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Development of chiral heteroleptic magnesium amides; asymmetric deprotonations mediated by 6-membered metallocyclic amidomagnesium naphtholates

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Development of chiral heteroleptic magnesium amides; asymmetric deprotonations mediated by 6-membered metallocyclic amidomagnesium naphtholates

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In memory of Professor Sandy McKillop – an inspiring organic chemist and educator of international impact.

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| ARTICLE INFO | ABSTRACT |
| Article history:  Received  Received in revised form  Accepted  Available online | A series of enantioenriched 6-membered metallocyclic amidomagnesium naphtholates were prepared and used to probe the structure-reactivity/selectivity relationships of heteroleptic magnesium base complexes within asymmetric deprotonation reactions. An effective complex was identified and applied within enantioselective enolisation processes, delivering good levels of enantioselectivity and also revealing key structural requirements for achieving such selectivity.  2014 Elsevier Ltd. All rights reserved. |
| Keywords:  Enantioselective deprotonation  Heteroleptic magnesium bases  Enolate  Asymmetric synthesis  Amidonaphtholate |

1. Introduction

Over recent years chiral magnesium amide complexes have been shown to be highly selective reagents for the asymmetric deprotonation of prochiral ketones.1-3 In particular, homoleptic magnesium bisamides have demonstrated very good levels of asymmetric efficiency.1a-e,g-i Additionally, the divalency of magnesium enables the exploration of heteroleptic complexes within enantioselective enolisation processes.1f In this regard, some initial investigations have been conducted with two classes of chiral heteroleptic base. Alkylmagnesium amides,1f comprising a chiral amide and achiral alkyl ligand, demonstrated that good levels of asymmetric induction may be obtained while using only half the quantity of parent amine relative to that required by the homochiral bisamide system. Additionally, it was shown that the key deprotonation event was mediated by the amide and not by the alkyl ligand.1f In the second heteroleptic base approach, chiral amidomagnesium phenolate complexes,1f revealed that replacement of the achiral spectator ligand can generate an unusual reactivity/selectivity profile: in this case, both a reversal in the sense of enantioselectivity was observed and, further, the maximum levels of asymmetric induction were achieved at the unusually high reaction temperature of 40 °C (Figure 1).1f



Inspired by the preliminary investigations with amidomagnesium alkoxides, we became intrigued by aminoalcohols which, when derivatised to the magnesium complex, would generate a conformationally rigid metallocycle that may deliver modified selectivity profiles and potentially enable effective asymmetric induction at more accessible reaction temperatures. Towards this end, we envisaged utilising a series of chiral aminonaphthols that could be expediently prepared following the diastereoselective Mannich processes detailed by the groups of Cimarelli and Gong.4 We anticipated that exposure to *n*-Bu2Mg5 would result in the formation of a 6-membered

**Fig. 1**. Structural development of amidomagnesium phenolates.

amidomagnesium naphtholate that could then be used to probe the effectiveness of such cyclic analogues (Figure 1).

1. Results and Discussion

Intially, we employed the synthetically flexible solvent-free procedure described by Cimarelli to prepare alkyl- and aryl-substituted aminonaphthols **3a-g**,4a,b and the convenient procedure of Gong to access the fluorinated derivative **3h**.4c Utilising (*R*)-1-phenylethylamine as the requisite chiral amine, alongside variation of the aldehyde component, provided a range of functionalised diastereomerically-enriched aminonaphthols after fractional recrystallisation (Table 1).

**Table 1**

Synthesis of aminonaphthols using the Cimarelli/Gong method4



|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Entry | R |  | Conv. (%)a | D.r. (*R*,*R*):(*S*,*R*)a | Yield (%)b |
| 1 | Ph | **3a** | 91 | 99:1 | 73 |
| 2 | 4-Me-C6H4 | **3b** | 67 | 85:15 | 32 |
| 3 | 4-MeO-C6H4 | **3c** | 59 | 83:17 | 20 |
| 4 | 4-Cl-C6H4 | **3d** | 86 | 98:2 | 63 |
| 5 | *c*-Hex | **3e** | 69 | 99:1 | 59 |
| 6 | *i*-Pr | **3f** | 57 | 79:21 | 27 |
| 7 | *n*-Pent | **3g** | 61 | 75:25 | 12 |
| 8c | CF3 | **3h** | 44d | 26:74 | 18e |

aDetermined by 1H NMR. bIsolated yield of (*R*,*R*)-diastereomer. cSee Experimental section for full details. dYield of diastereomeric mixture. eIsolated yield of (*S*,*R*)-diastereomer.

With these components in hand, we now required suitable conditions for the preparation of the corresponding amidomagnesium naphtholate complexes. Our previously disclosed system, **1**, required preparation at reflux in THF,1f however, 1H NMR analysis confirmed that simply stirring equimolar quantities of *n*-Bu2Mg and aminonaphthol at room temperature in THF was adequate to completely form the desired complex (Scheme 1).6



**Scheme 1.** Preparation of complexes **2a**-**2h** from aminonaphthols **3a**-**3h**.

With straightforward access to these novel complexes, we began to assess their ability to function as chiral base reagents. Utilising complex **2a** as a representative member of this class, we initially evaluated the impact of several Lewis basic additives, which revealed that DMPU was optimum for reactivity and selectivity at –78 °C, as had been observed with several preceding magnesium bases.1a-d,f-i Bearing in mind that base reagent **1** had demonstrated its greatest selectivity at the less conventional, and unexpected, reaction temperature of 40 °C,1f we next moved to establish the operating temperature for the new amidomagnesium naphtholate systems in benchmark asymmetric deprotonations of 4-*tert*-butylcyclohexanone **4a** (Table 2). From these results, it was apparent that this new base category did not display the unusual temperature/performance profile as shown by complex **1**. Indeed, **2a** exhibited reactivity that was much more analogous to magnesium bisamides and alkylmagnesium amides,1a-i where increasing the reaction temperature was generally detrimental to the levels of enantioselectivity observed within the asymmetric enolisation process (Entries 1-7). On the other hand, **2a** did display good levels of asymmetric induction at temperatures up to –20 °C, coupled with excellent reactivity between –60 and –20 °C (Entries 2-4). Accordingly, this establishes the first example of an amidomagnesium naphtholate displaying such enantioselectivity within an asymmetric deprotonation process, with an optimal efficiency balance conveniently achieved at the more accessible temperature of –40 °C (Entry 3).

**Table 2**

Temperature/performance profile of complex **2a**



|  |  |  |  |
| --- | --- | --- | --- |
| Entry | Temp. (°C) | Conv. (%)*a* | E.r. (*S*:*R*)*a* |
| 1 | –78 | 13 | 89:11 |
| 2 | –60 | 77 | 85:15 |
| 3 | –40 | 87 | 84:16 |
| 4 | –20 | 89 | 81:19 |
| 5 | 0 | 69 | 71:29 |
| 6 | 20 | 45 | 68:32 |
| 7 | 40 | 23 | 56:44 |

aDetermined by G. C. analysis.

Having developed reaction conditions that derive the best possible performance from complex **2a**, we focused our attention on appraising the remaining members of the set of amidomagnesium naphtholates, **2b-h**, within this benchmark reaction (Table 3). Based on that established to this stage, a reaction temperature of –40 °C was adopted throughout this extended base study.

**Table 3**

Evaluation of complexes **2a**-**h** under optimised conditions.



|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Entry | R |  | Conv. (%)*a* | E.r. (*S*:*R*)*a* |
| 1 | Ph | **2a** | 87 | 84:16 |
| 2 | 4-Me-C6H4 | **2b** | 87 | 84:16 |
| 3 | 4-MeO-C6H4 | **2c** | 84 | 85:15 |
| 4 | 4-Cl-C6H4 | **2d** | 85 | 83:17 |
| 5 | *c*-Hex | **2e** | 77 | 82:18 |
| 6 | *i*-Pr | **2f** | 84 | 83:17 |
| 7 | *n*-Pent | **2g** | 74 | 86:14 |
| 8 | CF3 | **2h** | 82 | 84:16 |

aDetermined by G. C. analysis.

In all cases, the overall performance of complexes **2a-h** were very similar, with selectivities at *c.a.* 84:16 (*S*:*R*) and reaction conversions generally above 80% (Entries 1-8). Since the range of R groups employed was diverse in stereoelectronic nature, these results seem to suggest that the stereocentre at this position has little effect on the overall reactivity and selectivity of the individual base species. In order to assess this hypothesis, we prepared the formaldehyde-derived aminonaphthol **3i** as well as the benzylamine-derived aminonaphthol **3j**, each lacking one of the stereocentres of **3a** (Figure 2). Subsequent application of the corresponding amidomagnesium naphtholate derivatives, **2i** and **2j**, within the benchmark asymmetric deprotonation reaction conversely demonstrated that the stereogenic centre at *a* is crucial for selectivity and that it is, in fact, the stereocentre at *b* that is significantly less influential. Indeed, the stereocentre at *b* serves only to bolster the selectivity very slightly and has little effect on the base reactivity (Figure 2). Accordingly, it does now appear that the stereocentre at *a*, while essential, is exceptionally tolerant of variations in the installed functionality.



**Fig. 2.** Selectivity and reactivity relevance of stereocentres *a* and *b*.

Considering the novel reactivity profile, relative to the preceding series of amidomagnesium phenolates,1f and the overall success of these new complexes within the benchmark enolisation reaction, we sought to ascertain their generality through application to a series of prochiral ketone substrates. Of the complexes surveyed in this study, **2a** was the most accessible, largely due to the highly diastereoselective Mannich reaction and efficient fractional recrystallisation employed in the synthesis of the parent compound **3a**.4a,b As such, **2a** was used to probe the applicability of this emerging chiral heteroleptic magnesium base category (Table 4).

**Table 4**

Enantioselective deprotonation of prochiral ketone substrates using complex **2a**.



|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Entry | R1 | R2 |  | Conv. (%)*a* | E.r. (*S*:*R*)*b* |
| 1 | H | *t*-Bu | **a** | 87 (80) | 84:16 |
| 2 | H | *n*-Pr | **b** | 90 (79) | 82:18 |
| 3 | H | Me | **c** | 87 (47) | 78:22 |
| 4 | H | Ph | **d** | 81 (74) | 74:26c |
| 5 | Me | Me | **e** | 56 (35) | 13:87 |

aDetermined by G.C. analysis; values in parentheses are isolated yields of products. bDetermined by G.C. analysis. cDetermined by HPLC analysis of the corresponding cyclohexenone; see the Experimental section.

Pleasingly, amidomagnesium naphtholate base **2a** performed effectively over the substrate range evaluated. Both 4-substituted and *cis*-2,6-disubstituted cyclohexanones were applicable at the conveniently accessed temperature of –40 °C, with comparable levels of selectivity being observed (Entries 1-5). Additionally, efficient deprotonation was achieved, with conversions being generally good (Entries 1-4) or more moderate when applied towards the sterically encumbered 2,6-disubstituted ketone (Entry 5). Based on the outcomes from this range of substrates, we believe that this new class of heteroleptic magnesium base has considerable potential for structural exploration and optimisation with a view to enhancing the reactivity and selectivity profile within asymmetric enolisation processes.

1. Conclusion

Using the diastereoselective Mannich reaction of Cimarelli and Gong, a series of enantiomerically-enriched aminonaphthols have been accessed and employed in the preparation of a series of chiral 6-membered metallocyclic amidomagnesium naphtholate complexes. These novel reagents were then used to survey the structural requirements and influences within this new category of chiral magnesium-centred base. Subsequently, this revealed the impact of both the various embedded substituents and, at least as importantly, the individual stereocentres on the selectivity within asymmetric deprotonations of prochiral ketone substrates. Further, good levels of selectivity and reaction efficiency were achieved at the more readily accessible and energy efficient1i reaction temperature of –40 °C. Investigations are now underway within our laboratory in order to further establish heteroleptic magnesium amides as competent and widely applicable bases in this arena.

1. Experimental section

4.1. General information.

All reagents and solvents were obtained from commercial suppliers and were used without further purification unless otherwise stated. Purification was carried out according to standard laboratory methods.7 Tetrahydrofuran and 1,4-dioxane were dried by heating to reflux over sodium wire, using benzophenone ketyl as an indicator, then distilled under nitrogen. Diethyl ether and petroleum ether 30-40 °C were used as obtained from suppliers without further purification. Di-*n*-butylmagnesium, *n*-Bu2Mg,5 obtained as a 1 M solution in heptane, was standardised using salicaldehyde phenylhydrazone as indicator.8 Aminonaphthols were dried by (i) placing under high vacuum for 18 h (if solid) or (ii) by heating to 100 °C under vacuum (0.1 mbar) using a Kugelrohr apparatus for 2 h, before being purged with, and stored under N2 over 4 Å molecular sieves (if liquid). 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) was dried by heating to reflux over calcium hydride and distilling under vacuum before being purged with and stored under N2 over 4 Å molecular sieves. Chlorotrimethylsilane was distilled under N2 and stored over 4 Å molecular sieves. 4-*t*-Butylcyclohexanone **4a** and 4-phenylcyclohexanone **4d** were recrystallised twice from dry hexane at 4 °C, purged with, and stored under, N2. 4-*n*-Propylcyclohexanone **4b**, 4-methylcyclohexanone **4c**, and *cis*-2,6-dimethylcyclohexanone **4e**, were dried by heating to reflux over calcium chloride and distilled under vacuum before being purged with and stored under N2 over 4 Å molecular sieves.

All deprotonation reactions were air sensitive and, as such, were carried out using flame dried Schlenk apparatus; purging refers to an evacuation/nitrogen refilling procedure carried out 3 times. 1H and 13C NMR spectra were recorded on a Bruker DPX 400 spectrometer at 400 MHz and 100 MHz, respectively. Chemical shifts are reported in ppm. Coupling constants are reported in Hz and refer to 3*J*H-H interactions unless otherwise specified. Note that CDCl3 is referenced at δ 7.26 and 77.16 ppm. FTIR spectra were obtained on a Perkin Elmer Spectrum One instrument. High Performance Liquid Chromatography was carried out on a Gilson Model 302 pump with a Milton Roy spectromonitor 3100 detector using: Chiracel OD column; 1 mL/min flow rate; and a 254 nm detector. Gas Chromatography was carried out using a Hewlett Packard 5890 Series 2 Gas Chromatograph and data was interpreted using Peaknet computer software. Optical rotation measurements were recorded using a Perkin Elmer 341 polarimeter, using a cell with a path length of 1 dm; concentrations are expressed in g/100 cm3. High resolution mass spectra were recorded on a Finnigan MAT 90XLT instrument at the EPSRC UK National Mass Spectrometry Facility at Swansea University (Wales). Thin layer chromatography was carried out using Camlab silica plates coated with indicator UV254. These were analysed using a Mineralight UVGL-25 lamp or developed using vanillin. Flash column chromatography was carried out using Prolabo silica gel (230-400 mesh).

4.2. Typical procedure for the synthesis of aminonaphthols 3a-g and 3i.

Using the procedure of Cimarelli,4a for example, synthesis of(*R*,*R*)-**3a**: A mixture of 2-naphthol (1 equiv., 5 mmol, 0.72 g), benzaldehyde (1.2 equiv., 6 mmol, 0.64 g) and (*R*)-1-phenylethylamine (1.05 equiv., 5.25 mmol, 0.64 g) was stirred at 60 °C under N2 for 8 h. After this time, the mixture was found to have solidified. After cooling to room temperature, the solid was dispersed with EtOH (50 mL) to afford a white crystalline solid. The solid was isolated by filtration and recrystallised twice from MeOH to provide the pure (*R*,*R*)-diastereomer, (*R*,*R*)-**3a**, as colourless crystals (1.29 g, 73%).

*4.2.1 1-((R)-Phenyl((R)-1-phenylethylamino)methyl)naphthalen-2-ol* ***(R,R)-3a***.4a Colourless crystals: M.Pt. 132-134 °C (MeOH). νmax (CH2Cl2): 3319, 2747, 1621, 1523 cm–1. 1H NMR (400 MHz, CDCl3) δ: 1.52 (d, 3H, *J* = 7.0 Hz), 2.31 (br s, 1H), 3.92 (q, 1H, *J* = 7.0 Hz), 5.47 (s, 1H), 7.18-7.76 (m, 16H), 13.65 (br s, 1H). [α]D20 (*R*,*R*): –220.0 (*c* 2.1, CHCl3); Lit. (*R*,*R*):4a –220.7 (*c* 2.1, CHCl3).

*4.2.2 1-((R)-(4-Methylphenyl)((R)-1-phenylethylamino)methyl)naphthalen-2-ol* ***(R,R)-3b***.4a 4.93 g, 32% (41.6 mmol reaction scale). Colourless crystals: M.Pt.: 112-114 °C (MeOH). νmax (CH2Cl2): 3319, 2742, 1621, 1517 cm–1. 1H NMR (400 MHz, CDCl3) δ: 1.51 (d, 3H, *J* = 7.0 Hz), 1.54 (br s, 1H), 2.25 (s, 3H), 3.90 (q, 1H, *J* = 7.0 Hz), 5.44 (s, 1H), 7.03-7.55 (m, 15H), 13.68 (br s, 1H). [α]D20 (*R*,*R*): –184.9 (*c* 3, CHCl3); Lit. (*R*,*R*):4a –191.9 (*c* 3.1, CHCl3).

*4.2.3 1-((R)-(4-Methoxyphenyl)((R)-1-phenylethylamino)methyl)naphthalen-2-ol* ***(R,R)-3c****.*4a 3.04 g, 20% (41.6 mmol reaction scale). Colourless crystals: M.Pt. 104-106 °C (MeOH). νmax (CH2Cl2): 3319, 2747, 1619, 1509 cm–1. 1H NMR (400 MHz, CDCl3) δ: 1.51 (d, 3H, *J* = 7.0 Hz), 2.27 (br s, 1H), 3.72 (s, 3H), 3.89 (q, 1H, *J* = 7.0 Hz), 5.43 (s, 1H), 6.74-7.75 (m, 15H), 13.71 (br s, 1H). [α]D20 (*R*,*R*): –188.6 (*c* 1.9, CHCl3); Lit. (*R*,*R*):4a –190.4 (*c* 1.9, CHCl3).

*4.2.4* *1-((R)-(4-Chlorophenyl)((R)-1-phenylethylamino)methyl)naphthalen-2-ol* ***(R,R)-3d****.*4a 10.11 g, 63% (41.6 mmol reaction scale). Colourless crystals: M.Pt. 122-124 °C (MeOH). νmax (CH2Cl2): 3319, 2747, 1621, 1520 cm–1. 1H NMR (400 MHz, CDCl3) δ: 1.52 (d, 3H, *J* = 7.0 Hz), 2.25 (br s, 1H), 3.90 (q, 1H, *J* = 7.0 Hz), 5.44 (s, 1H), 7.11-7.77 (m, 15H), 13.50 (br s, 1H). [α]D20 (*R*,*R*): –193.5 (*c* 3.5, CHCl3); Lit.4a (*R*,*R*): –192.0 (*c* 3.5, CHCl3).

*4.2.5 1-((R)-Cyclohexyl((R)-1-phenylethylamino)methyl)naphthalen-2-ol* ***(R,R)-3e***.4a 8.84 g, 59% (41.6 mmol reaction scale). Colourless crystals: M.Pt. 145-147 °C (MeOH). νmax (CH2Cl2): 3335, 2670, 1621, 1517 cm–1. 1H NMR (400 MHz, CDCl3) δ: 0.90-1.30 (m, 6H), 1.47 (d, 3H, *J* = 7.0 Hz), 1.53-1.90 (m, 5H), 2.32 (br s, 1H), 3.69 (q, 1H, *J* = 7.0 Hz), 4.17 (d, 1H, *J* = 6.0), 7.06-7.76 (m, 11H), 13.04 (br s, 1H). [α]D20 (*R*,*R*): –5.5 (*c* 2.1, CHCl3); Lit. (*R*,*R*):4a –5.93 (*c* 2.1, CHCl3).

*4.2.6 1-((R)-2-Methyl-1-((R)-1-phenylethylamino)propyl)naphthalen-2-ol* ***(R,R)-3f***.4a 3.36 g, 27% (41.6 mmol reaction scale). Colourless crystals: M.Pt. 117-119 °C (MeOH). νmax (CH2Cl2): 3335, 2747, 1621, 1517 cm–1. 1H NMR (400 MHz, CDCl3) δ: 0.75 (d, 3H, *J* = 7.0 Hz), 0.98 (d, 3H, *J* = 7.0 Hz), 1.49 (d, 3H, *J* = 6.5), 2.14-2.23 (m, 1H), 2.27 (br s, 1H), 3.70 (q, 1H, *J* = 7.0 Hz), 4.16 (d, 1H, *J* = 6.5 Hz), 7.08-7.76 (m, 11H), 13.09 (br s, 1H). [α]D20 (*R*,*R*): –11.6 (*c* 2, CHCl3); Lit. (*R*,*R*):4a –10.95 (*c* 2, CHCl3).

*4.2.7 1-((R)-1-((R)-1-Phenylethylamino)hexyl)naphthalen-2-ol* ***(R,R)-3g***. Following the typical procedure (4.2) on a 41.6 mmol scale, an oily diastereomeric mixture of **3g** was obtained (75:25 d.r.; *R*,*R*:*R*,*S*; 5.24 g, 36%). This was salted with saturated hydrochloric acid in ethereal solution and recrystallized from MeOH/MTBE. The hydrochloride salt (2.64 g) was neutralised with NaHCO3 resulting in the isolation of **(*R,R*)-3g** (1.8 g, 12%). Viscous oil. νmax (CH2Cl2): 3324, 2752, 1619, 1517 cm–1. 1H NMR (400 MHz, CDCl3) δ: 0.81 (t, 3H, *J* = 7.0 Hz), 1.08-1.41 (m, 6H), 1.48 (d, 3H, *J* = 7.0 Hz), 1.67-1.86 (m, 2H), 2.17 (br s, 1H), 3.74 (q, 1H, *J* = 7.0 Hz), 4.38 (dd, 1H, *J* = 5.0 Hz, 8.5 Hz), 7.10-7.78 (m, 11H), 13.10 (br s, 1H). 13C NMR (100 MHz, CDCl3) δ: 14.0, 22.5, 23.1, 25.7, 31.4, 34.9, 54.9, 55.5, 115.8, 119.8, 121.0, 122.2, 126.1, 126.6, 127.7, 128.7, 128.8, 128.9, 129.0, 132.7, 143.5, 156.5. [α]D20 (*R*,*R*): –5.9 (*c* 2, CHCl3). *m/z* [M+H+] for C24H30NO requires 348.2322, found 348.2325.

*4.2.8 (R)-1-((1-Phenylethylamino)methyl)naphthalen-2-ol* ***3i***.2.08 g, 54% (13.87 mmol reaction scale, with a reaction temperature of 65 °C). Colourless crystals. M.Pt. 67-69 °C (EtOAc/Hexane).νmax (CH2Cl2): 3302, 2802, 1619, 1520 cm–1.1H NMR (400 MHz, CDCl3) δ: 1.53 (d, 3H, *J* = 6.5 Hz), 3.92 (q, 1H, *J* = 6.5 Hz), 4.24 (d, 1H, *J* = 14.5 Hz), 4.34 (d, 1H, *J* = 14.5 Hz), 7.12-7.76 (m, 11H).13C NMR (100 MHz, CDCl3) δ: 23.4, 45.2, 57.7, 112.5, 119.6, 121.2, 121.3, 122.6, 126.4, 126.8, 127.9, 128.7, 129.0, 129.3, 132.5, 143.4, 157.1.[α]D20 (*R*,*R*): 43.6 (*c* 3.5, CHCl3).*m/z* [M+H+] for C19H20NO requires 278.1539, found 278.1539.

4.3. 1-((*S*)-2,2,2-Trifluoro-1-((*R*)-1-phenylethylamino)ethyl)naphthalen-2-ol (*S,R*)-3h.

Prepared following the procedure of Gong:4c Trifluoroacetaldehyde ethylhemiacetal (6.00 g, 41.64 mmol, 1.2 equiv.) was added to a solution of (*R*)-1-phenylethylamine (4.20 g, 34.7 mmol, 1.0 equiv.) in dry PhMe (40 mL). The mixture was stirred at room temperature for 15 min and then stirred at reflux for 2 h. After cooling, the solvent was evaporated under reduced pressure to afford a residue. A portion of the residue (3.49 g, 17.34 mmol) was dissolved in dry CH2Cl2 (50 mL) and 2-naphthol (2.50 g, 17.34 mmol, 1.0 equiv.) was added. The mixture was cooled to 0 °C and BF3.Et2O (2.46 g, 17.34 mmol, 1.0 equiv.) was added. The reaction mixture was then stirred overnight at room temperature before addition of H2O (40 mL). The mixture was then neutralized with sat. aq. NaHCO3 solution. The organic layer was separated and the aqueous layer was extracted with EtOAc (2x30 mL). The combined organic extracts were dried (MgSO4), filtered, and concentrated *in vacuo* to a residue that was purified by flash column chromatography eluting with EtOAc:Hexane (1:10-1:5) to provide the product as a mixture of diastereomers (2.64 g, 44%, 74:26 d.r. (*S*,*R*:*R*,*R*)). Crystallisation from MeOH yielded white crystals of 95% purity for (*S*,*R*)-**3h** as determined by 1H NMR (1.18 g, 20% yield). Further fractional recrystallisation from MeOH enriched the mixture to 97% purity (1.07 g, 18% yield).Colourless crystals: M.Pt. 114-116 °C (MeOH).νmax (CH2Cl2): 3324, 2929, 1621, 1523, 1185 cm–1. 1H NMR (400 MHz, CDCl3) δ: 1.56 (d, 3H, *J* = 7.0 Hz), 2.49 (br s, 1H), 3.76 (q, 1H, *J* = 7.0 Hz), 4.88 (q, 1H, 3*J*H-F = 7.5 Hz), 7.01-7.83 (m, 11H), 11.89 (br s, 1H).[α]D20 (*S*,*R*): –5.6 (*c* 1, CHCl3); Lit. (*S*,*R*):4c –2.3 (*c* 1, CHCl3).

**4.4 Preparation of (±)-1-(-Aminobenzyl)naphthalen-2-ol.**9

Prepared following the procedure of Betti:9 To a solution of 2-naphthol (1 equiv, 100 mmol, 14.4 g) in EtOH (95%, 20 mL) was added benzaldehyde (2 equiv, 21.2 g, 200 mmol) and saturated ammonia aq. solution (20 mL). The reaction mixture was stoppered and allowed to stand for 2 h at room temperature. The solution became red and warmed up spontaneously. The stopper was then removed and the excess ammonia allowed to escape. After 12 h the precipitate was removed by filtration and aq. HCl (20%, 120 mL) added. The mixture was then distilled to remove benzaldehyde. The remaining hydrochloride salt was suspended in water (45 mL) and stirred with aq. Na2CO3 (2 M, 240 mL) before extracting with EtOAc (4x90 mL). The combined organic extracts were dried (MgSO4), filtered, and concentrated *in vacuo* to afford the title compound as a white powder (15.89 g, 68%).

**4.5 Preparation of (*S*)-1-(-Aminobenzyl)naphthalen-2-ol.**9,10

Prepared following the procedure of Cardellicchio:11 A solution of L-tartaric acid (1 equiv, 38.1 mmol, 5.72 g) in 95% EtOH:MeOH (25 mL:13 mL) was added dropwise to a solution of (±)-1-(α-aminobenzyl)-2-naphthalen-2-ol (1 equiv, 38.1 mmol, 9.5 g) in EtOH (95%, 300 mL). The reaction mixture was slowly stirred for 6 h at room temperature. The formed tartarate salt was removed by filtration and then slurried in methanol (40 mL), dried *in vacuo*, and isolated as a white solid (6.51 g, 43% yield). The tartarate salt (5.48 g, 13.72 mmol) was suspended in water (55 mL) and aq. Na2CO3 (2 M, 55 mL) was added. The mixture was stirred for 45 min then extracted with Et2O (4 x 90 mL). The combined organic extracts were dried (MgSO4), filtered, and concentrated *in vacuo* to afford the title compound as a white solid (2.90 g, 61% based on the maximum possible yield of the (*S*)-isomer). Amorphous white powder. M.Pt. 110-113 °C (Et2O). νmax (CH2Cl2): 3384, 2830, 1621, 1520 cm–1. 1H NMR (400 MHz, CDCl3) δ: 2.38 (br s, 2H), 6.18 (s, 1H), 7.17-7.75 (m, 11H), 13.07 (br s, 1H). [α]D20 (*R*,*R*): +55.7 (*c* 4.4, C6H6). Lit. (*S*):10 +58.84 (*c* 5, C6H6).

**4.6 Preparation of 1-((*S*)-Phenyl(phenylmethylamino)methyl)naphthalen-2-ol (*S*)-3j.**11

Prepared following the procedure of Cardellicchio:11 A solution of benzaldehyde (1 equiv, 11.63 mmol, 1.23 g) in EtOH (95%, 19 mL) was added dropwise to a solution of (*S*)-1-(a-aminobenzyl)naphthalen-2-ol (1 equiv, 11.63 mmol, 2.90 g) and the reaction mixture stirred overnight. The precipitate was removed by filtration and dried under high vacuum giving a white solid (3.19 g, 81% yield). The solid was suspended in PhMe (80 mL) and hydrogenated using palladium on carbon (10%) in a Parr hydrogenator under an atmosphere of H2 (45 psi). The crude product was filtered through a plug of celite and recrystallised from EtOAc/hexane to afford the title compound (2.66 g, 89% yield). The enantiomeric excess was determined by chiral HPLC to be 98% (*S*). Colourless crystals. M.Pt. 109-112 °C (EtOAc/Hexane). νmax (CH2Cl2): 3324, 2742, 1621, 1520 cm–1. 1H NMR (400 MHz, CDCl3) δ: 2.34 (br s, 1H), 3.87 (d, 1H, *J* = 13.0 Hz), 4.09 (d, 1H, *J* = 13.0 Hz), 5.82 (s, 1H), 7.24-7.80 (m, 16H), 13.57 (br s, 1H). 13C NMR (100 MHz, CDCl3) δ: 52.9, 63.0, 113.2, 120.3, 121.4, 122.7, 126.7, 127.8, 128.0, 128.3, 128.8, 129.0, 129.1, 129.2, 129.3, 130.1, 132.9, 138.1, 141.5, 157.0. HPLC (Chiracel OD, 10% *i*-PrOH/Hexane, flow rate 1 ml/min, 254 nm detector): tR(*S*) = 7.85 min, tR(*R*) = 9.38 min. [α]D20 (*S*): –206.1 (*c* 1, C6H6), Lit. (*S*):11 –208 (*c* 1, C6H6).

**4.7. Typical procedure for the asymmetric deprotonation of prochiral ketones.**

For example, Table 4, Entry 1: A flame-dried Schlenk tube was cooled, purged with N2 (x 3), and charged with *n*-Bu2Mg (1 M in heptane, 1 equiv., 1 mmol, 1 mL). The heptane was then removed *in vacuo* to give a white solid. A solution of aminonaphthol **3a** (1 equiv., 1 mmol, 353 mg) in dry THF (10 mL) was added and the mixture was stirred for 1 h at room temperature. The mixture was then cooled to –40 °C before the addition of DMPU (0.5 equiv., 0.5 mmol, 60 μL) and Me3SiCl (4 equiv., 4 mmol, 0.5 mL). The mixture was stirred for 20 min before the addition of 4-*tert*-butylcyclohexanone, **4a** (0.8 equiv., 0.8 mmol, 123 mg) as a solution in THF (2 mL) over 1 h *via* syringe pump. The reaction mixture was then stirred at –40 °C under N2 for 18 h before being quenched with sat. aq. NaHCO3 solution (10 mL). The mixture was allowed to warm to room temperature before being extracted with Et2O (2 x 15 mL). The combined organic extracts were dried (MgSO4) and a representative sample was analysed by achiral G.C. to obtain the ketone to enol silane conversion (87%). The solution was then filtered and concentrated *in vacuo* to afford a residue that was purified by column chromatography eluting (1% Et2O/petroleum ether 30-40 °C) to afford **5a** as a colourless oil (145 mg, 80%). A representative sample of the product was analysed by chiral G.C. to obtain the enantiomeric ratio (84:16 (*S*:*R*)).

Achiral G.C. analysis: (i) CP SIL-19CB column; (ii) carrier gas, H2 (80 kPa): (i) injector/detector temperature, 200 °C; (ii) initial oven temperature, 45 °C; (iii) temperature gradient, 20 °C min–1; (iv) final oven temperature, 190 °C; and (v) detection method, FID.

Chiral G.C. analysis: (i) CP Chirasil-DEX CB column; (ii) carrier gas, H2 (80 kPa): (i) injector/detector temperature, 200 °C; (ii) initial oven temperature, 70 °C; (iii) temperature gradient, 1.5 °C min–1; (iv) final oven temperature, 120 °C; and (v) detection method, FID.

*4.7.1 4-tert-Butyl-1-trimethylsilyloxy-1-cyclohexene* ***5a****.*12-16 νmax (KBr): 1674 cm–1. 1H NMR (400 MHz, CDCl3) δ: 0.19 (s, 9H), 0.90 (s, 9H), 1.21-1.29 (m, 2H), 1.78-1.85 (m, 2H), 1.98-2.09 (m, 3H), 4.84-4.86 (m, 1H). 13C NMR (100 MHz, CDCl3) δ: 0.13, 24.7, 26.9, 27.0, 30.7, 31.8, 43.8, 103.6, 149.9. Achiral G.C. analysis: tR (**4a**) = 5.27 min, tR (**5a**) = 5.49 min. Chiral G.C. analysis: tR ((*S*)-**5a**) = 25.67 min, tR ((*R*)-**5a**) = 25.95 min.

*4.7.2 4-n-Propyl-1-trimethylsilyloxy-1-cyclohexene* ***5b***.12νmax (KBr): 1671 cm–1. 1H NMR (400 MHz, CDCl3) δ: 0.19 (s, 9H), 0.90 (t, 3H, *J* = 7.1 Hz), 1.20-1.39 (m, 5H), 1.40-1.51 (m, 1H), 1.61-1.79 (m, 2H), 1.92-2.00 (m, 1H), 2.01-2.14 (m, 2H), 4.81-4.85 (m, 1H). 13C NMR (100 MHz, CDCl3) δ: 0.43, 14.5, 20.4, 29.4, 29.8, 30.5, 33.1, 38.4, 103.7, 150.3.Achiral G.C. analysis: tR (**4b**) = 4.75 min, tR (**5b**) = 5.03 min.Chiral G.C. analysis: tR ((*S*)-**5b**) = 20.53 min, tR ((*R*)-**5b**) = 20.85 min.

*4.7.3 4-Methyl-1-trimethylsilyloxy-1-cyclohexene****5c***.12-16νmax (CH2Cl2): 1668 cm–1. 1H NMR (400 MHz, CDCl3) δ: 0.18 (s, 9H), 0.95 (d, 3H, *J* = 6.3 Hz), 1.25-1.37 (m, 2H), 1.57-1.73 (m, 3H), 1.92-2.15 (m, 2H), 4.81-4.85 (m, 1H). 13C NMR (100 MHz, CDCl3) δ: 0.40, 21.3, 28.4, 29.7, 31.4, 32.4, 103.7, 150.2.Achiral G.C. analysis: tR (**4c**) = 3.07 min, tR (**5c**) = 3.57 min. Chiral G.C. analysis: tR ((*S*)-**5c**) = 9.23 min, tR ((*R*)-**5c**) = 9.40 min.

*4.7.4 4-Phenyl-1-trimethylsilyloxy-1-cyclohexene* **5d**.12,13,16 νmax (CH2Cl2): 1670 cm–1. 1H NMR (400 MHz, CDCl3) δ: 0.24 (s, 9H), 1.81-2.01 (m, 2H), 2.03-2.13 (m, 1H), 2.15-2.36 (m, 3H), 2.72-2.82 (m, 1H), 4.95-4.98 (m, 1H), 7.23-7.37 (m, 5H). 13C NMR (100 MHz, CDCl3) δ: 0.15, 29.6, 29.9, 31.6, 39.6, 103.3, 125.6, 126.5, 127.9, 146.3, 149.9. Achiral G.C. analysis: tR (**4d**) = 7.83 min, tR (**5d**) = 7.93 min. [α]D20: –22.1 (*c* 2.3, CHCl3) corresponding to 74:26 e.r. (*S*:*R*). Lit. [α]D20 (*S*):12 ­­–33.5 (*c* 2.3, CHCl3, 87:13 e.r. (*S*:*R*)).

The enantiomeric ratio was further confirmed by HPLC analysis of the corresponding cyclohexenone obtained *via* palladium-catalysed oxidation (Saegusa-Ito) of **5d** in the following manner:

**(*S*)-4-Phenylcyclohexenone**17

To a stirred solution of **5d** (120 mg, 0.49 mmol, 1.0 equiv) in dry MeCN (2 mL) was added Pd(OAc)2 (55 mg, 0.24 mmol, 0.5 equiv) and 1,4-benzoquinone (26 mg, 0.24 mmol, 0.5 equiv) under N2. The reaction was stirred for 3 h at room temperature then concentrated *in vacuo* to give a residue that was purified by flash chromatography (10% Et2O:petrol 30-40 °C) to afford the title compound as a colourless solid (60 mg, 72% yield). νmax (CH2Cl2): 2934, 1679, 1492 cm–1. 1H NMR (400 MHz, CDCl3) δ: 2.02-2.11 (m, 1H), 2.34-2.42 (m, 1H), 2.45-2.60 (m, 2H), 3.72-3.77 (m, 1H), 6.18 (ddd, 1H, *J* = 10.0, 2.5, 0.5 Hz), 7.00 (ddd, 1H, *J* = 10.0, 3.0, 1.5 Hz), 7.22-7.39 (m, 5H). [α]D20: +152.8 (*c* 1.0, CHCl3). Lit. [α]D20 (*S*):17 +195.0 (*c* 1.0, C6H6). HPLC (Chiracel AD, 10% EtOH/Isohexane, flow rate 1 ml/min, 254 nm detector): tR(*S*) = 7.40 min, tR(*R*) = 7.96 min. (74:26 e.r (*S*:*R*)).

*4.7.5 2,6-Dimethyl-1-trimethylsilyloxy-1-cyclohexene* ***5e***.14,18 νmax (CH2Cl2): 1679 cm–1. 1H NMR (400 MHz, CDCl3) δ: 0.18 (s, 9H), 1.05 (d, 3H, *J* = 6.9 Hz), 1.35-1.43 (m, 2H), 1.56 (s, 3H), 1.57-1.67 (m, 1H), 1.74-1.82 (m, 1H), 1.94 (t, 2H, *J* = 6.1 Hz), 1.98-2.19 (m, 1H). 13C NMR (100 MHz, CDCl3) δ: 0.72, 16.9, 19.0, 20.5, 30.8, 32.3, 34.1, 112.1, 147.1.Achiral G.C. analysis: tR (**4e**) = 3.23 min, tR (**5e**) = 3.88 min.Chiral G.C. analysis: tR ((*S*)-**5e**) = 9.96 min, tR ((*R*)-**5e**) = 9.67 min.

Acknowledgments

We would like to thank the EPSRC for studentship support (E.L.C. and M.P.) and Organon Research Scotland for additional funding. Mass spectrometry data were acquired at the EPSRC UK National Mass Spectrometry Facility at Swansea University.

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