 × NCHCH_3, CH(CH_3)CHNHCH$_3$); δ_C (75 MHz; $CDCl_3$) 169.7, 143.6, 138.0, 134.5, 132.2, 129.5, 128.4, 128.2, 128.1, 128.0, 126.9, 126.5, 125.7, 125.1, 123.7, 71.8, 50.9, 46.2, 42.9, 34.7, 21.1, 20.8, 20.7, 20.5 and 19.3; *m*/*z* (CI) 403 (71%, M + H$^+$) and 120 (100, PhCHNHCH$_3$); *m*/*z* (EI) 402 (1%, M$^+$), 85 (100), 84 (100), 48 (100) and 35 (100) (Found: M$^+$, 402.2667. $C_{27}H_{34}N_2O$ requires *M*, 402.2671).

(*R*$_a$*,2′*R**)-*N*,*N*-Diisopropyl-2-[2′-(methylamino)-2′-phenylethyl]-1-naphthamide 23a

In the same way, *sec*-butyllithium (0.77 ml, 1.00 mmol; 1.3 M in hexanes), naphthamide[31] **11** (223 mg, 0.83 mmol) in THF (7 ml)

and *N*-benzylidenemethylamine (0.11 ml, 0.91 mmol) gave a crude product containing a single atropisomer (by ^{1}H NMR). Purification by flash chromatography[58] [2 : 1 petrol (bp 40–60 °C)–EtOAc + 1% triethylamine] afforded *amine* **23a** (226 mg, 71%) as a sticky white oil, ν_{max}/cm^{-1} 3330, 1621; δ_H (300 MHz; $CDCl_3$) 7.70 (2H, m, ArH), 7.56 (1H, d, J = 8.5, ArH), 7.37 (2H, m, ArH), 7.3–7.1 (5H, m, ArH), 7.03 (1H, d, J = 8.5, ArH), 3.80 (1H, dd, J = 8.1 and 5.6, C*H*NCH$_3$), 3.53 (1H, sept, J = 6.9, NCH), 3.37 (1H, sept, J = 6.6, NCH), 3.01 (1H, dd, J = 13.3 and 8.2, C*H*HCHNHCH$_3$), 2.82 (1H, dd, J = 13.3 and 5.6, CH*H*CHNHCH$_3$), 2.12 (3H, s, NCH$_3$), 1.98 (1H, br m, NH), 1.71 (3H, d, J = 6.9, NCHC*H*$_3$), 1.67 (3H, d, J = 6.7, NCHC*H*$_3$), 0.92 (3H, d, J = 6.7, NCHC*H*$_3$), 0.88 (3H, d, J = 6.7, NCHC*H*$_3$); δ_C (75 MHz; $CDCl_3$) 169.6, 144.5, 135.2, 132.1, 132.0, 129.5, 128.3, 127.9, 127.7, 127.6, 127.4, 126.9, 126.5, 125.7, 124.8, 66.8, 51.1, 46.1, 42.5, 34.9, 20.9, 20.9, 20.7 and 20.6; *m*/*z* (CI) 389 (100%, M + H$^+$) and 120 (28, PhCHNHCH$_3$); *m*/*z* (EI) 120 (100%, PhCHNHCH$_3$) (Found: M$^+$, 388.2518. $C_{26}H_{32}N_2O$ requires *M*, 388.2515).

(*R*$_a$*,*R**)-*N*,*N*-Diisopropyl-2-(1-benzoylethyl)-1-naphthamide 28a

A solution of oxalyl chloride (0.09 ml, 0.61 mmol) in dichloromethane (2.4 ml) at −78 °C under a drying tube ($CaSO_4$) was treated with a solution of dimethyl sulfoxide (0.13 ml, 1.11 mmol) in dichloromethane (0.5 ml) and stirred for 2 minutes. A solution of the alcohols **20** obtained by lithiation of **12** (215 mg, 0.55 mmol) in dichloromethane (1 ml) was added dropwise over a period of 5 minutes. After 15 minutes, diisopropylethylamine (0.83 ml, 2.77 mmol) was added. After a further 5 minutes the mixture was allowed to warm to ambient temperature (*ca.* 15 minutes) and saturated aqueous sodium hydrogen sulfate (2 ml) was added. The solution was extracted with dichloromethane (4 × 7 ml) and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the crude product. ^{1}H NMR of the crude product showed a 10 (**28a**) : 1 (**28b**) mixture of atropisomers. Purification by flash chromatography on silica gel [4 : 1 petrol (bp 40–60 °C)–EtOAc] afforded a mixture of naphthamides **28a** and **28b** (201 mg, 94%) as a white solid.

Alternatively, the 1.7 : 1 mixture of amides **20a** and **20b** obtained from silane **17a** (95 mg, 0.244 mmol) gave *amide* **28a** as a white solid (94 mg, 100%) requiring no further purification. mp 168–170 °C; R_f [3 : 1 petrol (bp 40–60 °C)–EtOAc] 0.33; ν_{max} (film)/cm^{-1} 3056, 2996, 2975, 2934, 1686, 1623; δ_H (300 MHz; $CDCl_3$) 8.06 (2H, d, J = 7.3, ArH), 7.94–7.70 (4H, m, ArH), 7.59 (1H, t, J = 7.1, ArH), 7.54–7.43 (4H, m, ArH), 5.13 (1H, q, J = 7.4, C*H*(CH$_3$)COPh), 3.46 (1H, sept, J = 6.6, NCH), 3.39 (1H, sept, J = 6.6, NCH), 1.77 (3H, d, J = 6.9, NCHC*H*$_3$), 1.71 (3H, d, J = 7.3, CH(C*H*$_3$)COPh), 1.60 (3H, d, J = 6.9, NCHC*H*$_3$), 0.87 (3H, d, J = 6.6, NCHC*H*$_3$), 0.55 (3H, d, J = 6.6, NCHC*H*$_3$); δ_C (75 MHz; $CDCl_3$) 201.1, 169.4, 136.0, 134.5, 133.4, 133.2, 132.4, 129.2, 128.7, 128.6, 128.0, 127.8, 127.1, 126.2, 126.0, 125.1, 51.0, 46.1, 43.8, 20.8, 20.7, 20.6 and 20.3; *m*/*z* (CI) 388 (100%, M + H$^+$); *m*/*z* (EI) 387 (28, M$^+$), 282 (30, M − COPh) and 105 (100, COPh) (Found: C, 80.20; H, 7.70; N, 3.78%; M$^+$, 387.2203. $C_{26}H_{29}NO_2$ requires C, 80.6; H, 7.5; N, 3.6%; *M*, 387.2198).

N,*N*-Diisopropyl-2-benzoylmethyl-1-naphthamide 29

Jones reagent [2.72 ml of a solution of CrO_3 (2.5 g)–conc. H_2SO_4 (2 ml)–water (8 ml), 6.80 mmol] was added to a solution of atropisomeric naphthamides **21a** and **21b** (327 mg, 0.872 mmol) in acetone (18 ml) at 0 °C. After 60 minutes, the mixture was warmed to ambient temperature, stirred for a further 30 minutes and added to saturated aqueous sodium hydrogen carbonate (52 ml). The solution was extracted with ethyl acetate (4 × 30 ml), and the combined organic extracts washed with water (50 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the crude product. Purification by flash chromatography[58] [2 : 1 petrol (bp 40–60 °C)–EtOAc] afforded the *ketone* **29** (268 mg, 82%) as a white solid, mp 162–163 °C; ν_{max} (film)/cm^{-1} 2957, 2932, 2870, 1687, 1624; λ_{max}/nm (ε_{max}) (CH_2Cl_2) 232 (41050), 278 (15110), 324 (10210); δ_H (300 MHz; $CDCl_3$) 8.11 (2H, m, ArH), 7.87–7.75 (3H, m, ArH), 7.80 (1H, m, ArH), 7.61–7.43 (5H, m, ArH), 7.33 (1H, d, J = 8.5, ArH), 4.60 (1H, d, J = 16.9, CH_AH$_B$COPh), 4.38 (1H, d, J = 16.9, CH$_A$$H_B$COPh), 3.59 (1H, sept, J = 6.6, NCH), 3.56 (1H, sept, J = 6.9, NCH), 1.77 (3H, d, J = 6.9, CH$_3$), 1.60 (3H, d, J = 6.9, CH$_3$), 0.98 (3H, d, J = 6.6, CH$_3$), 0.93 (3H, d, J = 6.7, CH$_3$); δ_C (75 MHz; $CDCl_3$) 197.4, 169.3, 136.3, 135.3, 133.3, 132.3, 129.6, 128.7, 128.5, 128.1, 127.9, 127.8, 126.5, 126.0, 124.9, 51.1, 46.2, 42.9, 21.0, 20.9, 20.6 and 20.4; *m*/*z* (CI) 374 (100%, M + H$^+$); *m*/*z* (EI) 373 (6%, M$^+$) and 49 (100) (Found: M$^+$, 373.2042. $C_{25}H_{27}NO_2$ requires *M*, 373.2042).

N,*N*-Diisopropyl-2-[(*Z*)-2′-phenyl-2′-(trimethylsilyloxy)-ethenyl]naphthalene-1-carboxamide 30

A solution of naphthamide **29** (413 mg, 1.11 mmol) in THF (9 ml) was added to a solution potassium hexamethyldisilazide (2.44 ml, 0.5 M solution in toluene) in THF 4 ml at −78 °C under nitrogen. After 60 minutes, chlorotrimethylsilane (0.17 ml, 1.33 ml) was added and after 30 minutes the mixture was warmed to ambient temperature and concentrated to dryness under reduced pressure. ^{1}H NMR of the crude product showed only isomer, which was shown to be the (*Z*)-isomer by ^{1}H NOE experiments. Purification by flash chromatography[58] on neutral alumina [25 : 1 petrol (bp 40–60 °C)–EtOAc] afforded the *enol ether* **30** (483 mg, 98%) as a sticky white solid, R_f [10 : 1 petrol (bp 40–60 °C)–EtOAc] 0.34; ν_{max} (film)/cm^{-1} 2964, 2927, 2854, 1621; δ_H (300 MHz; $CDCl_3$) 8.32 (1H, d, J = 8.8, ArH), 7.72 (3H, m, ArH), 7.53 (2H, d, J = 8.2 and 1.8, *ortho* H on Ph), 7.37 (2H, m, ArH), 7.26 (3H, m, ArH), 6.32 (1H, s, CH=CO), 3.55 (2H, m, 2 × NCH), 1.72 (6H, m, 2 × CH$_3$), 1.01 (3H, d, J = 6.7, CH$_3$), 0.92 (3H, d, J = 6.7, CH$_3$), 0.00 (9H, s, SiMe$_3$); δ_C (75 MHz; $CDCl_3$) 169.6, 151.8, 139.6, 133.9, 131.9, 129.8, 129.7, 128.1, 127.8, 127.0, 126.5, 126.4, 125.9, 125.6, 124.9, 107.3, 51.1, 46.1, 29.6, 21.0, 21.0, 20.6 and 0.7; *m*/*z* (CI) 446 (100%, M + H$^+$); *m*/*z* (EI) 445 (0.5%, M$^+$), 345 (M − N^{i}Pr$_2$) and 49 (100) (Found: M$^+$, 445.2439. $C_{28}H_{35}NO_2Si$ requires *M*, 445.2437).

N,*N*-Diisopropyl-2-(1-benzoylethyl)-1-naphthamide 28b

A solution of naphthamide **29** (122 mg, 0.33 mmol) in THF (5 ml) was added to a solution of potassium hexamethyldisilazide (0.65 ml, 0.33 mmol; 0.5 M solution in toluene) in THF (1.3 ml) at −78 °C under nitrogen. After 60 minutes the mixture was added to a solution of methyl iodide (0.10 ml, 1.64 mmol) in THF (1.3 ml) *via* cannula, stirred for 5 hours, treated with saturated aqueous ammonium chloride (5 ml) and warmed to ambient temperature. The solution was extracted with dichloromethane (4 × 7 ml) and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the crude product. Analytical HPLC of the crude product showed a ratio of 25 (**28a**) : 75 (**28b**). Purification by preparative HPLC (10 : 1 hexane–EtOAc) afforded the *ketones* **28a** and **28b** (combined yield 102 mg, 81%) as white solids. **28b**: t_R 7.7 min (10 : 1 hexane–EtOAc); mp 159–161 °C; R_f [3 : 1 petrol (bp 40–60 °C)–EtOAc] 0.44; ν_{max} (film)/cm^{-1} 3062, 2978, 2934, 1679, 1620; δ_H (300 MHz; $CDCl_3$) 8.27 (2H, m, ArH), 7.88 (1H, m, ArH), 7.80 (1H, m, ArH), 7.75 (1H, d, J = 8.7, ArH), 7.55–7.36 (6H, m, ArH), 4.98 (1H, q, J = 6.9, C*H*(CH$_3$)COPh), 3.80–3.55 (2H, m, 2 × NCH), 1.88 (3H, d, J = 6.9, NCHC*H*$_3$), 1.80 (3H, d, J = 6.9, NCHC*H*$_3$), 1.65 (3H, d, J = 6.9, CH(C*H*$_3$)COPh), 1.24 (3H, d, J = 6.6, NCHC*H*$_3$), 1.06 (3H, d, J = 6.6, NCHC*H*$_3$); δ_C (75 MHz; $CDCl_3$) 200.6, 169.4, 136.2, 134.2, 133.5, 132.8, 132.3, 129.8, 129.3, 128.6, 128.3, 128.0, 126.4, 126.0, 125.3, 124.8, 50.7, 46.4, 44.2, 21.4, 21.0,

20.9, 20.4 and 19.4; *m/z* (CI) 388 (100%, M + H^+); *m/z* (EI) 387 (0.6, M^+) and 49 (100) (Found: M + H^+, 388.2269. $C_{26}H_{29}NO_2$ requires *M* + H, 388.2276).

(*R*$_a$*,*S**)-*N*,*N*-Diisopropyl-2-(1-hydroxyethyl)-1-naphthamide 31

Following the method of Fleming,[37] silane **18a** (100 mg, 0.239 mmol) was dissolved in a solution of peracetic acid (0.545 g, 1.5 M solution in dilute acetic acid, 7.17 mmol) and concentrated sulfuric acid (15 μl). Mercuric acetate (114 mg, 0.359 mmol) was added and the mixture kept at room temperature for 5 h. Ether (50 ml) was added and the solution was washed with sodium thiosulfate solution (30 ml), water (30 ml), sodium hydrogen carbonate solution (30 ml) and brine (30 ml). The organic phase was dried over magnesium sulfate, filtered and concentrated. Purification by flash chromatography[58] [3 : 2 ethyl acetate–light petroleum] gave the alcohol **31** (55 mg, 76%) as a white solid, with ^{1}H NMR data identical to those quoted in the literature.[31]

N,*N*-Diisopropyl-2,4,6-triethylbenzamide 32

By the method of Fuson,[45] 1,3,5-triethylbenzene (9.3 ml, 49.30 mmol) was stirred in carbon tetrachloride (5 ml) in a 3-neck flask fitted with a reflux condenser and dropping funnel. Iron filings (250 mg, 4.44 mmol) were added and the mixture was cooled to 0 °C. The flask was wrapped in foil to protect the reaction mixture from light. Bromine (2.54 ml, 49.30 mmol) in carbon tetrachloride (5 ml) was added dropwise with vigorous stirring over a period of 2.5 h. The mixture was then left to stir overnight. Dichloromethane (20 ml) was added and the organic solution washed with water (2 × 15 ml), 10% sodium hydroxide solution (20 ml) and again with water until the aqueous layer was neutral to litmus. The organic layer was dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to afford 2,4,6-triethylbromobenzene (11.0 g, 92%) as a colourless oil which was used without further purification. δ_H (300 MHz; $CDCl_3$) 6.98 (2H, s, 2 × ArH), 2.82 (4H, *J* = 7.5, 2 × *o*-ArCH_3), 2.63 (2H, q, *J* = 7.6, *p*-ArCH_3), 1.27 (9H, t, *J* = 7.5, 3 × CH_2CH_3).

A solution of 2,4,6-triethylbromobenzene (4.00 g, 16.50 mmol) in dry ether (6 ml) was added dropwise to magnesium turnings (0.403 g, 16.59 mmol) in a 3-neck flask under a reflux condenser. A few drops of 1,2,-dibromoethane were added to initiate the reaction. The mixture was stirred for 3 h after the addition was complete by which time all the magnesium had reacted. The solution was then cooled in an ice-bath and small pieces of solid carbon dioxide were added to it. The mixture was allowed to come to room temperature and stirred overnight, ether (20 ml) was added and then poured into ice–water (10 ml) containing ammonium chloride (1.5 g) and concentrated hydrochloric acid (0.7 ml). The ether layer was separated and washed with dilute hydrochloric acid (0.25 M, 2 × 10 ml). The aqueous layers were washed with ether (10 ml) and the combined organic layers were extracted with aqueous sodium hydroxide solution (10%, 3 × 10 ml). The combined basic extracts were acidified, re-extracted with ether (3 × 10 ml) and the combined organic layers were dried over magnesium sulfate and filtered. The solvent was evaporated to afford 2,4,6-triethylbenzoic acid as a white solid (2.0 g, 60%). δ_H (300 MHz; $CDCl_3$) 7.00 (2H, s, ArH), 2.80 (4H, q, *J* = 7.7, 2 × *o*-CH_2), 2.69 (2H, q, *J* = 7.7, *p*-CH_2), 1.31 (6H, t, *J* = 7.7, 2 × *o*-CH_2CH_3), 1.29 (3H, t, *J* = 7.7, *p*-CH_2CH_3); δ_C (75 MHz; $CDCl_3$) 176.0 (s, CO), 146.2, 141.4, 129.1, 125.9 (Ar), 28.7 (t, *p*-CH_2), 27.0 (t, 2 × *o*-CH_2), 15.8 (q, 2 × *o*-CH_2CH_3), 15.3 (q, *p*-CH_2CH_3).

2,4,6-Triethylbenzoic acid (500 mg, 2.42 mmol) and thionyl chloride (0.354 ml, 4.85 mmol) were stirred in dichloromethane (5 ml) under a drying tube. DMF (0.2 ml) was added and the solution was stirred for 5.5 h. Volatile materials were removed under reduced pressure and the residual acid chloride was cooled in an ice-bath. Diisopropylamine (5 ml) was added and the mixture stirred overnight at room temperature. The mixture was made slightly acidic with 3 M hydrochloric acid and the aqueous phase was extracted with dichloromethane (3 × 15 ml). The combined extracts were washed with water (2 × 15 ml) and saturated aqueous sodium hydrogen carbonate solution (15 ml), dried over magnesium sulfate, filtered and the solvent was evaporated. Purification by flash chromatography[58] [3% ethyl acetate in light petroleum] gave the *amide* **32** (148 mg, 21%) as a colourless oil. R_f [10% EtOAc in petrol] 0.53; ν_{max} (film)/cm^{-1} 1630; δ_H (300 MHz; $CDCl_3$) 6.93 (2H, s, 2 × ArH), 3.65 (1H, sept, *J* = 6.7, NCH), 3.52 (1H, sept, *J* = 6.7, NCH), 2.74–2.46 (6H, m, 3 × CH_2CH_3), 1.62 (6H, d, *J* = 6.7, 2 × NCHCH_3), 1.27 (6H, t, *J* = 7.6, 2 × *o*-CH_2CH_3), 1.26 (3H, t, *J* = 7.6, *p*-CH_2CH_3), 1.11 (6H, d, *J* = 6.7, 2 × NCHCH_3); δ_C (75 MHz; $CDCl_3$) 170.1 (s, CO), 143.5 (s, Ar), 139.1 (s, 2 × *o*-CCH_2), 134.5 (s, Ar), 124.9 (d 2 × CH), 50.4 (d, NCH), 45.5 (d, NCH), 28.7 (t, *p*-CH_2), 25.7 (t, 2 × *o*-CH_2), 20.9 (q, NCH(CH_3)$_2$), 20.4 (q, NCH(CH_3)$_2$), 15.3 (q, *p*-CH_2CH_3), 15.1 (q, 2 × *o*-CH_2CH_3); *m/z* (CI) 291 (19%), 290 (100), 260 (4), 189 (20), 188 (11) (Found: M^+, 289.2399. $C_{19}H_{31}NO$ requires *M*, 289.24055).

Alternatively, a solution of 2,4,6-triethylbromobenzene (4.00 g, 16.59 mmol) in dry ether (5 ml) was added dropwise to dry magnesium turnings (0.403 g, 16.59 mmol) placed in a 3-neck flask equipped with a reflux condenser. A few drops of 1,2-dibromoethane were added to initiate the reaction. The solution was stirred at room temperature for 5 h, then added dropwise to a solution of diisopropylcarbamyl chloride (2.99 g, 18.27 mmol) in ether (20 ml), cooled in an ice-bath. Stirring was continued at room temperature overnight, followed by heating at reflux for 2 h. After cooling, water (20 ml) was added and the aqueous layer was extracted with ether (3 × 15 ml). The combined organic layers were then washed with water (15 ml), dried over magnesium sulfate, filtered and the solvent was evaporated. Purification by flash chromatography[58] [5% ethyl acetate in light petroleum] gave the *amide* **32** (1.14 g, 24%) as a colourless oil, spectroscopically identical to a sample prepared as above.

(*R*$_a$*,*S**)-*N*,*N*-Diisopropyl-2,4-diethyl-6-(1′-trimethylsilylethyl)-benzamide 33

sec-Butyllithium (0.33 ml, 1.3 M solution in cyclohexane, 0.429 mmol) was added dropwise to a solution of the benzamide **32** (113 mg, 0.390 mmol) in THF (40 ml) at −78 °C under nitrogen. After 1 h, trimethylsilyl chloride (74 μl, 0.586 mmol) was added, and after a further 15 min the mixture was allowed to warm to 0 °C. Water (30 ml) was then added and the THF was removed under reduced pressure. The aqueous phase was extracted with dichloromethane (3 × 20 ml), the combined organic extracts were washed with water (30 ml), dried over magnesium sulfate, filtered and the solvent was evaporated. Purification by flash chromatography[58] [3% ethyl acetate in light petroleum] gave the *silane* **33** (101 mg, 72%) as a colourless oil; R_f [5% EtOAc–petrol] 0.32; ν_{max} (film)/cm^{-1} 1631; δ_H (300 MHz; $CDCl_3$) 6.84 (1H, s, Ar), 6.79 (1H, s, Ar), 3.71 (1H, sept, *J* = 6.7, NCH), 3.51 (1H, sept, *J* = 6.7, NCH), 2.74–2.43 (4H, m, *o*-$CH_AH_BCH_3$ and *p*-CH_2CH_3), 2.15 (1H, q, *J* = 7.4, Ar$CH$$CH_3$), 1.63 (3H, d, *J* = 6.7, NCHCH_3), 1.60 (3H, d, *J* = 6.7, NCHCH_3), 1.36 (3H, d, *J* = 7.4, ArCHCH_3), 1.26 (6H, t, *J* = 7.6, 2 × ArCH_2CH_3), 1.14 (3H, d, *J* = 6.6, NCHCH_3), 1.08 (3H, d, *J* = 6.6, NCHCH_3), 0.00 (9H, s, Si(CH_3)$_3$); δ_C (75 MHz; $CDCl_3$) 170.2 (s, CO), 143.1 (s, Ar), 142.1 (s, Ar), 139.4 (s, Ar), 133.5 (s, Ar), 123.6 (d, Ar), 122.8 (d, Ar), 49.9 (d, NCH), 45.5 (d, NCH), 28.8 (t, ArCH_2), 25.8 (d, ArCH), 25.1 (t, ArCH_2), 20.9 (q, 2 × NCHCH_3), 20.3 (q, NCHCH_3), 20.2 (q, NCHCH_3), 16.3 (q, ArCHCH_3), 15.4 (q, CH_2CH_3), 15.1 (q, CH_2CH_3), 2.6 (q, Si(CH_3)$_3$); *m/z* (CI) 364 (19%), 362 (100), 361 (18), 332 (19), 189 (33), 90 (17), 73 (65) (Found: M^+, 361.2796. $C_{22}H_{39}NOSi$ requires *M*, 361.2801).

(r_a,*R**,*S**)-*N*,*N*-Diisopropyl-4-ethyl-2,6-bis(1-trimethylsilyl-ethyl)benzamide 34a

sec-Butyllithium (0.194 ml, 1.3 M solution in hexanes, 0.252 mmol) was added dropwise to a solution of silane **33** (83 mg, 0.230 mmol) in THF (30 ml) at −78 °C under nitrogen. The resulting orange solution was stirred for 1 h at −78 °C and trimethylsilyl chloride (44 μl, 0.345 mmol) was added. After 10 min the solution was allowed to warm to 0 °C. Water (20 ml) was added and the THF was removed under reduced pressure. The aqueous residue was extracted with dichloromethane and the combined extracts were washed with water (30 ml), dried over magnesium sulfate, filtered and the solvent evaporated. Purification by flash chromatography[58] [2–4% ethyl acetate in light petroleum] gave the *bis-silane* **34a** (60 mg, 60%) as a white crystalline solid, mp 127.5–128 °C; R_f [5% EtOAc in petrol] 0.77; δ_H (300 MHz; $CDCl_3$) 6.70 (2H, s, 2 × ArH), 3.77 (1H, sept, *J* = 6.7, NCH), 3.46 (1H, sept, *J* = 6.9, NCH), 2.62 (2H, q, *J* = 7.6, CH_2CH_3), 2.12 (2H, q, *J* = 7.4, 2 × ArCH), 1.61 (6H, d, *J* = 6.9, $NCH(CH_3)_2$), 1.35 (6H, d, *J* = 7.4, 2 × $CHCH_3$), 1.25 (3H, t, *J* = 7.6, CH_2CH_3), 1.12 (6H, d, *J* = 6.7, $NCH(CH_3)_2$), 0.00 (18H, 2 × $Si(CH_3)_3$); δ_C (75 MHz; $CDCl_3$) 170.4 (s, CO), 143.0 (s, Ar), 142.5 (d, Ar), 132.3 (s, Ar), 121.7 (d, Ar), 49.5 (d, NCH), 45.4 (d, NCH), 28.9 (d, 2 × CH), 25.3 (t, CH_2), 20.9 (q, 2 × $NCHCH_3$), 20.2 (q, 2 × $NCHCH_3$), 16.4 (q, 2 × $ArCHCH_3$), 15.7 (q, *p*-CH_2CH_3), −2.7 (q, 2 × $Si(CH_3)_3$); *m*/*z* (EI) 433 (16), 405 (18), 404 (60), 261 (37), 73 (100) (Found: M^+, 433.3191. $C_{25}H_{47}NOSi_2$ requires *M*, 433.3196).

HPLC analysis of the crude product was carried out on a phenosphere 5 μ 80 Å column (100 × 8.00 mm), eluant 1% ethanol in hexane, flow rate 2 ml min^{-1}, UV at 255 nm, t_R 1.67 (73.8%, disilane). 2.20 min (starting silane, 22.0%). A small shoulder is on the major peak (<3%) is tentatively assigned to the diastereoisomer **34b**.

(R_a*,*S**)-*N*,*N*-Diisopropyl-2,4-diethyl-6-*sec*-butylbenzamide 35

sec-Butyllithium (0.585 ml, 1.3 M solution in cyclohexane, 0.760 mmol) was added dropwise to a solution of benzamide **32** (200 mg, 0.691 mmol) in THF (40 ml) at −78 °C. The red solution was stirred at −78 °C for 1 h and ethyl iodide (83 μl, 1.04 mmol) was added. The colourless solution was allowed to warm to 0 °C, water (30 ml) was added and the THF was removed under reduced pressure. The aqueous phase was extracted with dichloromethane (3 × 30 ml) and the combined extracts were washed with water (30 ml), dried over magnesium sulfate, filtered and the solvent was evaporated. Purification by flash chromatography[58] [5% ethyl acetate in light petroleum] gave the *amide* **35** (164 mg, 75%) as a colourless oil which crystallised on standing in the freezer; R_f [10% EtOAc in petrol] 0.44; ν_{max} (film)/cm^{-1} 1637; δ_H (300 MHz; $CDCl_3$) 6.93 (2H, s, ArH), 3.72 (1H, sept, *J* = 6.7, NCH), 3.52 (1H, sept, *J* = 6.7, NCH), 2.76–2.46 (3H, m, ArCH and *o*-$ArCH_AH_BCH_3$), 2.66 (2H, q, *J* = 7.5, *p*-$ArCH_2CH_3$), 1.78–1.36 (2H, m, $CHCH_2$), 1.63 (3H, d, *J* = 6.7, $NCHCH_3$), 1.62 (3H, d, *J* = 6.7, $NCHCH_3$), 1.27 (6H, t, *J* = 7.5, 2 × $ArCH_2CH_3$), 1.26 (3H, d, *J* = 7.5, $ArCHCH_3$), 1.13 (3H, d, *J* = 6.7, $NCHCH_3$), 1.11 (3H, d, *J* = 6.7, $NCHCH_3$), 0.88 (3H, t, *J* = 7.5, $CHCH_2CH_3$); δ_C (75 MHz; $CDCl_3$) 170.0 (s, CO), 143.4 (s, Ar), 143.4 (s, Ar), 139.1 (s, Ar), 134.3 (s, Ar), 125.0 (d, Ar), 122.3 (d, Ar), 50.2 (d, NCH), 45.6 (d, NCH), 37.2 (d, ArCH), 32.4 (t, $CHCH_2$), 28.8 (t, $ArCH_2$), 25.7 (t, $ArCH_2$), 20.8 (q, 2 × $NCHCH_3$), 20.3 (q, $NCHCH_3$), 20.3 (q, $NCHCH_3$), 20.0 (q, $ArCHCH_3$), 15.3 (q, $ArCH_2CH_3$), 15.0 (q, $ArCH_2CH_3$), 12.1 (q, $CHCH_2CH_3$); *m*/*z* (CI) 320 (22%), 318 (100), 217 (12), 216 (7), 102 (5) (Found: M^+, 317.2722. $C_{21}H_{35}NO$ requires *M*, 317.2719).

HPLC analysis of the crude product (phenosphere 5 μ, 80 Å silica column, 100 × 8.00 mm, Merck-Hitachi system, UV at 255 nm, eluant 0.5% ethanol in hexane, flow rate 2 ml min^{-1}, t_R 6.82 (**35**, 91.9%), 9.37 min (tentatively identified as the diastereoisomer, 8.1%).

(r_a,*R**,*S**)- and (*R**,*R**)-*N*,*N*-Diisopropyl-2,6-di-*sec*-butyl-4-ethylbenzamide 36a and 36b

sec-Butyllithium (0.20 ml, 1.3 M solution in cyclohexane, 0.263 mmol) was added dropwise to a solution of amide **35** (76 mg, 0.239 mmol) in THF (30 ml) at −78 °C under nitrogen. The resultant orange–red solution was stirred at −78 °C for 1 h and ethyl iodide (29 μl, 0.359 mmol) was added. The solution was allowed to warm to 0 °C, water (30 ml) was added and the THF was removed under reduced pressure. The aqueous phase was extracted with dichloromethane (3 × 20 ml), the combined organic extracts were washed with water (30 ml), dried over magnesium sulfate, filtered and the solvent was evaporated. Purification by flash chromatography[58] [5% ethyl acetate in light petroleum] gave the *diastereoisomer* **36a** (36 mg, 44%) as a solid, mp 25–27 °C; R_f [5% EtOAc in petrol] 0.32; ν_{max}(film)/cm^{-1} 1636; δ_H (300 MHz; $CDCl_3$) 6.92 (2H, s, ArH), 3.76 (1H, sept, *J* = 6.6, NCH), 3.50 (1H, sept, *J* = 6.9, NCH), 2.70–2.58 (4H, m, 2 × ArCH and $ArCH_2$), 1.78–1.61 (2H, m, 2 × $ArCH-CH_AH_B$), 1.62 (6H, d, *J* = 6.9, $NCH(CH_3)_2$), 1.50–1.34 (2H, m, 2 × $ArCHCH_AH_B$), 1.26 (6H, d, *J* = 6.9, 2 × $ArCHCH_3$), 1.25 (3H, t, *J* = 7.6, $ArCH_2CH_3$), 1.12 (6H, d, *J* = 6.6, $NCH(CH_3)_2$), 0.86 (6H, t, *J* = 7.4, 2 × $CHCH_2CH_3$); δ_C (75 MHz; $CDCl_3$) 170.0 (s, CO), 143.4 (s, 2 × *C*CH), 134.1 (s, *C*CH_2), 126.6 (s, *C*CO), 122.4 (d, 2 × *C*H), 50.0 (d, NCH), 45.6 (d, NCH), 37.3 (d, 2 × ArCH), 32.7 (t, 2 × $CHCH_2$), 28.9 (t, $ArCH_2$), 20.8 (q, 2 × $NCHCH_3$), 20.2 (q, 2 × $CHCH_3$), 20.1 (q, 2 × $NCHCH_3$), 15.3 (q, $ArCH_2CH_3$), 12.2 (q, 2 × $CHCH_2CH_3$); *m*/*z* (CI) 347 (23%), 346 (100), 245 (14), 244 (8), 86 (5), 74 (13), 58 (6) (Found: M^+, 345.3028. $C_{23}H_{39}NO$ requires *M*, 345.3031).

Also obtained was the *diastereoisomer* **36b** (27 mg, 33%) as an oil, R_f [5% EtOAc in petrol] 0.29; δ_H (300 MHz; $CDCl_3$) 6.91 (2H, s, ArH), 3.76 (1H, sept, *J* = 6.7, NCH), 3.51 (1H, sept, *J* = 6.9, NCH), 2.71–2.50 (4H, m, 2 × ArCH and CH_2CH_3), 1.77–1.33 (4H, m, 2 × $CHCH_2$), 1.61 (6H, d, *J* = 6.9, $NCH(CH_3)_2$), 1.26 (3H, t, *J* = 7.6, $ArCH_2CH_3$), 1.26 (3H, d, *J* = 6.9, $ArCHCH_3$), 1.20 (3H, d, *J* = 6.7, $ArCHCH_3$), 1.13 (3H, d, *J* = 6.9, $NCHCH_3$), 1.10 (3H, d, *J* = 6.7, $NCHCH_3$), 0.99 (3H, t, *J* = 7.4, $CHCH_2CH_3$), 0.87 (3H, t, *J* = 7.4, $CHCH_2CH_3$); δ_C (75 MHz; $CDCl_3$) 170.0 (s, CO), 144.0 (s, Ar), 143.6 (s, Ar), 143.4 (s, Ar), 134.0 (s, Ar), 122.6 (d, Ar), 122.4 (d, Ar), 50.1 (d, NCH), 45.6 (d, NCH), 38.1 (d, ArCH), 37.3 (d, ArCH), 32.6 (t, $ArCHCH_2$), 29.4 (t, $ArCHCH_2$), 28.9 (t, $ArCH_2$), 22.5 (q, $ArCHCH_3$), 20.8 (q, 2 × $NCHCH_3$), 20.4 (q, $NCHCH_3$), 20.2 (q, $NCHCH_3$), 19.9 (q, $ArCHCH_3$), 15.3 (q, $ArCH_2CH_3$), 12.6 (q, $CHCH_2CH_3$), 12.2 (q, $CHCH_2CH_3$); *m*/*z* (CI) 347 (26%), 346 (100), 245 (18), 244 (9), 91 (6), 86 (7), 74 (20), 60 (6), 58 (18) (Found: M^+, 345.3031. $C_{23}H_{39}NO$ requires *M*, 345.3031.

HPLC analysis of the crude product mixture was carried out using a phenosphere 5 μ silica column (100 × 8.00 mm), Merck-Hitachi system; eluant 0.5% EtOH in hexane; flow 2 ml min^{-1}; UV at 255 nm; t_R 3.12 (**36a**, 46.6%) and 3.67 min (**36b**, 32.8%).

(R_a*,2′*S**)- and (R_a*,2′*R**)-*N*,*N*-Diisopropyl-2,4-dimethyl-6-(2′-hydroxy-2′-phenylethyl)benzamide 37a and 37b

By the method used for **21a** and **21a**, *sec*-butyllithium (1.7 ml, 2.2 mmol), *N*,*N*-diisopropyl-2,4,6-trimethylbenzamide **7**[21] (0.5 g, 2 mmol) and freshly distilled benzaldehyde (0.31 ml, 3 mmol) gave a crude product which was purified by flash chromatography [90 : 10 petroleum ether (bp 60–80 °C)–ethyl acetate] to yield a 65 : 35 mixture of the *alcohols* **37a** and **37b** (0.51 g, 72%). δ_H (300 MHz; $CDCl_3$) [major diastereoisomer] 7.08 (1H, s, ArH), 6.95 (1H, s, ArH), 5.4 (1H, br s, OH), 4.78 (1H, dd, *J* 8.5, 3.1, $ArCHOH$), 3.70 (1H, sept, *J* 6.7, $CHMe_2$), 3.60 (1H, sept, *J* 6.7, CHMe), 2.95 (1H, dd, *J* 12.0, 3.3, $ArCH_AH_B$), 2.36 (3H, s, ArMe), 2.30 (3H, s, ArMe), 1.71 (3H, d, *J* 6.7, CHMe), 1.65 (1 H, m, $ArCH_AH_B$), 1.63 (3H, d, *J* 6.7, CHMe), 1.21 (3H, d, *J* 6.7, CHMe), 0.99 (3H, d, *J* 6.7, CHMe); [minor diastereoisomer] 6.90 (1H, s, ArH), 6.58 (1H, s, ArH), 5.4 (1H, br s, OH), 5.07 (1H, dd, *J* 6.5, 3.1, $ArCHOH$), 3.70

(1H, sept, *J* 6.7, CHMe), 3.60 (1H, sept, *J* 6.7, CHMe), 3.05 (1H, dd, *J* 11.0 and 3.1, ArCH_AH$_B$), 2.28 (3H, s, ArMe), 2.22 (3H, s, ArMe), 1.67 (1H, m, ArCHH$_A$$H_B$), 1.65 (3H, d, *J* 6.7, CHMe), 1.62 (3H, d, *J* 6.7, CHMe), 1.17 (3H, d, *J* 6.7, CHMe), 1.03 (3H, d, *J* 6.7, CHMe).

(R_a*,2′*S**)- and (R_a*,2′*R**)-*N*,*N*-Diisopropyl-2,4-dimethyl-6-[2′-(methylamino)-2′-phenylethyl]benzamide 38a and 38b

In the same way as for compound **23a**, benzamide[21] **7** (490 mg, 1.98 mmol) in THF (16 ml) at −78 °C was lithiated with *sec*-butyllithium (1.53 ml, 1.98 mmol; 1.3 M in hexanes), treated with *N*-benzylidenemethylamine (0.27 ml, 2.18 mmol) and stirred for a further 4 hours. After work-up in the manner of **23a**, ^{1}H NMR showed a 96 : 4 ratio of atropisomers **38a** and **38b**. Purification by flash chromatography[58] gave the *amines* **38a** and **38b** (626 mg, 86%) as an oil; R_f [10 : 10 : 1 petrol (bp 40–60 °C)–EtOAc–triethylamine] 0.30; ν_{max} (film)/cm^{-1} 3336, 3060, 3026, 2967, 2927, 2870, 2890, 1631; δ_H (300 MHz; $CDCl_3$) 7.40–7.22 (5H, m, ArH), 7.00 (1H, s, ArH^{minor}), 6.96 (1H, s, ArH^{minor}), 6.87 (1H, s, ArH^{major}), 6.65 (1H, s, ArH^{major}), 3.98 (1H, dd, *J* = 9.4 and 2.8, C*H*NHCH$_3^{minor}$), 3.79 (1H, dd, *J* = 8.1 and 5.9, C*H*NHCH$_3^{major}$), 3.58 (2H, m, 2 × NCH^{major}), 2.88 (1H, dd, *J* = 8.2 and 13.3, ArC*H*H^{major}), 2.73 (1H, dd, *J* = 13.3 and 5.6, ArCH*H*^{major}), 2.31 (3H, s, CH$_3^{major}$), 2.25 (3H, s, CH$_3^{major}$), 2.23 (3H, s, CH$_3^{major}$), 1.72 (3H, d, *J* = 6.9, NCHC*H*$_3^{major}$), 1.66 (3H, d, *J* = 6.9, NCHC*H*$_3^{major}$), 1.14 (3H, d, *J* = 6.6, NCHC*H*$_3^{major}$), 1.05 (3H, d, *J* = 6.6, NCHC*H*$_3^{major}$); δ_C (75 MHz; $CDCl_3$) (**38a** only) 170.4, 144.6, 137.0, 135.7, 134.7, 133.0, 128.8, 128.1, 127.7, 127.3, 126.8, 67.2, 50.7, 45.8, 42.1, 34.9, 21.0, 20.9, 20.6, 20.4 and 19.0; *m*/*z* (CI) 367 (100%, M + H$^+$) (Found: M$^+$, 366.2673. $C_{23}H_{34}N_2O$ requires *M*, 366.2671).

(R_a*,2′*S**)- and (R_a*,2′*R**)-*N*,*N*-Diisopropyl-2-{2′-[benzyl(methyl)amino]-2′-phenylethyl}-4,6-dimethylbenzamide 39a and 39b

In the same way, benzamide[21] **7** (626 mg, 2.53 mmol) in THF (15 ml) at −78 °C was lithiated with *sec*-butyllithium (2.14 ml, 2.79 mmol), and treated sequentially with *N*-benzylidenemethylamine (0.31 ml, 2.53 mmol) and benzyl bromide (0.30 ml, 2.53 mmol) and stirred for a further 3 hours. After work-up in the manner of **23a**, ^{1}H NMR showed a 92 : 8 ratio of **39a** and **39b**. Purification by flash chromatography[58] [9 : 1 petrol (bp 40–60 °C)–EtOAc + 1% triethylamine] gave the *amines* **39a** and **39b** (860 mg, 74%) as a colourless oil; R_f [6 : 1 petrol (bp 40–60 °C)–EtOAc + 1% triethylamine] 0.34; ν_{max} (film)/cm^{-1} 3060, 3027, 2968, 2929, 2872, 2791, 1630; δ_H (300 MHz; $CDCl_3$) 7.20–7.10 (10H, m, ArH), 6.79 (1H, s, ArH^{minor}), 6.76 (1H, s, ArH^{minor}), 6.68 (1H, s, ArH), 6.09 (1H, s, ArH), 4.13 (1H, dd, *J* = 8.2 and 6.2, C*H*NCH$_3^{minor}$), 3.82 (1H, dd, *J* = 8.9 and 5.8, C*H*NCH$_3^{major}$), 3.53 (1H, m, NCH^{major}), 3.52 (1H, d, *J* = 13.5, NC*H*HPh^{major}), 3.43 (1H, sept, *J* = 6.9, NCH^{major}), 3.31 (1H, dd, *J* = 13.3 and 5.9, ArC*H*HCH^{major}), 3.21 (1H, d, *J* = 13.5, NCH*H*Ph^{major}), 3.10 (1H, dd, *J* = 14.4 and 8.4, ArC*H*-HCH^{minor}), 2.96 (1H, dd, *J* = 14.4 and 6.2, ArCH*H*CH^{minor}), 2.67 (1H, dd, *J* = 13.3 and 9.1, ArCH*H*CH^{major}), 2.17 (3H, s, CH$_3^{major}$), 2.11 (3H, s, CH$_3^{major}$), 1.98 (3H, s, CH$_3^{minor}$), 1.96 (3H, s, CH$_3^{major}$), 1.58 (3H, d, *J* = 6.9, NCHC*H*$_3^{major}$), 1.54 (3H, d, *J* = 6.7, NCHC*H*$_3^{major}$), 1.48 (3H, d, *J* = 6.7, NCHC*H*$_3^{minor}$), 1.28 (3H, d, *J* = 6.7, NCHC*H*$_3^{minor}$), 1.00 (3H, d, *J* = 6.6, NCHC*H*$_3^{major}$), 0.99 (3H, d, *J* = 6.6, NCHC*H*$_3^{major}$); δ_C (75 MHz; $CDCl_3$) (**39a** only) 170.4, 140.8, 140.2, 136.2, 135.4, 134.4, 132.7, 128.9, 128.7, 128.6, 128.4, 127.9, 127.6, 126.7, 126.5, 69.0, 59.4, 50.6, 45.8, 38.2, 37.2, 21.1, 21.0, 20.8, 20.3 and 18.9; *m*/*z* (CI) 457 (100%, M + H$^+$) (Found: M + H$^+$, 457.3222. $C_{31}H_{40}N_2O$ requires *M* + H, 457.3219).

Alternatively, a solution of benzamide **38** (96 : 4 **38a** : **38b**; 146 mg, 0.40 mmol) in THF (2 ml) at −78 °C under nitrogen was treated with *n*-butyllithium (0.25 ml, 0.40 mmol; 1.6 M solution in hexanes) and stirred for 25 minutes. The red solution was quenched with benzyl bromide (0.05 ml, 0.44 mmol), stirred for a further 3.5 hours, warmed to ambient temperature, treated with saturated aqueous ammonium chloride (5 ml) and extracted with dichloromethane (4 × 10 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the crude product. ^{1}H NMR of the crude product showed an 86 : 14 mixture of atropisomers. Purification by flash chromatography[58] [6 : 1 petrol (bp 40–60 °C)–EtOAc] afforded amine **39a** (132 mg, 73%) as a pale yellow oil.

(R_a*,2′*S**)-*N*,*N*-Diisopropyl-2-{2′-[benzyl(methyl)amino]-2′-phenylethyl}-4-methyl-6-[^{2}H]methylbenzamide 41

sec-Butyllithium (0.17 ml, 1.22 mmol; 1.3 M in hexanes) was added dropwise to a solution of benzamide **39a** (102 mg, 0.22 mmol) in THF (3 ml) at −78 °C under nitrogen. After 55 minutes, deuterium oxide (1 ml, excess) was added to the orange solution, and the mixture was warmed to ambient temperature. The solution was extracted with dichloromethane (4 × 7 ml) and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure at low temperature to give the *deuterobenzamide* **41** as a colourless oil (99 mg, 97%), δ_H (300 MHz; $CDCl_3$) 7.20–7.10 (10H, m, ArH), 6.68 (1H, s, ArH), 6.09 (1H, s, ArH), 3.82 (1H, dd, *J* = 8.9 and 5.8, C*H*NCH$_3$), 3.53 (1H, m, NCH), 3.52 (1H, d, *J* = 13.5, NC*H*HPh), 3.43 (1H, sept, *J* = 6.9, NCH), 3.31 (1H, dd, *J* = 13.3 and 5.9, ArC*H*HCH), 3.21 (1H, d, *J* = 13.5, NCH*H*Ph), 2.67 (1H, dd, *J* = 13.3 and 9.1, ArCH*H*CH), 2.17 (2H, s, CH_2D), 2.11 (3H, s, CH_3), 1.96 (3H, s, CH_3), 1.58 (3H, d, *J* = 6.9, NCHC*H*$_3$), 1.54 (3H, d, *J* = 6.7, NCHC*H*$_3$), 1.00 (3H, d, *J* = 6.6, NCHC*H*$_3$), 0.99 (3H, d, *J* = 6.6, NCHC*H*$_3$); *m*/*z* (EI) 457.5 (11%, M$^+$), 366.4 (16, M − Bn), 210.2 (100, PhCHN-(Me)Bn) and 91.2 (64, Bn).

(3*R**,2′*S**)-8-{2-[Benzyl(methyl)amino]-2-phenylethyl}-2,6-dimethyl-3-phenyl-1,2,3,4-tetrahydroisoquinolin-1-one 43

sec-Butyllithium (0.77 ml, 1.00 mmol; 1.3 M solution in hexanes) was added to a solution of benzamide **7**[21] (199 mg, 0.91 mmol) in THF (6 ml) at −78 °C under nitrogen. After 60 minutes, *N*-benzylidenemethylamine (0.11 ml, 0.91 mmol) was added to give a dark pink–red solution. After a further 60 minutes benzyl bromide (0.11 ml, 0.91 mmol) was added. After a further 60 minutes the pale yellow solution was treated with *sec*-butyllithium (0.77 ml, 1.00 mmol; 1.3 M solution in hexanes) to give a dark red–brown solution and stirred for an additional 45 minutes. *N*-Benzylidenemethylamine (0.11 ml, 0.91 mmol) and, after a further 15 minutes, DMPU (0.22 ml, 1.82 mmol) were added. After 4 hours, saturated aqueous ammonium chloride solution (5 ml) was added and the mixture was allowed to warm to ambient temperature, diluted with water (10 ml) and the THF was removed under reduced pressure. Diethyl ether (30 ml) was added and the layers were separated. The ethereal extract was washed with water (5 × 10 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give pale yellow oil. Purification by preparative HPLC (4 : 1 hexane–EtOAc) afforded the *isoquinolinone* **43** (25 mg, 6%) as a colourless oil, t_R 28 min (4 : 1 hexane–EtOAc); ν_{max} (film)/cm^{-1} 3059, 3025, 3003, 2924, 2873, 2849, 2790, 1642; δ_H (300 MHz; $CDCl_3$) 7.25–7.10 (10H, m, ArH), 7.04 (3H, m, ArH), 6.83 (2H, m, ArH), 6.55 (1H, s, ArH), 6.47 (1H, s, ArH), 4.56 (1H, dd, *J* = 6.6 and 2.7, PhCH(NMeCO)), 4.03 (1H, t, *J* = 7.6, PhCHN(Bn)Me), 3.81 (2H, d, *J* = 7.4, PhCH-(NMeCO)CH_2), 3.49 (1H, d, *J* = 13.5, CHHPh), 3.52 (1H, dd, *J* = 15.3 and 6.5, PhCH(N(Bn)Me)CHH), 3.28 (1H, d, *J* = 13.6, CHHPh), 3.02 (3H, s, N(CH$_3$)CO), 2.79 (1H, dd, *J* = 15.4 and 2.7, PhCH(N(Bn)Me)CHH), 2.15 (3H, s, ArCH$_3$), 1.98 (3H, s, CH$_3$); δ_C (75 MHz; $CDCl_3$) 140.3, 139.7, 135.8, 132.6, 129.1, 128.6, 128.5, 127.9, 127.6, 127.3, 126.7, 126.4, 126.2, 125.1,

70.2, 61.5, 58.5, 38.5, 36.8, 36.5, 34.5 and 20.9; *m*/*z* (CI) 475 (17%, M + H^+) and 120 ($PhCH_2NMe$) (Found: M + H^+, 475.2757. $C_{33}H_{34}N_2O$ requires *M* + H, 475.2749).

(*R*$_a$*,2′*S*,2″*S*)-*N*,*N*-Diisopropyl-2-{(2*S**)-[benzyl(methyl)-amino]-2-phenylethyl}-4-methyl-6-[(2*R**)-2-(methylamino)-2-phenylethyl]benzamide 44

sec-Butyllithium (0.76 ml, 1.05 mmol; 1.39 M solution in hexanes) was added to a solution of benzamide[21] **36** (217 mg, 0.88 mmol) in THF (5 ml) at −78 °C under nitrogen. After 60 minutes, *N*-benzylidenemethylamine (0.108 ml, 0.88 mmol) was added to give a dark pink–red solution. After a further 45 minutes, the reaction mixture was treated with benzyl bromide (0.104 ml, 0.88 mmol), stirred for a further 70 minutes to give a pale yellow solution, treated with *sec*-butyllithium (0.76 ml, 0.88 mmol; 1.39 M solution in hexanes) to give a dark red–brown solution and stirred for an additional 45 minutes. *N*-Benzylidenemethylamine (0.108 ml, 0.88 mmol) was added and the mixture was stirred for a further 15 minutes. HMPA (0.31 ml, 1.76 mmol) was added, and after an additional 60 minutes saturated aqueous ammonium chloride solution (5 ml) was added and the mixture allowed to warm to ambient temperature. Water (10 ml) was added and the THF was removed under reduced pressure. Diethyl ether (30 ml) was added and the layers were separated. The ethereal extract was washed with water (5 × 10 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a pale yellow oil. Purification by flash chromatography[58] [1 : 1 petrol (bp 40–60 °C)–EtOAc + 1% triethylamine] afforded the *diamine* **44** (481 mg, 95%) as a yellow oil that crystallised on standing, ν_{max}/cm^{-1} 3339, 3083, 3060, 3027, 2966, 2933, 2871, 2847, 2790; δ_H (300 MHz; $CDCl_3$) 7.4–7.2 (15H, m, 3 × Ph), 6.38 (1H, s, ArH), 6.17 (1H, s, ArH), 4.02 (1H, dd, *J* = 9.2 and 5.9, C*H*-NHMe), 3.89 (1H, t, *J* = 7.1, C*H*NMeBn), 3.71 (1H, d, *J* = 13.5, $N(CH_3)CHPh$), 3.59 (2H, m, 2 × NCH), 3.48 (1H, dd, *J* = 12.9 and 6.0, C*H*HCHNMe), 3.35 (1H, d, *J* = 13.5, $N(CH_3)CHPh$), 2.97 (1H, dd, *J* = 13.2 and 7.4, C*H*HCHN-MeBn), 2.76 (1H, dd, *J* = 12.6 and 9.3, CH*H*CHNMe), 2.68 (1H, dd, *J* = 13.2 and 7.1, CH*H*CHNMeBn), 2.34 (3H, s, CH_3), 2.27 (3H, s, CH_3), 1.93 (3H, s, CH_3), 1.76 (6H, d, *J* = 6.7, 2 × $NCHCH_3$), 1.12 (3H, d, *J* = 6.6, $NCHCH_3$), 1.05 (3H, d, *J* = 6.6, $NCHCH_3$); δ_C (75 MHz; $CDCl_3$) 170.5, 144.3, 141.3, 140.4, 136.1, 135.4, 134.3, 134.1, 129.5, 128.8, 128.7, 128.5, 128.0, 127.9, 127.6, 127.5, 126.7, 126.5, 69.4, 67.1, 59.6, 50.6, 45.8, 42.4, 38.5, 37.8, 35.0, 21.0, 21.0, 20.7 and 20.5; *m*/*z* (CI) 576 (5%, M + H^+) and 120 (100) (Found: M + H^+, 576.3955. $C_{39}H_{49}N_3O$ requires *M* + H, 576.3954).

(*r*$_a$,*R**,*S**)- and (*R**,*R**)-*N*,*N*-Diisopropyl-2-{(2*R**)-2-[benzyl-(methyl)amino]-2-phenylethyl}-6-{(2*S**)-2-[benzyl(methyl)-amino]-2-phenylethyl}-4-methylbenzamide 45a and 45b

In the same way, a solution of benzamide[21] **7** (1.260 g, 5.10 mmol) in THF (30 ml) at −78 °C was treated sequentially with *sec*-butyllithium (4.71 ml, 6.12 mmol; 1.3 M solution in hexanes), *N*-benzylidenemethylamine (0.63 ml, 5.10 mmol), benzyl bromide (0.61 ml, 5.10 mmol), *sec*-butyllithium (4.71 ml, 6.12 mmol; 1.3 M solution in hexanes), *N*-benzylidenemethylamine (0.63 ml, 5.10 mmol), HMPA (1.77 ml, 10.20 mmol), benzyl bromide (0.61 ml, 888 mmol) and saturated aqueous ammonium chloride solution (10 ml). After work-up in the manner of **44**, purification by flash chromatography[58] [7 : 1 petrol (bp 40–60 °C)–EtOAc + 1% triethylamine] afforded *diamine* **45a** (2.503 g, 74%) as a colourless oil which crystallised upon standing. ^1H NMR showed two atropisomers in a ratio of >92 (**45a**) : <8 (**45b**), mp 115–118 °C; ν_{max}/cm^{-1} 3060, 3028, 2967, 2931, 2872, 2846, 2791, 1624; δ_H (300 MHz; $CDCl_3$) 7.45–7.20 (20H, m, ArH), 6.00 (2H, s, ArH^{major}), 6.82 (1H, s, ArH^{minor}), 6.10 (1H, s, ArH^{minor}), 4.00 (2H, dd, *J* = 9.5 and 5.6, 2 × $CHN(CH_3)CH_2Ph^{major}$), 3.71 (2H, d, *J* = 13.5, 2 × $CHHPh^{major}$), 3.59 (2H, m, 2 × NCH^{major}), 3.48 (2H, dd, *J* = 12.6 and 5.5, 2 × $CHHCHN(CH_3)CH_2Ph^{major}$), 3.37 (2H, d, *J* = 13.3, 2 × $CHHPh^{major}$), 2.73 (2H, dd, *J* = 12.8 and 9.6, 2 × $CHHCHN(CH_3)CH_2Ph^{major}$), 2.30 (6H, s, 2 × NCH_3^{major}), 1.79 (6H, m, 2 × $NCHCH_3^{major}$), 1.78 (3H, s, $ArCH_3^{major}$), 1.08 (6H, d, *J* = 6.6, 2 × $NCHCH_3^{major}$); δ_C^{major}(75 MHz; $CDCl_3$) 170.6, 141.5, 140.5, 133.9, 129.3, 128.9, 128.7, 128.6, 128.1, 128.0, 127.6, 126.6, 126.5, 69.8, 59.8, 50.5, 45.8, 38.6, 38.1, 21.0, 20.7 and 20.6; *m*/*z* (CI) 666 (12%, M + H^+), 210 (77, CH(Ph)-$N(CH_3)Bn$) and 120 (100); *m*/*z* (EI) 210 (100%, CH(Ph)-$N(CH_3)Bn$) and 666 (3, M + H^+) (Found: M + H^+, 666.4436. $C_{31}H_{40}N_2O$ requires *M* + H, 666.4423).

N,*N*-Diisopropylbenzamide 46[59]

Diisopropylamine (12 ml, 85 mmol) was added dropwise over 10 minutes to benzoyl chloride (5.40 g, 38.4 mmol) in THF (200 ml) at 0 °C and the mixture was stirred for 3 hours. Water (50 ml) was added and the THF was removed under reduced pressure. The aqueous residue was extracted with diethyl ether (4 × 40 ml) and the combined organic extracts were washed with aqueous 1 M hydrochloric acid (3 × 30 ml) and saturated aqueous sodium hydrogen carbonate (3 × 20 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the crude product as a white solid. Recrystallisation from petrol (bp 40–60 °C) afforded the amide **46**[59] as white platelets (6.766 g, 86%), mp 68–70 °C (lit.[59] 68–69 °C).

N,*N*-Diisopropyl-2-ethylbenzamide 4[19]

sec-Butyllithium (9.48 ml, 1.3 M solution in cyclohexane, 12.32 mmol) was added dropwise to a solution of *N*,*N*-diisopropylbenzamide (2.30 g, 11.20 mmol) in THF (120 ml) at −78 °C under nitrogen. After 1 h before ethyl iodide (1.79 ml, 22.40 mmol) was added. The solution was allowed to warm to room temperature, water (50 ml) was added and the THF was removed under reduced pressure. The aqueous residue was extracted with dichloromethane (3 × 30 ml) and the combined extracts were washed with water (30 ml), dried over magnesium sulfate, filtered and concentrated under reduced pressure. Purification by flash chromatography[58] [5% ethyl acetate in light petroleum] gave the amide **4**[19] (2.61 g, 100%) as a white crystalline solid, mp 90–92 °C (lit.[19] 91–93 °C); R_f [10% EtOAc: petrol] 0.47; δ_H (300 MHz; $CDCl_3$) 7.34–7.17 (3H, m, ArH), 7.11 (1H, d, *J* = 7.3, ArH), 3.71 (1H, sept, *J* = 7, NCH), 3.54 (1H, sept, *J* = 7, NCH), 2.79–2.58 (2H, m, $ArCH_ACH_B$), 1.61 (6H, d, *J* = 7, $NCHCH_3$), 1.29 (3H, t, *J* = 7.5, CH_2CH_3), 1.14 (3H, d, *J* = 7, $NCHCH_3$), 1.11 (3H, d, *J* = 7, $NCHCH_3$) [lit.[19] 4.81 (1H, m), 3.84 (4H, m), 2.71 (2H, m), 1.63 (4H, m)]; δ_C (75 MHz; $CDCl_3$) 170.5 (s, CO), 139.8 (s, Ar), 138.0 (s, Ar), 128.5 (d, Ar), 128.1 (d, Ar), 125.6 (d, Ar), 124.6 (d, Ar), 50.6 (d, NCH), 45.6 (d, NCH), 25.6 (t, CH_2), 20.6 (q, $NCHCH_3$), 20.6 (q, $NCHCH_3$), 20.5 (q, $NCHCH_3$), 20.4 (q, $NCHCH_3$), 15.1 (q, CH_2CH_3).

N,*N*-Diisopropyl-2-propylbenzamide 50

In the same way, *sec*-butyllithium (2.47 ml, 1.3 M solution in cyclohexane, 3.21 mmol), benzamide **46** (0.60 g, 2.92 mmol) in THF (60 ml) and *n*-propyl iodide (0.57 ml, 5.84 mmol) gave, after purification by flash chromatography[58] [8 : 2 light petroleum–ethyl acetate], the *amide* **50** (0.653 g, 91%) as a colourless oil; R_f [EtOAc–petrol, 3 : 7] 0.69; ν_{max} (film)/cm^{-1} 1632; δ_H (300 MHz; $CDCl_3$) 7.34–7.10 (4H, m, ArH), 3.71 (1H, sept, *J* = 6.7, NCH), 3.54 (1H, sept, *J* = 6.7, NCH), 2.62 (2H, t, *J* = 7.8, $ArCH_2$), 1.86–1.50 (2H, m, $CH_2CH_2CH_3$), 1.61 (6H, d, *J* = 6.7, 2 × $NCHCH_3$), 1.15 (3H, d, *J* = 6.7, $NCHCH_3$), 1.12 (3H, d, *J* = 6.7, $NCHCH_3$), 0.99 (3H, t, *J* = 7.3, CH_2CH_3); δ_C (75 MHz; $CDCl_3$) 170.5 (s, CO), 138.5 (s, Ar), 138.1 (s, Ar), 129.2 (d, Ar), 128.0 (d, Ar), 125.6 (d, Ar), 124.8 (d, Ar), 50.6 (d, NCH), 45.6 (d, NCH), 34.9 (t, $ArCH_2$), 24.0 (t, CH_2CH_3), 20.7 (q, $NCHCH_3$), 20.6 (q, $NCHCH_3$), 20.5 (q, $NCHCH_3$), 20.4

(q, NCHCH_3), 14.1 (q, CH_2CH_3); *m*/*z* (EI) 247 (13%), 204 (25), 147 (100), 131 (20), 129 (30), 91 (33) (Found: M^+, 247.1943. $C_{16}H_{25}NO$ requires *M*, 247.1936).

(R_a*,*S**)-*N*,*N*-Diisopropyl-2-methyl-6-*sec*-butylbenzamide 49a

sec-Butyllithium (0.66 ml, 1.3 M solution in cyclohexane, 0.857 mmol) was added dropwise to a solution of *N*,*N*-diisopropyl-2-ethylbenzamide **4** (0.20 g, 0.857 mmol) in THF (60 ml) at −78 °C under nitrogen. The pink solution was stirred at −78 °C for 1 h and ethyl iodide (69 µl, 0.857 mmol) was added. *sec*-Butyllithium (0.66 ml, 1.3 M solution in cyclohexane, 0.857 mmol) was added. The orange solution was stirred for a further 1 h and methyl iodide (54 µl, 0.857 mmol) was added. The solution was allowed to warm to 0 °C, water (40 ml) was added and the THF was removed under reduced pressure. The aqueous phase was extracted with dichloromethane (3 × 40 ml), the combined organic extracts were washed with water (40 ml), dried over magnesium sulfate, filtered and concentrated. Purification by flash chromatography[58] [5% ethyl acetate in light petroleum] gave the *amide* **49a** (147 mg, 62%) as a white crystalline solid, mp 49–49.5 °C; R_f [10% EtOAc–petrol] 0.47; δ_H (300 MHz; $CDCl_3$) 7.22 (1H, t, *J* = 7.5, *p*-ArH), 7.11 (1H, d, *J* = 7.5, *m*-ArH), 7.04 (1H, d, *J* = 7.5, *m*-ArH), 3.70 (1H, sept, *J* = 6.7, NCH), 3.54 (1H, sept, *J* = 6.7, NCH), 2.74–2.58 (1H, m, ArCH), 2.33 (3H, s, $ArCH_3$), 1.80–1.39 (2H, m, ArCHCH_2), 1.64 (6H, d, *J* = 6.7, NCH(CH_3)$_2$), 1.27 (3H, d, *J* = 6.9, ArCHCH_3), 1.14 (6H, d, *J* = 6.7, NCH(CH_3)$_2$), 0.87 (3H, t, *J* = 7.4, $ArCHCH_2CH_3$); δ_C (75 MHz; $CDCl_3$) 169.8 (s, CO), 143.5 (s, Ar), 137.3 (s, Ar), 133.1 (s, Ar), 127.6 (d, Ar), 127.5 (d, Ar), 122.9 (d, Ar), 50.3 (d, NCH), 45.7 (d, NCH), 37.2 (d, ArCH), 32.4 (t, CH_2CH_3), 20.9 (q, NCHCH_3), 20.9 (q, NCHCH_3), 20.3 (q, NCHCH_3), 20.3 (q, NCHCH_3), 20.2 (ArCHCH_3), 19.2 (t, $ArCH_3$), 12.0 (q, CH_2CH_3); *m*/*z* (CI) 277 (22%), 276 (100), 260 (1), 175 (7), 174 (3) (Found: C, 78.74; H, 10.56; N, 5.06%, M^+, 275.2244. $C_{18}H_{29}NO$ requires C, 78.49; H, 10.61; N, 5.09%, *M* 275.2249).

HPLC analysis of the crude product showed a 91 : 9 ratio of **49a** : **49b**.

(R_a*,*R**)-*N*,*N*-Diisopropyl-2-methyl-6-*sec*-butylbenzamide 49b

sec-Butyllithium (0.62 ml, 1.3 M solution in cyclohexane, 0.808 mmol) was added dropwise to a solution of *N*,*N*-diisopropyl-2-propylbenzamide (200 mg, 0.808 mmol) in THF (60 ml) cooled to −78 °C under an atmosphere of nitrogen. The resultant dark pink solution was stirred at −78 °C for 1 h before the addition of methyl iodide (50 µl, 0.808 mmol). *sec*-Butyllithium (0.62 ml, 1.3 M solution in cyclohexane, 0.808 mmol) was then added and the yellow solution stirred at −78 °C for a further 1 h, followed by a second addition of methyl iodide (50 µl, 0.808 mmol). The solution was allowed to warm to 0 °C, water (40 ml) was added and the THF was removed under reduced pressure. The aqueous phase was extracted with dichloromethane (3 × 40 ml), the combined organic extracts were washed with water (40 ml), dried over magnesium sulfate, filtered and the solvent was evaporated to give the *amide* **49b**. HPLC analysis of the crude product showed a 93 : 7 ratio of **49b** : **49a**.

Crystal data for 22a §§

$C_{27}H_{34}N_2O$, *M* = 402.56, monoclinic, *a* = 14.030(3), *b* = 12.956(4), *c* = 14.047(3) Å, *β* = 114.457(13)°, *U* = 2324.3(9) Å^3, *T* = 123(1) K, space group $P2_1/n$, 22259 reflections measured, 4734 unique (R_{int} = 0.0200) which were used in all calculations. The final *wR*(F^2) was 0.0995 (all data).

Crystal data for 28a §§

$C_{26}H_{29}NO_2$, *M* = 387.50, monoclinic, *a* = 7.4893(18), *b* = 13.585(4), *c* = 11.005(4) Å, *β* = 99.39(2)°, *U* = 1104.7(5) Å^3, *T* = 123(1) K, space group $P2_1$, 11086 reflections measured, 4494 unique (R_{int} = 0.0218) which were used in all calculations. The final *wR*(F^2) was 0.0917 (all data).

Crystal data for 45a §§

$C_{46}H_{55}N_3O$, *M* = 665.93, triclinic, *a* = 11.350(2), *b* = 12.9829(18), *c* = 14.928(3) Å, *α* = 71.775(12)°, *β* = 79.479(16)°, *γ* = 70.577(16)°, *U* = 1962.9(6) Å^3, *T* = 123(1) K, space group $P\bar{1}$, 18961 reflections measured, 7883 unique (R_{int} = 0.0196) which were used in all calculations. The final *wR*(F^2) was 0.1144 (all data).

§§ CCDC reference numbers 177854–177856. See http://www.rsc.org/suppdata/p1/b2/b200358a/ for crystallographic files in .cif or other electronic format.

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