

## Chiral lithium amide mediated asymmetric synthesis of 3-aryl-3,4-dihydroisocoumarins

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### Abstract

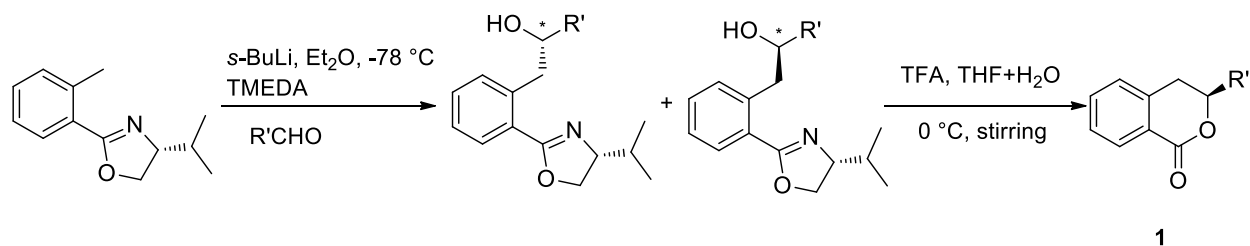
An asymmetric synthesis of 3-aryl-3,4-dihydroisocoumarins using the reaction of laterally lithiated 4,4-dimethyl-2-(*o*-tolyl)oxazoline with aromatic aldehydes, in the presence of an external chiral ligand, gave products with enantiomeric excess (ee) in the range of 60-70%.

**Keywords:** Dihydroisocoumarins, oxazoline, lateral lithiations, sparteine, (*S*)-2-(pyrrolidinomethyl)pyrrolidine

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### Introduction

The 3-aryl-3,4-dihydroisocoumarins **1** constitute a class of natural products, which exhibit a wide range of pharmacological activities such as antifungal, antiulcer, antileukemic, antiallergic, differentiation-inducing and antimalarial activities.<sup>1</sup> In the past two decades, asymmetric syntheses of 3-substituted 3,4-dihydroisocoumarins, having different functionalities, have been achieved by using several different types of key reactions with moderate to high enantioselectivity.<sup>2-4</sup> In the majority of these approaches the chiral moiety is present in the substrate and needs removal after reaction.<sup>2a-g</sup> Recently, Kurosaki *et al.* reported the stereoselective addition of laterally lithiated (*S*)-4-isopropyl-2-(*o*-tolyl)oxazoline to aldehydes followed by diastereomer-selective lactonization and obtained **1** with good to high optical activity (Scheme 1).<sup>3</sup>



Scheme 1

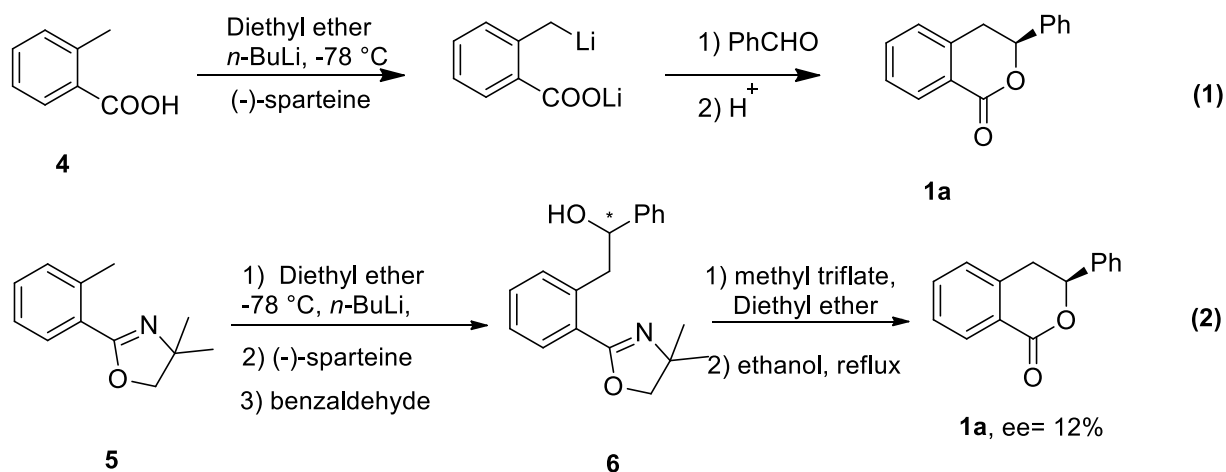
Another parallel approach for the asymmetric synthesis of **1** is the use of chiral lithium amide as base for lateral lithiation of toluic acid derivatives, which could first generate a carbanion and then serve as a chiral complexing agent, thus leading to the possibility of asymmetric induction in addition reactions.<sup>4</sup> Although attractive, since the process is facile and the ligand can be recovered and re-used, this approach has received little attention.



Staunton has reported the asymmetric synthesis of mellein methyl ether **2** using a chiral amide base for lateral lithiation of *o*-toluic acid followed by addition of benzaldehyde to obtain the product with moderate (53%) enantioselectivity.<sup>4</sup> Recently, Liu applied successfully this methodology for the asymmetric synthesis of protoberberine alkaloid **3** with ee 77%, using (-)-sparteine as external chiral ligand.<sup>5</sup> In the present paper, we report the asymmetric synthesis of 3-aryl-3,4-dihydroisocoumarins **1** using (*S*)-2-(1-pyrrolidinylmethyl)pyrrolidine **11** as external chiral ligand.

## Results and Discussion

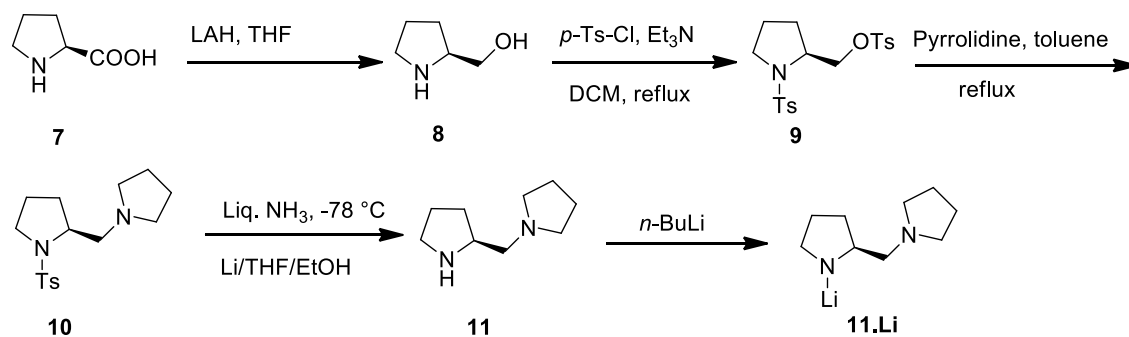
Initially we investigated the reaction of *o*-toluic acid **4** with benzaldehyde using *n*-BuLi as base and (-)-sparteine as external chiral ligand at -78 °C (Scheme 2; Equation 1). This resulted in the formation of the desired product **1a** in 37% yield, however, without any appreciable enantiomeric excess.



### Scheme 2

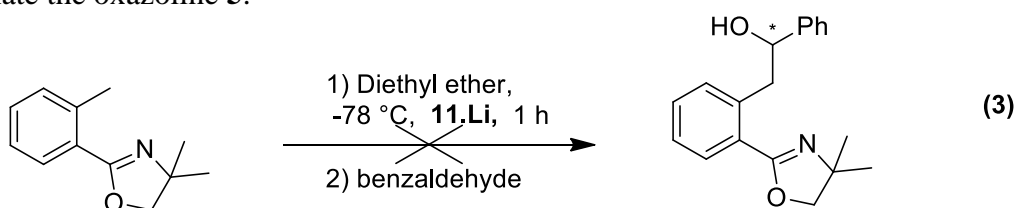
Next, we used 4,4-dimethyl-2-(*o*-tolyl)oxazoline **5** as the substrate and (-)-sparteine as the chiral ligand. After quenching the reaction with benzaldehyde, the intermediate alcohol **6** was lactonised with methyl triflate<sup>7</sup> to afford **1a** in 51% yield with an enantiomeric excess (ee) of 12% (Scheme 2; Equation 2). Reducing the reaction temperature from -78 °C to -100 °C did not increase the enantiomeric excess. We believe that the lower enantioselectivity with sparteine is indicative of low energy differentiated diastereomeric transition states at the time of addition of the aldehyde.

Assuming that the use of a chiral lithium amide as base in the above reaction may have a strong influence on the enantio-face differentiation during the addition of lithiated species to the aldehydes, we decided to use the lithium amide derived from (*S*)-2-(1-pyrrolidinylmethyl)pyrrolidine **11**, for the deprotonation of **5**. Eleveld and Hogeveen<sup>8</sup> used this ligand for the enantioselective addition of organolithiums to aldehydes and obtained addition products with ee values in the range of 70-90%. For the present work, (*S*)-2-(1-pyrrolidinylmethyl)pyrrolidine **11** was prepared by the route shown in Scheme 3.<sup>9</sup>



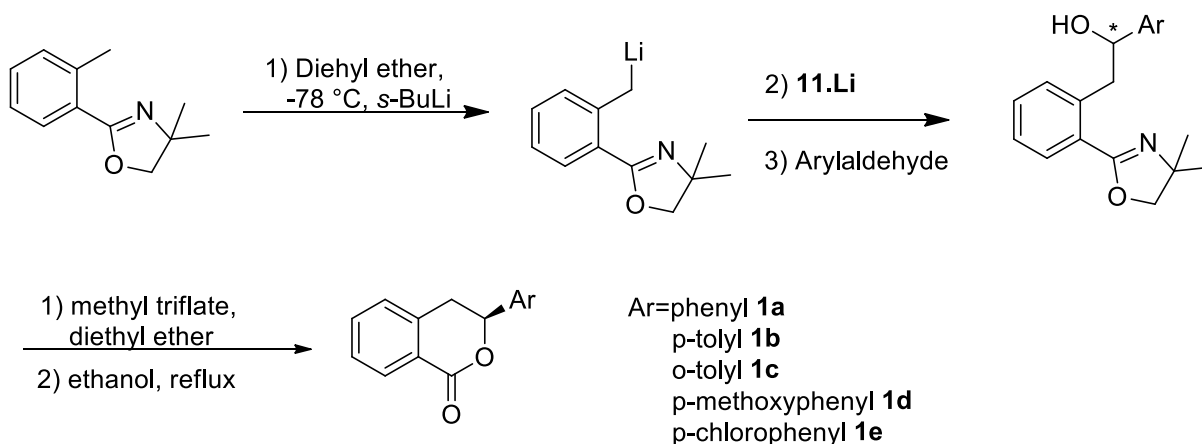
### Scheme 3

Use of **11.Li** as base for deprotonation of oxazoline **5** led to the isolation of starting material only (Equation 3), presumably because the lithium amide was not sufficiently basic to laterally deprotonate the oxazoline **5**.



#### Scheme 4

Accordingly, the oxazoline was first deprotonated with *s*-BuLi followed by the addition of **11.Li** at  $-78\text{ }^{\circ}\text{C}$ . After stirring the reaction mixture for one hour at  $-78\text{ }^{\circ}\text{C}$ , the lithiated species was reacted with benzaldehyde and the corresponding alcohol was isolated in 61% yield by column chromatography. Hydrolysis of the oxazoline moiety with methyl triflate,<sup>7</sup> under mild conditions, afforded **1a** in 58% yield (two steps) with a 53% ee.



#### Scheme 5

By decreasing the reaction temperature to  $-100\text{ }^{\circ}\text{C}$ , the product ee was raised to 68%. Interestingly, the absolute configuration of compound **1a** is the same as that obtained by Kurosaki *et al.* by the lateral lithiation of (*S*)-4-isopropyl-2-(*o*-tolyl)oxazoline. Results with other aldehydes are given in Table 1.

**Table 1**

Entry	Solvent	Ligand	1 <sup>a</sup>	Temp.	Yield	ee (%)	[ $\alpha$ ] <sup>25</sup> , Conf. <sup>e</sup>
1.	Et <sub>2</sub> O	(-)-sparteine	<b>1a</b>	-78 °C	63	12 <sup>c</sup>	-19, ( <i>S</i> )
2.	Et <sub>2</sub> O	<b>11</b>	<b>1a</b>	-78 °C	58	53 <sup>c</sup>	-83.7, ( <i>S</i> )
3.	Et <sub>2</sub> O	-	<b>1a</b>	-100 °C	54	68 <sup>c</sup>	-108, ( <i>S</i> )
4.	Et <sub>2</sub> O	-	<b>1b</b>	-100 °C	57	62 <sup>c</sup>	-82.8, ( <i>S</i> )
5.	Et <sub>2</sub> O	-	<b>1c</b>	-100 °C	60	67 <sup>c</sup>	-84.8, ( <i>S</i> )
6.	Et <sub>2</sub> O	-	<b>1d</b>	-100 °C	46	56 <sup>d</sup>	-61.1, ( <i>S</i> )
7.	Et <sub>2</sub> O	-	<b>1e</b>	-100 °C	49	65 <sup>d</sup>	-81.1, ( <i>S</i> )

<sup>a</sup>Analytical data for all these compounds are in good agreement with literature values (Ref. 3).

<sup>b</sup>isolated yield.

<sup>c</sup>ee determined from HPLC analysis.

<sup>d</sup>ee determined by the comparison of optical rotation with literature values.

<sup>e</sup>absolute configuration determined by sign of rotation.

While contemplating the inferior results with (-)-sparteine in comparison to chiral lithium amides, we reasoned that the tertiary nitrogen in the former could not bind as tightly with lithium compared to the secondary nitrogen of **11**, and hence gave a lower enantio-induction.<sup>10</sup>

## Conclusions

In conclusion, the external chiral ligand methodology has given the products with modest ee values, however, the variations in ee with change in aldehyde cannot be easily rationalized. It is likely that both electronic and steric effects in the aldehyde substituents have key roles to play in these reactions. We have also developed an effective method for the hydrolysis of the oxazoline moiety using methyl triflate for the synthesis of 3-aryl-3,4-dihydroisocoumarins.

## Experimental Section

**General.** All starting materials were purified by standard methods before use. All yields refer to isolated products after purification. Products were characterized by comparison with authentic samples and by spectroscopic data (IR, <sup>1</sup>H NMR and mass spectroscopy). <sup>1</sup>H NMR spectra were recorded at 300 MHz. The spectra were measured in CDCl<sub>3</sub> unless otherwise stated, relative to tetramethylsilane (TMS) (0.00 ppm).

**4,4-Dimethyl-2-(*o*-tolyl)oxazoline (5).** A solution of *o*-toluoyl chloride (7.9 g, 4.90 mL, 38 mmol) in DCM (25 mL) was added drop-wise to a mixed solution of 2-amino-2-methylpropanol (3.1 g, 3.4 mL, 34 mmol) and triethylamine (4.04 g, 5.6 mL, 40 mmol) in dry DCM (50 mL) at 0 °C. After being stirred for 1 h, saturated aqueous NaHCO<sub>3</sub> was added, the organic layer was separated and the aqueous layer extracted with dichloromethane. The combined organic extract was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and evaporated. The residual solid was dried in vacuo to give the intermediate *o*-toluamide which was used as such in the next step. Thionyl chloride (13.2 g, 21.5 mL, 295 mmol) was added dropwise to the amide at 0 °C and the mixture was stirred at room temperature for 4 h. The solution was then poured into a 1L beaker containing crushed ice and excess sodium carbonate. The aqueous layer was extracted with chloroform (3x20 mL), the combined organic layer washed with brine and dried over sodium sulphate. After removal of solvent the residual oil was purified by vacuum distillation to give oxazoline **5** as a colourless liquid. bp 78-80 °C/0.2 mm (lit<sup>6</sup> bp 90 °C/1.6mm). IR (CHCl<sub>3</sub>): 1644 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 1.34 (s, 6H), 2.53 (s, 3H), 4.32-4.5 (m, 2H), 7.10-7.35 (m, 3H), 7.73 (d, 1H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 22.52, 58.12, 73.02, 125.36, 127.22, 129.68, 129.87, 130.13, 138.35, 163.45.

**(S)-2-(Pyrrolidinomethyl)pyrrolidine (11).** The title compound was prepared in 65% yield by the reported procedure.<sup>9</sup>

**Preparation of a solution of the lithiated amide of 11 (11.Li).** Into a flame dried two necked round bottom flask equipped with a septum cap and a stir bar, a solution of **11** (1 mmol) in dry diethyl ether (4 mL) was placed under nitrogen. The solution was cooled to -78 °C and *s*-BuLi (1.1 mmol) was added via syringe in a dropwise manner with constant stirring.

#### **Lateral lithiation in the presence of chiral ligands. General procedure-1**

A solution of compound **4** or **5** (1 mmol) in dry diethyl ether (5 mL), under a nitrogen atmosphere, was cooled to the specified temperature and *s*-BuLi (2.2 mmol for **4** and 1.2 mmol for **5**) was added to it in a dropwise manner, giving a red coloured solution. After 30 min stirring, a solution of (-)-sparteine (1 mmol) in dry diethyl ether (entry 1, table 1) {or freshly prepared lithium amide **11.Li** (1mmol); entry 2-7, table-1} was added and the reaction was stirred continuously at the given temperature. After 30 min, an appropriate aldehyde (1.3 mmol), dissolved in diethyl ether (10 mL), was added and the resulting solution stirred for 1 h. Then, the reaction was allowed to attain ambient temperature and quenched with water. The aqueous layer was extracted with ether and the combined organic layer was washed with brine and dried over sodium sulphate. The solvent was evaporated and the residue was purified through column chromatography to obtain intermediate alcohol **6**.

#### **Hydrolysis of the oxazoline moiety of compound 6 using methyl triflate and subsequent cyclization to dihydroisocoumarins. General procedure-2**

To a flame dried two necked round bottom flask equipped with a septum cap and a stir bar, a solution of alcohol **6** in dry diethyl ether was placed under nitrogen. Methyl triflate (1.1 equiv)

was added dropwise to this solution and stirred for 2-3 h. During this period an oily layer was formed at the bottom of the flask. The progress of the reaction was monitored with TLC. After the disappearance of the starting material, the diethyl ether was removed and the residue was dissolved in 95% ethanol and refluxed for 3 h. After the completion of the reaction, the ethanol was evaporated under vacuum, the residue was taken into chloroform and washed with water, brine and dried over sodium sulphate. The solvent was evaporated and the crude product was purified through column chromatography. The product ee was determined through HPLC analysis. Analytical data for all these compounds (**1a-e**) are in good agreement with literature values.<sup>3</sup>

**(S)-3-Phenyl-3,4-dihydroisocoumarin (1a).** Reaction of compound **5** with benzaldehyde at -100 °C using **11.Li** as chiral ligand, according to general procedure 1, gave the intermediate alcohol which was further cyclized by general procedure 2 to obtain 3-(phenyl)-3,4-dihydroisocoumarin (**1a**, 54%). CSP HPLC analysis of the product using a CHIRALPAK **AS-H** column {20% isopropanol/hexane, 0.5 mL/minute flow rate} showed 68% ee;  $[\alpha]_{\text{D}} = -108$  (c 0.90, MeOH) (lit.<sup>3</sup>  $[\alpha]_{\text{D}} = -158$  (c 0.99, MeOH, 99% ee). Mp 74-76 °C (lit.<sup>3</sup> Mp 76.5-77 °C). IR (CHCl<sub>3</sub>): 1719, 1604 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  3.05 (dd,  $J=3.2$ , 12 Hz, 1H), 3.26 (dd,  $J=12$ , 16.5 Hz, 1H), 5.45 (dd,  $J=3.2$ , 12 Hz, 1H), 7.29 (d,  $J=7.4$  Hz, 1H) 7.30-7.55 (m, 6H), 7.57 (dt,  $J=1.2$ , 7.4, 1H), 8.16 (dd,  $J=1.2$ , 7.6 Hz, 1H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  35.54, 79.83, 125.01, 125.96, 127.21, 127.67, 128.51, 128.53, 130.23, 133.74, 138.33, 138.75, 165.11.

**(S)-3-(*p*-Tolyl)-3,4-dihydroisocoumarin (1b).** Reaction of compound **5** with *p*-tolualdehyde at -100 °C using **11.Li** as chiral ligand, according to general procedure 1, gave the intermediate alcohol which was further cyclized by general procedure 2 to obtain 3-(*p*-tolyl)-3,4-dihydroisocoumarin (**1b**, 57%). CSP HPLC analysis of the product using a CHIRALPAK **AS-H** column {20% isopropanol/hexane, 0.5 mL/minute flow rate} showed 62% ee; rotation  $[\alpha]_{\text{D}} = -82.8$  (c 0.8, MeOH) {lit.<sup>3</sup>  $[\alpha]_{\text{D}} = -124$  (c 1.02, MeOH, 98% ee)}. Mp 96-98 °C (lit.<sup>3</sup> Mp 98-98.5 °C). IR (CHCl<sub>3</sub>): 1715, 1604 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  2.35 (s, 3H), 3.09 (dd,  $J=3.2$ , 12.0 Hz, 1H), 3.31 (dd,  $J=12.0$ , 16.5 Hz, 1H), 5.51 (dd,  $J=3.2$ , 12.0 Hz, 1H), 7.25 (d,  $J=8.0$  Hz, 2H), 7.26-7.58 (m, 5H), 8.12 (d,  $J=7.6$  Hz, 1H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  20.97, 37.12, 81.27, 124.87, 124.24, 127.69, 127.93, 130.38, 130.20, 133.67, 135.43, 138.39, 138.16, 166.08.

**(S)-3-(*o*-Tolyl)-3,4-dihydroisocoumarin (1c).** Reaction of compound **5** with *o*-tolualdehyde at -100 °C using **11.Li** as chiral ligand, according to general procedure 1, gave the intermediate alcohol which was further cyclized by general procedure-2 to obtain 3-(*o*-tolyl)-3,4-dihydroisocoumarin (**1c**, 60%). CSP HPLC analysis of the product using a CHIRALPAK **AS-H** column {20% isopropanol/hexane, 0.5 mL/minute flow rate} showed 67% ee; rotation  $[\alpha]_{\text{D}} = -84.8$  (c 0.6, MeOH). Mp 86-88 °C. IR (CHCl<sub>3</sub>): 1715, 1606 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  2.32 (s, 3H), 3.07 (dd,  $J=3.1$ , 15.8 Hz, 1H), 3.30 (dd, 11.5, 15.8 Hz, 1H), 5.51 (dd,  $J=3.1$ , 11.5 Hz, 1H), 7.20 (d,  $J=7.6$  Hz, 1H), 7.26-7.58 (m, 5H), 8.13 (d,  $J=7.5$  Hz, 1H). <sup>13</sup>C NMR (75 MHz,

CDCl<sub>3</sub>):  $\delta$  21.15, 35.48, 79.80, 125.01, 125.93, 127.19, 127.63, 129.14, 130.20, 133.67, 135.43, 138.28, 138.86, 165.18.

**(S)-3-(*p*-Methoxyphenyl)-3,4-dihydroisocoumarin (1d).** Reaction of compound **5** with *p*-methoxybenzaldehyde at -100 °C using **11.Li** as chiral ligand, according to general procedure 1, gave the intermediate alcohol which was further cyclized by general procedure 2 to obtain 3-(*p*-methoxyphenyl)-3,4-dihydroisocoumarin (**1d**, 46%). The enantiomeric excess was found to be 56% on the basis of rotation,  $[\alpha]_D -61.1$  (c 0.9, MeOH) {lit.<sup>3</sup>  $[\alpha]_D -93.8$  (c 1.02, MeOH, 86% ee)}. Mp 85-86 °C (lit.<sup>3</sup> Mp 84-86 °C). IR (CHCl<sub>3</sub>): 1717, 1612 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  3.09 (dd,  $J=3.0, 16.4$  Hz, 1H), 3.35 dd,  $J=12, 16.4$  Hz, 1H, 3.82 s, 3H, 5.50 dd,  $J=3.0, 12$  Hz, 1H, 6.93 d,  $J=8.7$  Hz, 2H, 7.28 d,  $J=7.5$  Hz, 1H, 7.40 (d,  $J=8.7$ Hz, 2H) 7.42 (t,  $J=7.5$  Hz, 1H), 7.56 (t,  $J=7.5$  Hz, 1H), 8.14 (d,  $J=7.5$  Hz, 1H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  35.37, 55.24, 79.71, 113.85, 124.98, 127.20, 127.48, 127.63, 130.18, 130.46, 133.68, 138.90, 159.62, 165.25.

**(S)-3-(*p*-Chlorophenyl)-3,4-dihydroisocoumarin (1e).** Reaction of compound **5** with *p*-chlorobenzaldehyde at -100 °C using **11.Li** as chiral ligand, according to general procedure 1, gave the intermediate alcohol which was further cyclized by general procedure 2 to obtain 3-(*p*-chlorophenyl)-3,4-dihydroisocoumarin (**1e**, 49%). The enantiomeric excess was found to be 65% on the basis of rotation,  $[\alpha]_D -81.1$  (MeOH) {lit.<sup>3</sup>  $[\alpha]_D -91.3$ (c 1.01, MeOH, 73% ee)}. Mp 73-74 °C (lit.<sup>3</sup> Mp 74-75 °C). IR (CHCl<sub>3</sub>): 1725, 1606 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  3.12 (dd,  $J=3.3, 16.4$  Hz, 1H), 3.30 (dd,  $J=11.8, 16.4$  Hz, 1H), 5.54 (dd,  $J=3.3, 11.8$  Hz, 1H), 7.29 (d,  $J=7.5$  Hz, 1H), 7.36-7.43 (m, 4H), 7.44 (t,  $J=7.5$  Hz, 1H), 7.58 (dt,  $J=1.3, 7.5$  Hz, 1H), 8.15 (d,  $J=7.5$  Hz, 1H) . <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  35.47, 79.04, 124.80, 127.20, 127.32, 127.83, 128.72, 130.28, 133.86, 134.28, 136.93, 138.42, 164.81.

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