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Asymmetric synthesis of enantiomerically enriched atropisomeric amides by desymmetrisation of *N*,*N*-dialkylmesitamides †

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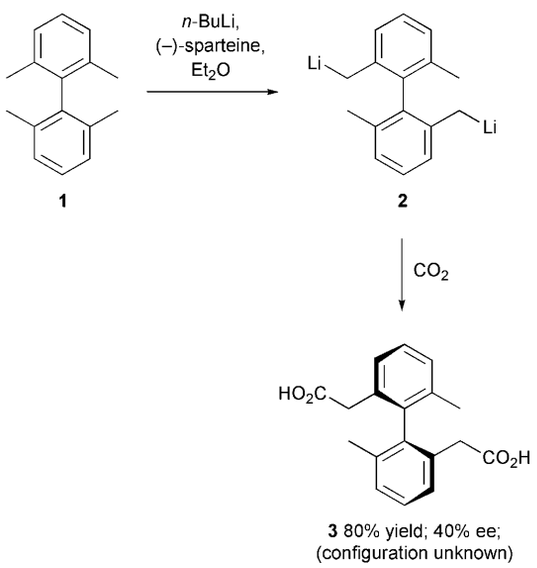
Lithiation and silylation of *N*,*N*-dialkylmesitamides using chiral lithium amide bases leads to enantiomerically enriched atropisomeric amides (up to 89% ee) by desymmetrisation of the enantiotopic methyl groups.

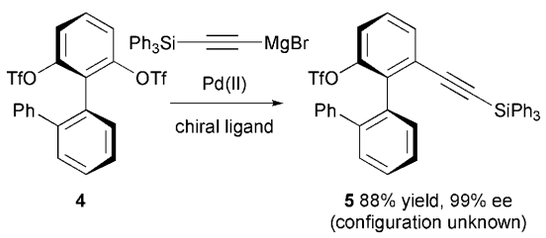
Desymmetrisation of an achiral precursor is a powerful way of producing chiral molecules as single enantiomers, often with the creation of several stereogenic centres in one step.[1] However, desymmetrisation as a method for the asymmetric synthesis of atropisomers (for example, biaryls) as single enantiomers has been explored only in a very limited way. An early result in this area was Raston's synthesis[2] of the biaryl **3**. Desymmetrisation of **1** by benzylic lithiation with *n*-BuLi in the presence of (−)-sparteine, gave **2** in 40% ee (Scheme 1). More



Scheme 1 Desymmetrisation of a biphenyl by enantioselective lithiation.

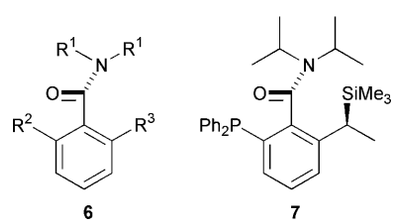
recently, Hayashi and co-workers[3–5] have succeeded in carrying out the desymmetrising couplings of achiral aryl bis-triflates such as **4** with aryl and alkynyl Grignards to yield products such as **5** with near complete atroposelectivity (Scheme 2). A desymmetrising acetal-forming reaction between 2,2′,6,6′-tetrahydroxybiphenyl and menthone has been used to synthesise atropisomeric biphenol derivatives.[6]

For some years, we have been investigating the stereoselective reactions of the hindered tertiary aromatic amides **6**,[7,8] which can exhibit atropisomerism about the Ar–CO bond.[9,10] Most of our work has been carried out in the racemic series, where we have shown that the chiral Ar–CO axis of **6** is a powerful agent for stereocontrol over long distances.[11–14] We recently found that a chiral Ar–CO axis can be the stereocontrolling



Scheme 2 Desymmetrisation of a biphenyl by enantioselective Pd-catalysed coupling.

element in a ligand-controlled metal-catalysed reaction, making **7** the first example of a new class of chiral ligands for palladium chemistry.[15] We made the ligand **7** as a single enantiomer by



a method whose success derives from the powerful thermodynamic influence that the configuration of a stereogenic centre may have over the conformation of an adjacent axis.[16] We have also published a method for the synthesis of enantiomerically pure atropisomeric amides based on a dynamic thermodynamic resolution,[17] at the heart of which is the same concept.

Given the tendency for 2-alkyl substituted tertiary benzamides to undergo lateral lithiation with great ease,[18,19] we realised that the desymmetrisation of a 2,6-dialkylbenzamide ought to be possible by employing a chiral base to distinguish between two enantiotopic alkyl groups.[20] In this paper we describe a method for achieving this desymmetrisation, and demonstrate the means by which the products may be converted to functionalised atropisomeric amides.

We made some *N*,*N*-dialkylmesitamides **9a–c** by treating mesitoyl chloride **8** with diethylamine, diisopropylamine or dicyclohexylamine. These three achiral amides were treated with a range of chiral bases and the resulting organolithiums were quenched with electrophiles to give the chiral atropisomers **10** (Scheme 3). The yields and enantiomeric excesses of the products **10** are shown in Table 1.

Entries 1–3 indicate that the mesitamides **9** are deprotonated by either *s*-BuLi **11** or LDA **12**, and may be quenched with electrophiles (Me_3SiCl or acetone) to give racemic **10** in good yield. In the light of this, we tried two types of chiral base: firstly, *s*-BuLi complexed with the chiral diamine (−)-sparteine (**13**)[21] and, secondly, a range of chiral lithium amide bases

† The IUPAC name for mesitamide is 2,4,6-trimethylbenzamide.

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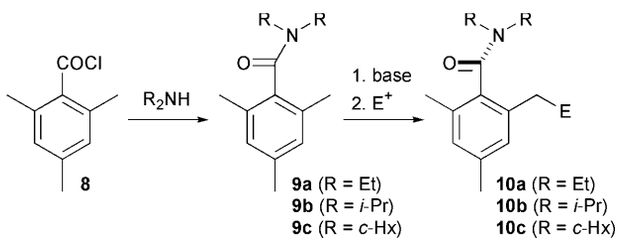
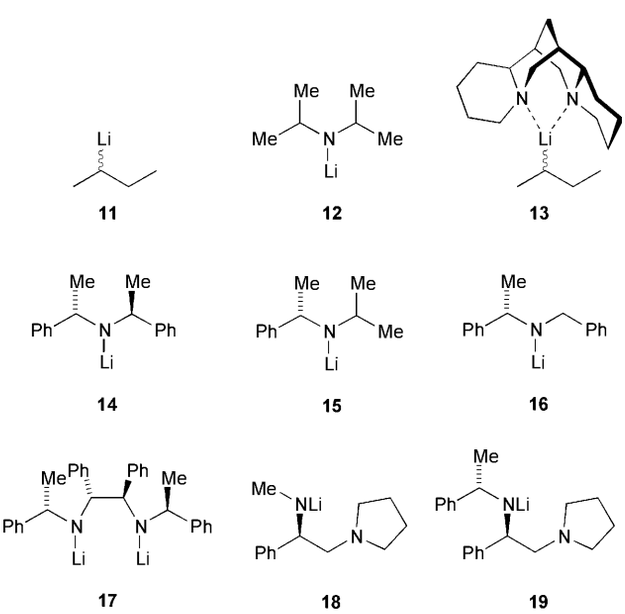
Table 1 Desymmetrisation of **9**

Entry	Base	Starting material	R =	E^+ =	Method[a]	Yield (%)	Ee (%)
1	**11**	**9b**	*i*-Pr	Me_3SiCl	A	100	—
2	**11**	**9c**	*c*-Hx	Me_3SiCl	A	95	—
3	**12**	**9b**	*i*-Pr	$Me_2C{=}O$	A	74	—
4	**13**	**9a**	Et	Me_3SiCl	A	61	4
5	**14**	**9b**	*i*-Pr	Me_3SiCl	A	54	78
6	**14**	**9c**	*c*-Hx	Me_3SiCl	A	57	85
7	**14**	**9b**	*i*-Pr	Me_3SiCl	B	55	89
8	**14**	**9b**	*i*-Pr	Me_3SiCl	C	33	75
9	**15**	**9b**	*i*-Pr	Me_3SiCl	B	64	62
10	**16**	**9b**	*i*-Pr	Me_3SiCl	A	25	59
11	**16**	**9b**	*i*-Pr	Me_3SiCl	B	45	79
12	**17**	**9b**	*i*-Pr	Me_3SiCl	A	0	—
13	**18**	**9b**	*i*-Pr	Me_3SiCl	A	0	—
14	**19**	**9b**	*i*-Pr	Me_3SiCl	A	0	—

[a] Method A: electrophile added after deprotonation is complete (external quench). Method B: electrophile present during deprotonation (*in situ* quench). Method C: external quench with LiCl added before deprotonation.



Scheme 3 Desymmetrisation of a mesitamide by enantioselective deprotonation.



14–**19** which have performed well in a number of other classes of desymmetrisation reactions.[22,23]

The complex **13** rarely performs well in THF,[21] and we found that the product of lithiation and silylation of **9a** with this base was essentially racemic (entry 4). In fact, unless the (−)-sparteine was carefully degassed prior to use, the major product from these lithiations was that of oxidation, **10a** (E = OH), in unknown ee.

Experiments with lithium amide bases were much more successful. The amides **9b** and **9c** were deprotonated by all of **14**–**16** (but not **17**–**19**, which failed to lithiate **9c**) and gave **10** ($E = SiMe_3$) in good to excellent enantiomeric excess after quenching with Me_3SiCl. The technique of including the electrophile (Me_3SiCl) *in situ* in the reaction mixture appeared to lead to a slight improvement in enantiomeric excess, and also an improvement in yield in one case. The addition of LiCl (which is present during the deprotonation when an *in situ* quench is used[24]) simply lowered the yield of product. The best base of those tried was **14**, which gave yields above 50% and enantiomeric excesses in the range 75–90%. Base **15** gave better yields, but poorer enantiomeric excesses, while **16** gave good enantiomeric excesses but poorer yields.‡

The use of the product **10** ($E = SiMe_3$) in the synthesis of enantiomerically enriched atropisomers depends on its thermal stability to racemisation.[9,25] We determined the barrier to racemisation[9] $\Delta G^{\ddagger}_{rac}$ of **10b** ($E = SiMe_3$) to be 101.9 ± 0.3 kJ mol^{-1} at 50 °C (giving a half-life to racemisation of approximately 24 h at 25 °C) by following the decay in optical rotation with time, and the barrier to racemisation $\Delta G^{\ddagger}_{rac}$ of **10c** ($E = SiMe_3$) to be 99.5 ± 0.3 kJ mol^{-1} at 35 °C (giving a half-life to racemisation of approximately 9 h at 25 °C) by following the decay in ee with time by HPLC.§ Both barriers are too low for this method to be a truly practical route to enantiomerically pure ligands related to **7** since some racemisation must be expected during subsequent transformations of **10**.

Nonetheless, we found that it was possible to use a regioselective lithiation of **10b** ($E = SiMe_3$) to introduce further functionality.¶ Lithiation of **10b** ($E = SiMe_3$) with *s*-BuLi is irreversible, and gave a mixture of organolithiums, leading to a 2:1 mixture of methylated products **20** and **21** on treatment with MeI (Scheme 4). However, by using LDA to carry out a reversible lithiation, leading to the most thermodynamically stable organolithium, we were able to obtain a single regioisomer of the product **20**. Further functionalisation of the remaining methyl group and removal of the silyl group opens up many possibilities for using the desymmetrisation as the starting point for a range of enantiomerically enriched atropisomeric amides. Alternatively, alkenes can be made from **10** by Peterson olefination: lithiation of **10b** ($E = SiMe_3$) with LDA followed by a cyclobutanone quench gave the unsaturated amide **22** in 92% yield.

Experimental

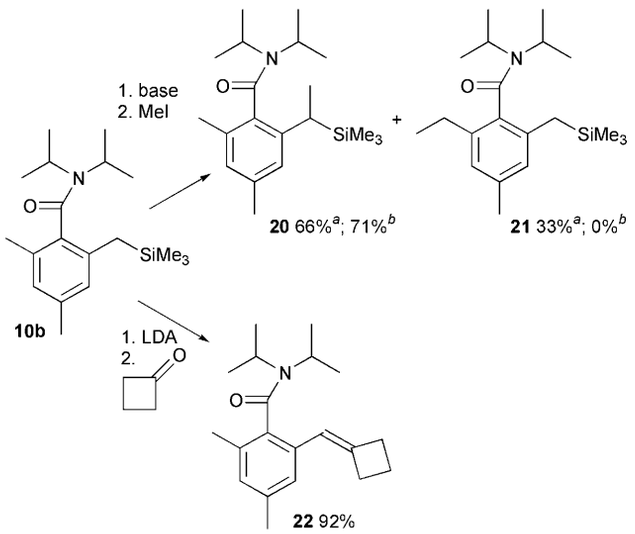
General

^1H and ^{13}C NMR spectra were recorded on either Varian XL300 (300 and 75 MHz) or Bruker XC300 (300 and 75 MHz)

‡ The absolute stereochemistry of the products **10** is unknown.

§ Values for rates of racemisation at 25 °C are estimated assuming $\Delta G^{\ddagger}_{rac}$ to be constant (*i.e.* $\Delta S^{\ddagger}_{rac} \approx 0$). Entropies of activation for bond rotations are frequently,[26] though not always,[27] small, and in a similar compound to **10** ($E = SiMe_3$) we determined a value of $|\Delta S^{\ddagger}_{rac}| < 30$ J mol^{-1} K^{-1}.[15]

¶ The reactions in Scheme 4 were carried out using racemic **10b**.



Scheme 4 Transformations of **10b**. [a] Yield from ^{1}H NMR spectrum of crude reaction product on using *s*-BuLi as the base. [b] Isolated yield on using LDA as the base (100% **20**).

spectrometers. Mass spectra were recorded using Chemical Ionisation (CI) on a Fisons VG Trio 2000 or a Concept IS (HRMS) spectrometer. Infra-red spectra were recorded on an ATi Genesis Series FTIR spectrometer. All samples were run as an evaporated film on a sodium chloride plate. Petrol refers to petroleum ether, bp 40–60 °C.

N,*N*-Diethyl-2,4,6-trimethylbenzamide 9a

2,4,6-Trimethylbenzoyl chloride (0.80 ml, 4.82 mmol) was added dropwise to a rapidly stirred diethylamine (10 ml) cooled in an ice-bath. The reaction mixture was allowed to stir under a nitrogen atmosphere at room temperature for 16 h. Dichloromethane (20 ml) and water (20 ml) were added and the aqueous phase was extracted with dichloromethane (2 × 20 ml). The combined organic extracts were washed with water (20 ml), dilute HCl (2 M, 20 ml), saturated aqueous sodium hydrogen carbonate solution (20 ml) and brine (20 ml), dried over magnesium sulfate and filtered. The solvent was removed under reduced pressure and the residue was purified by flash chromatography[28] [4:1 light petroleum–ethyl acetate (R_f 0.36, 7:3 light petroleum–ethyl acetate)] to afford the amide as a white crystalline solid (0.92 g, 87%), mp 35 °C; ν_{max} (Nujol mull)/cm^{-1} 1643; δ_H (300 MHz, $CDCl_3$) 6.86 (2H, s, ArH), 3.63 (2H, q, *J* 7, NCH_2CH_3), 3.14 (2H, q, *J* 7, NCH_2CH_3), 2.29 (3H, s, *p*-$ArCH_3$), 2.23 (6H, s, 2 × *o*-$ArCH_3$), 1.29 (3H, t, *J* 7, NCH_2CH_3), 1.15 (3H, t, *J* 7, NCH_2CH_3); δ_C (75 MHz, $CDCl_3$) 170.5 (s, CO), 137.5 (s, *p*-CCH_3), 134.0 (s, *C*CO), 133.3 (s, 2 × *o*-CCH_3), 128.1 (d, 2 × ArH), 42.2 (t, NCH_2), 38.2 (t, NCH_2), 21.0 (q, *p*-$ArCH_3$), 18.8 (q, 2 × *o*-CCH_3), 13.8 (q, NCH_2CH_3), 12.6 (q, NCH_2CH_3); *m*/*z* (CI) 221 (22%), 220 (100%), 147 (39%). Found: M^+ 219.1625; $C_{14}H_{21}NO$ requires *M* 219.1623.

N,*N*-Diisopropyl-2,4,6-trimethylbenzamide 9b

2,4,6-Trimethylbenzoyl chloride (3 g) was added to diisopropylamine (10 ml). The reaction mixture was heated to reflux for 6 h, cooled to room temperature, dissolved in CH_2Cl_2, washed with saturated aqueous ammonium chloride and dried over magnesium sulfate. The solvent was removed under reduced pressure. Recrystallisation of the crude product (petrol–EtOAc) gave the pure title compound (3.21 g, 79%) as a white crystalline solid, mp 106–107 °C, R_f 0.50 (petrol–EtOAc 2:1), ν_{max} (film)/cm^{-1} 2963, 2929, 1621; δ_H (300 MHz, $CDCl_3$) 6.82 (2 H, s), 3.65 (1 H, sept, *J* 6.5), 3.51 (1 H, sept, *J* 7.0), 2.27 (3 H, s), 2.25 (6 H, s), 1.60 (6 H, d, *J* 7.0), 1.11 (6 H, d, *J* 6.5); δ_C (75 MHz, $CDCl_3$) 170.5, 137.0, 135.4, 133.2, 128.1, 50.7, 45.8, 21.1, 20.6, 18.9; *m*/*z* (CI) 248 (MH^+, 100%), 147 (15%), [Found M^+ 247.1939, $C_{16}H_{25}NO$ requires *M* 247.1936].

N,*N*-Dicyclohexyl-2,4,6-trimethylbenzamide 9c

2,4,6-Trimethylbenzoyl chloride (2 g) was added to dicyclohexylamine (10 ml). The reaction mixture was stirred at room temperature for 4 days, dissolved in CH_2Cl_2, washed with saturated aqueous ammonium chloride and dried over magnesium sulfate. The solvent was removed under reduced pressure. Purification of the crude product by flash chromatography[28] (petrol–EtOAc 9:1) gave the *title compound* (1.51 g, 42%) as a white foam which slowly solidified, mp 114–115 °C; δ_H (300 MHz, $CDCl_3$) 6.79 (2 H, s), 3.15 (2 H, tt, *J* 3.5, 11.5), 3.04, (2 H, tt, *J* 3.5, 11.5), 2.77 (2 H, br dq, *J* 3.5, 12.5), 2.26 (3 H, s), 2.22 (6 H, s), 1.82–1.84 (2 H, m), 1.61–1.70 (6 H, m), 1.39–1.50 (4 H, m), 1.26–1.30 (4 H, m), 1.00 (2 H, br s); δ_C (75 MHz, $CDCl_3$) 170.6, 136.7, 135.5, 132.9, 128.0, 59.8, 55.9, 31.6, 29.9, 26.6, 25.7, 25.3, 25.1, 21.0, 18.9; *m*/*z* (CI) 328 (MH^+, 100%), 147 (15%). Found M^+, 327.2563; $C_{22}H_{33}NO$ requires *M* 327.2562.

(±)-*N*,*N*-Diisopropyl-2,4-dimethyl-6-trimethylsilylmethylbenzamide (±)-10b (E = $SiMe_3$)

sec-Butyllithium (0.4 ml, 1.4 M) was added to a solution of *N*,*N*-diisopropyl-2,4,6-trimethylbenzamide **9b** (124 mg) in THF (10 ml) under an atmosphere of nitrogen at −78 °C. The orange reaction mixture was stirred at this temperature for 30 min, chlorotrimethylsilane (0.5 ml) was added, and the mixture was allowed to warm to room temperature. Saturated aqueous ammonium chloride was added and the mixture was extracted with ether. The combined extracts were washed with water, dried over magnesium sulfate, and concentrated under reduced pressure to give the crude product. Purification of the crude product by flash chromatography[28] (petrol–EtOAc 9:1) gave the *title compound* (318 mg, quantitative) as a colourless oil, R_f 0.19 (petrol–EtOAc 9:1), ν_{max} (film)/cm^{-1} 2962, 2900, 1631, 853; δ_H (300 MHz, $CDCl_3$) 6.72 (1 H, s), 6.66 (1 H, s), 3.62 (1 H, sept, *J* 6.5), 3.47 (1 H, sept, *J* 7.0), 2.25 (3 H, s), 2.22 (3 H, s), 2.00 (1 H, d, *J* 13.5), 1.93 (1 H, d, *J* 13.5), 1.58 (6 H, d, *J* 7.0), 1.10 (3 H, d, *J* 6.5), 1.07 (3 H, d, *J* 6.5), 0.02 (9 H, s); δ_C (75 MHz, $CDCl_3$) 170.38, 136.4, 136.3, 134.1, 133.3, 126.6, 126.5, 50.5, 45.5, 23.5, 21.1, 21.1, 20.9, 20.4, 20.4, 19.0, −1.2; *m*/*z* (CI) 320 (MH^+, 100%), 304 (35%), 147 (55%). Found: M^+ 319.2327; $C_{19}H_{33}NOSi$ requires *M*, 319.2331.

The enantiomers of (±)-**10b** (E = $SiMe_3$) could be resolved analytically by HPLC using a Chiralpak AD 250 × 4.6 mm chiral stationary phase, Merck–Hitachi system, eluant 2% EtOH in hexane, flow rate 1 ml min^{-1}, UV detection at 255 nm, retention times 7.08 and 8.71 min.

(±)-*N*,*N*-Diisopropyl-2,4-dimethyl-6-(2-hydroxy-2-methylpropyl)benzamide (±)-10b (E = Me_2COH)

sec-Butyllithium (0.37 ml, 1.3 M solution in cyclohexane, 0.481 mmol) was added dropwise to a solution of the *N*,*N*-diisopropyl-2,4,6-trimethylbenzamide **9b** (108 mg, 0.437 mmol) in THF (30 ml) at −78 °C under an atmosphere of nitrogen. The resultant orange solution was stirred at −78 °C for 1.25 h. Acetone (48 μl, 0.656 mmol) was added, the mixture was warmed 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 organic extracts were washed with water (30 ml), brine (30 ml), dried over magnesium sulfate and filtered. The solvent was evaporated and the crude product purified by flash chromatography[28] [5:1 light petroleum–ethyl acetate, R_f 0.13] to give *the title compound* as a white crystalline solid (98 mg, 74%), mp 106 °C; ν_{max} (Nujol mull)/cm^{-1} 1598; δ_H (300 MHz, $CDCl_3$) 6.92 (2H, s, ArH), 4.59 (1H, s, OH), 3.59 (1H, sept, *J* = 6.7,

NCH), 3.57 (1H, sept, J = 6.7, NCH), 2.71 (2H, AB q, J = 13.6, ArCH_AH_BCOH), 2.35 (3H, s, ArCH_3), 2.29 (3H, s, ArCH_3), 1.68 (3H, d, J = 6.9, NCHCH_3), 1.61 (3H, d, J = 6.7, NCHCH_3), 1.34 (3H, s, COHCH_3), 1.23 (3H, s, COHCH_3), 1.19 (3H, d, J = 6.7, NCHCH_3), 1.07 (3H, d, J = 6.6, NCHCH_3); δ_C (75 MHz, $CDCl_3$) 172.5 (s, CO), 137.0 (s, Ar), 135.3 (s, Ar), 134.1 (s, Ar), 132.8 (s, Ar), 129.0 (d, Ar), 129.0 (d, Ar), 69.2 (s, COH), 50.9 (d, NCH), 46.0 (d, NCH), 46.0 (t, ArCH_2), 32.6 (q, CH_3COH), 28.1 (q, CH_3COH), 21.1 (q, ArCH_3), 21.1 (q, NCHCH_3), 20.5 (q, NCHCH_3), 20.5 (q, NCHCH_3), 20.3 (q, NCHCH_3), 18.9 (q, ArCH_3); *m*/*z* (CI) 306 (100%), 288 (10), 247 (9), 232 (8), 147 (9). Found: $(M + H)^+$ 306.2436; $C_{19}H_{32}NO_2$ requires M 306.2433.

(±)-*N*,*N*-Dicyclohexyl-2,4-dimethyl-6-trimethylsilylmethylbenzamide (±)-10c (E = SiMe$_3$)

sec-Butyllithium (0.21 ml, 1.3 M solution in hexanes, 0.336 mmol) was added dropwise to a solution of *N*,*N*-dicyclohexyl-2,4,6-trimethylbenzamide **9c** (100 mg, 0.305 mmol) in THF (20 ml) at −78 °C under an atmosphere of nitrogen. The resultant orange solution was stirred for 1 h at −78 °C. Chlorotrimethylsilane (58 μl, 0.458 mmol) was added. The colourless solution was allowed to warm to 0 °C, water (20 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 (20 ml), dried over magnesium sulfate, filtered and concentrated. Flash chromatography[28] (7% ethyl acetate in light petroleum) gave the *silane* (±)-**10c** (E = SiMe$_3$) as a colourless oil (105 mg, 95%), ν_{max} (film)/cm^{-1} 1626; δ_H (300 MHz, $CDCl_3$) 6.69 (1H, s, ArH), 6.63 (1H, s, ArH), 3.20–2.92 (2H, br m, 2 × NCH), 2.86–2.66 (2H, br m, CH_2's), 2.24 (3H, s, ArCH_3), 2.19 (3H, s, ArCH_3), 2.40–1.87 (2H, AB q, J 13.5, ArCH_AH_B), 1.90–0.80 (18H, br m, CH_2's), 0.00 (9H, s, Si(CH_3)$_3$); δ_C (75 MHz, $CDCl_3$) 170.6 (s, CO), 136.2 (s Ar), 135.9 (s, Ar), 134.2 (s, Ar), 133.1 (s, Ar), 126.5 (d, Ar), 126.4 (d, Ar), 59.6 (d, NCH), 55.8 (d, NCH), 31.5, 31.5, 29.8, 29.8, 29.6, 26.7, 26.6, 25.6, 25.3, 25.1 and 23.4 (d, CH_2's), 21.1 (q, ArCH_3), 19.1 (q, ArCH_3), −1.2 (q, Si(CH_3)$_3$); *m*/*z* (EI) 399 (8%), 384 (27), 316 (28), 302 (100), 220 (30), 147 (45), 73 (46). Found: M^+ 399.2953; $C_{19}H_{41}NOSi$ requires M 399.2957.

The enantiomers of (±)-**10c** (E = SiMe$_3$) could be resolved analytically by HPLC using a Chiralpak AD 250 × 10 mm chiral stationary phase, Merck–Hitachi system, flow rate 2.4 ml min^{-1}, eluant 1% ethanol in hexane, UV at 255 nm, retention times 7.62 and 8.70 min.

Desymmetrisation of *N*,*N*-diethyl-2,4,6-trimethylbenzamide 9a with *s*-BuLi-(−)-sparteine

sec-Butyllithium (0.386 ml, 1.3 M solution in hexanes, 0.502 mmol) was added to a solution of freshly distilled and degassed sparteine (0.115 ml, 0.502 mmol) in THF (10 ml) at −78 °C and under an atmosphere of nitrogen. After stirring for 15 min the solution was transferred *via* a cannula to a solution of *N*,*N*-diethyl-2,4,6-trimethylbenzamide **9a** (100 mg, 0.456 mmol) in THF (20 ml) at −78 °C. The resultant orange–red solution was stirred for 5 min, and chlorotrimethylsilane (87 μl, 0.684 mmol) was added. The colourless solution was allowed to warm to 0 °C. Water (20 ml) was added and the THF was removed under reduced pressure. The aqueous phase was extracted with dichloromethane (3 × 15 ml) and the combined organic extracts were washed with water (20 ml), dried over magnesium sulfate, filtered and concentrated. Purification by flash chromatography[28] (10% ethyl acetate in light petroleum, R_f 0.19) afforded the silane as a colourless oil (81 mg, 61%); δ_H (300 MHz, $CDCl_3$) 6.70 (1H, s, ArH), 6.66 (1H, s, ArH), 3.66–3.42 (2H, m, CH_2CH$_3$), 3.16–2.96 (2H, m, CH_2CH$_3$), 2.24 (3H, s, ArCH_3), 2.16 (3H, s, ArCH_3), 1.96–1.82 (2H, AB q, J 13.7, CH_AH_BTMS), 1.23 (3H, t, J 7.1, CH_2CH_3), 0.98 (3H, t, J 7.1, CH_2CH_3), 0.00 (9H, s, Si(CH_3)$_3$); δ_C (75 MHz, $CDCl_3$) 170.4 (s, CO), 136.9 (s, Ar), 136.4 (s, Ar), 133.6 (s, Ar), 132.8 (s, Ar), 126.7 (d, Ar), 126.6 (d, Ar), 42.3 (t, NCH_3), 38.5 (t, NCH_3), 23.4 (t, CH_2Si), 21.1 (q, ArCH_3), 19.2 (q, ArCH_3), 13.8 (q, CH_2CH_3), 12.6 (q, CH_2CH_3), 1.1 (q, Si(CH_3)$_3$); *m*/*z* (EI) 294 (12%), 293 (44%), 292 (100%), 276 (21%), 219 (11%). Found: M 291.2023; $C_{17}H_{29}NOSi$ requires M 291.2018.

HPLC analysis was performed on a Chiralpak stationary phase (250 × 10 mm), eluant 1% ethanol in hexane, flow rate 2.4 ml min^{-1}, UV detection at 255 nm, retention times 9.00 (47.3%) and 9.81 min (50.87%), ee = 3.6%.

General method for desymmetrisation of 9 with chiral lithium amide bases

(+)-*N*,*N*-Diisopropyl-2,4-dimethyl-6-trimethylsilylmethylbenzamide (+)-10b (E = SiMe$_3$). *sec*-Butyllithium (1.2 eq.) was added to a solution of chiral amine (1.3 eq.) in THF (*ca.* 0.1 M) at −78 °C. The solution was allowed to warm to 0 °C for 15 min and cooled to −78 °C. For the internal quench experiments, chlorotrimethylsilane (5 eq.) was added, followed by the amide **9** (1 eq.) in THF. For the external quench experiments, amide **9** (1 eq.) in THF was added, the reaction mixture was stirred at −78 °C for 30 min, and chlorotrimethylsilane (2 eq.) was added. The product was poured into ice-cold saturated aqueous ammonium chloride and quickly extracted into ether, dried over magnesium sulfate and concentrated to give a crude product which was purified by flash chromatography[28] (eluting with chilled petrol–EtOAc 4:1, and cooling collected fractions in ice) to give the silylated amide with spectroscopic data identical with that of the racemic material. Enantiomeric excesses were calculated by ^{1}H NMR in the presence of 4 eq. of the shift reagent 2,2,2-trifluoro-1-(9-anthryl)ethanol,[29,30] examining splitting of the signals of the 4- and 6-methyl singlets. The optical rotation of a sample of **10b** (E = SiMe$_3$) of 39% ee was found to be: $[\alpha]_D^{24}$ = +15.0 [c = 1.0, $CHCl_3$].

The barrier to racemisation of **10b** (E = SiMe$_3$) was established by monitoring the optical rotation of a solution of the amide (in chloroform, using a mercury source at 578 nm) in a jacketed cell at a constant temperature of 50 °C. A smooth first-order decay curve was obtained from which the rate constant for racemisation (k) was calculated using the curve-fitting application "Ultrafit" for the Macintosh.[9]

The barrier to racemisation of **10c** (E = SiMe$_3$) was established by resolving a small sample of racemic material using an analytical Chiralpak-AD HPLC column and monitoring by HPLC its racemisation on heating in hexane at 35 °C.[9]

***N*,*N*-Diisopropyl-2-(1-trimethylsilyl)ethyl-4,6-dimethylbenzamide 20.** *sec*-Butyllithium (0.8 ml, 1.4 M solution in hexanes, 1.1 eq.) was added to a solution of diisopropylamine (0.16 ml, 1.2 eq.) in THF (20 ml) at −78 °C under nitrogen. The solution was allowed to warm to 0 °C for 15 min, cooled to −78 °C, and *N*,*N*-diisopropyl-2,4-dimethyl-6-trimethylsilylmethylbenzamide **10b** (E = SiMe$_3$) (260 mg, 1 eq.) was added. The dark brown solution was stirred for 30 min at −78 °C, methyl iodide (0.15 ml) was added, and the mixture was allowed to warm to room temperature. Phosphoric acid (aqueous, 0.5 M) was added, and the mixture was extracted into EtOAc, dried over magnesium sulfate and concentrated. The crude product was purified by flash chromatography[28] to give the *title compound* (196 mg, 71%) as a waxy solid; ν_{max} (film)/cm^{-1} 2975, 2949, 2924, 2904, 2872, 1618, 1332; δ_H (300 MHz, $CDCl_3$) 6.78 (2 H, s), 3.73 (1 H, sept, J 6.5), 3.50 (1 H, sept, J 6.5), 2.27 (3 H, s), 2.24 (3 H, s), 2.01 (1 H, q, J 7.5), 1.59 (3 H, d, J 6.5), 1.57 (3 H, d, J 6.5), 1.29 (3 H, d, J 7.5), 1.12 (3 H, d, J 6.5), 1.11 (3 H, d, J 6.5), 0.09 (9 H, s); δ_C (75 MHz, $CDCl_3$) 170.3, 142.9, 137.0, 135.8, 133.4, 127.7, 126.3, 50.3, 45.7, 26.1, 21.9, 21.3, 20.9, 20.5, 20.3, 19.5, 19.3, −1.7; *m*/*z* (CI) 334 (MH^+, 100%). Found $(M + H)^+$ 334.2571. $C_{20}H_{36}NOSi$ requires M 334.2566.

***N*,*N*-Diisopropyl-2-cyclobutylidenemethyl-4,6-dimethylbenzamide 22.** In a similar way, *sec*-butyllithium (0.24 ml, 1.4 M solution in hexanes), diisopropylamine (0.06 ml), *N*,*N*-diisopropyl-2,4-dimethyl-6-trimethylsilylmethylbenzamide **10b** (E = $SiMe_3$) (79 mg) and cyclobutanone (0.04 ml, 2 eq.) gave a crude product which was purified by flash chromatography[28] to give the *title compound* (68 mg, 92%) as an oil; ν_{max} (film)/cm^{-1} 2976, 2946, 2899, 2862, 1616, 1330; δ_H (300 MHz, $CDCl_3$) 6.93 (1 H, s), 6.84 (1 H, s), 6.10 (1 H, quintet, *J* 2.2), 3.62 (1 H, sept, *J* 6.5), 3.51 (1 H, sept, *J* 6.5), 3.1 (1 H, m), 2.9 (2 H, m), 2.8 (1 H, m), 2.31 (3 H, s), 2.26 (3 H, s), 2.1 (2 H, m), 1.63 (3 H, d, *J* 6.5), 1.61 (3 H, d, *J* 6.5), 1.51 (3 H, d, *J* 7.5); δ_C (75 MHz, $CDCl_3$) 170.3, 145.3, 136.7, 134.2, 133.5, 133.3, 128.4, 124.5, 118.2, 50.8, 45.8, 32.6, 32.6, 21.3, 21.0, 20.55, 20.5, 20.4, 18.8, 18.1.

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