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## A Novel Chiral Cyclopentadienyl Ligand Based on Ephedrine

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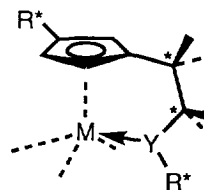
**Abstract:** natural (-)-(1*R*,2*S*)-ephedrine was used as a starting material for the preparation of a novel chiral cyclopentadienyl ligand in a three-step procedure. The new ligand contains a nitrogen atom suitable for chelation to a transition metal, as well as two stereogenic centres.

### Introduction:

The design of novel ligands as effective chiral auxiliaries in transition metal catalysed asymmetric conversions is a rapidly growing area of interest in synthetic chemistry.<sup>1</sup> Apart from the traditional phosphine-based systems, chirally-substituted cyclopentadienyl (Cp) ligands become increasingly important in this sense.<sup>2</sup> This is because Cp ligands can be used as complexing agents for almost any transition metal, as well as the enormous synthetic potential to modify this type of ligand. The initial strategy in the development of chiral Cp ligands was the introduction of sterically crowded substituents, like the menthyl group, by a single C-C bond to the Cp backbone.<sup>3</sup> Optical inductions in catalytic processes using these ligands were low, which was probably due to the dynamic nature of these ligands. Therefore, a further development was focused on the attachment of the chiral substituents to the Cp ring by more than one C-C bond, so-called annulated Cp's, in order to get a more rigid system.<sup>2</sup> Accordingly, high enantiomeric excesses were obtained during catalytic hydrogenations of olefins by titanocene derivatives.

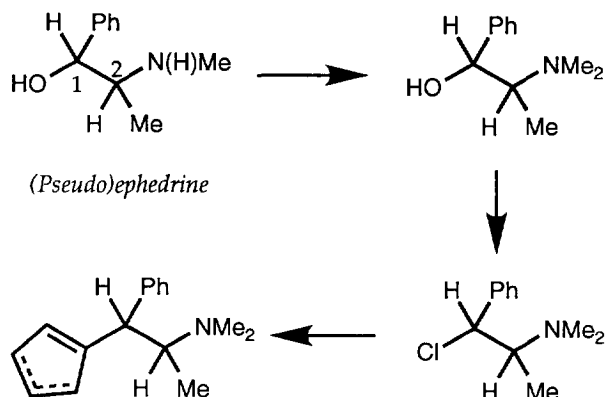
We pursue here another strategy to obtain rigidly metal-coordinated chiral Cp systems, namely the introduction of a heteroatom in the chiral Cp, which creates a fixed chiral pocket around the complexed metal by additional intramolecular coordination. Chirality in these systems may be introduced in three ways: (1) substitution of a second group onto the Cp ring (planar chirality), (2) attachment of chiral substituents on the bridging carbons or (3) on the heteroatom.

Some scattered reports based on this approach have appeared in literature.<sup>4</sup> We wish to report here our results on the synthesis of a novel chiral Cp ligand using ephedrine and pseudoephedrine as a source of chirality.

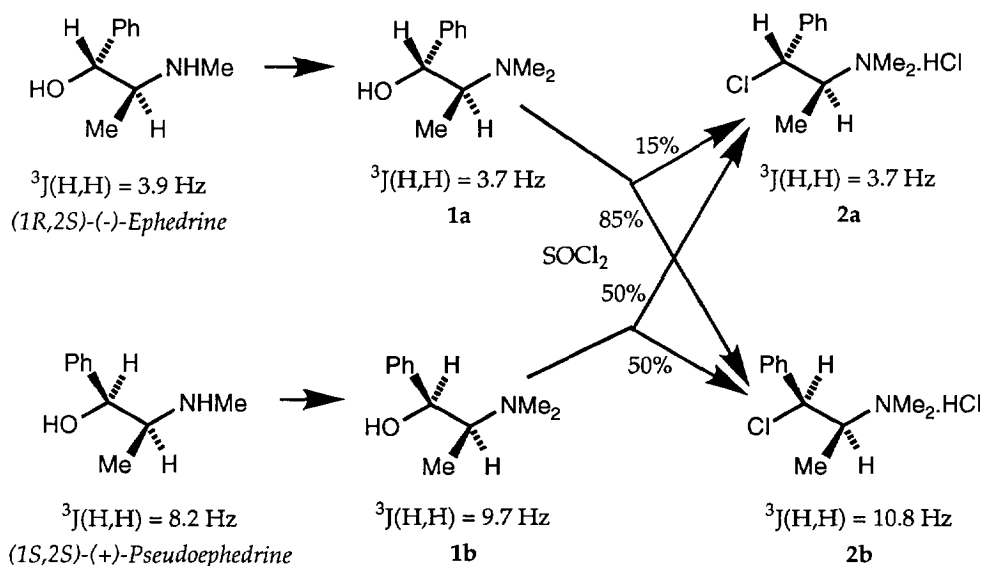


**Results and discussion:**

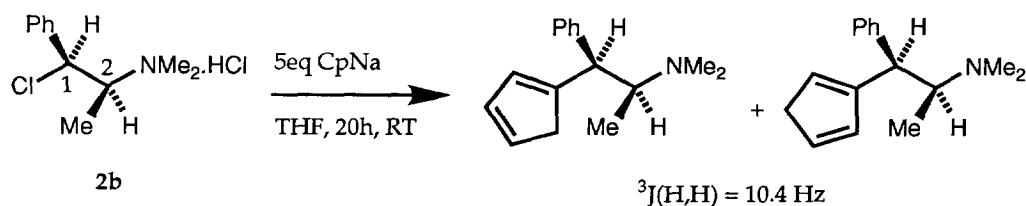
Our synthetic strategy is outlined below.



Commercially available (-)-(1*R*,2*S*)-ephedrine and (+)-(1*S*,2*S*)-pseudoephedrine were used as starting materials. Their conversion to *N*-methylephedrine (**1a**) and *N*-methylpseudoephedrine (**1b**) was straightforward.<sup>5</sup> They were reacted with SOCl<sub>2</sub> in CHCl<sub>3</sub> to obtain the alkyl chlorides (see below).<sup>6</sup> With **1a** this conversion proceeded with 15% retention and 85% inversion at C<sub>1</sub> (yielding **2a** and **2b**, respectively), whereas with **1b** a *ca* 50:50 mixture of **2a** and **2b** was obtained.<sup>7,8</sup> Several recrystallisations afford the 1*S*,2*S*-diastereomer **2b** in high purity. For this reason it is better to start with **1a**, in which case **2b** can be obtained in an overall yield of 40-50%.

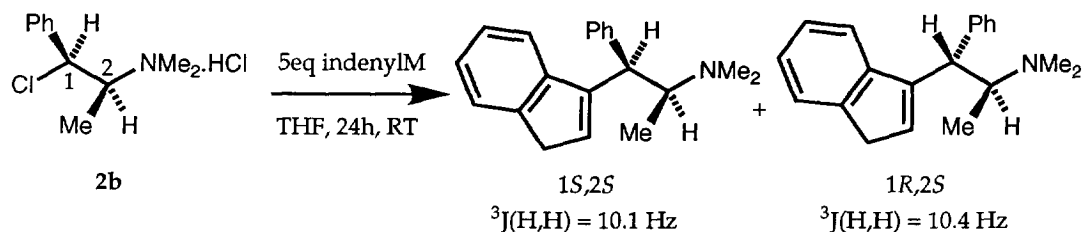


Reaction of **2b** and an excess of CpNa afforded a quantitative amount of the Cp ligand (abbreviated as Cp<sup>E</sup>(*phedrine*)H).<sup>†</sup> It consists of a 1:1 mixture of two olefinic regioisomers. Therefore, the reaction seems to have gone stereoselectively, i. e. either with complete inversion or retention at C<sub>1</sub>. Usually, the C<sub>1</sub>-C<sub>2</sub> <sup>3</sup>J(H,H) coupling constant is taken to distinguish between the 1*S*,2*S* (or 1*R*,2*R*) and 1*R*,2*S* (or 1*S*,2*R*) diastereomers of (pseudo)ephedrine derivatives; its value of 10.4 Hz suggests an *S* configuration at C<sub>1</sub>. However, in Cp<sup>E</sup>H the Cp and Ph groups at C<sub>1</sub> are more or less isosteric and therefore it is possible that both the *R* and the *S* configurations show coupling constants in the same range. This was corroborated by the results of the reaction of a 40:60 batch of **2a** and **2b** (obtained from **1b** and SOCl<sub>2</sub>) with CpNa. The isolated mixture of Cp derivatives contained 40% of the two regioisomers of Cp<sup>E</sup>H (with presumed 1*S*,2*S* configuration) as well as 60% of the two regioisomers of what is considered to be the 1*R*,2*S* diastereomer. The latter shows a <sup>3</sup>J(H,H) coupling of 10.8 Hz, which indeed is close to the value of the presumed 1*S*,2*S* isomer (10.4 Hz).



Normally, this kind of alkylation proceeds by the S<sub>N</sub>2 mechanism, and should lead to inversion at C<sub>1</sub>.<sup>9</sup> However, the neighbouring effect of the NMe<sub>2</sub> group probably causes retention at C<sub>1</sub>, by forming an aziridinium salt as an intermediate.<sup>9</sup> This is corroborated by results of Carboni *et al.*, who showed that similar conversions of (pseudo)ephedrine chlorides with NaN<sub>3</sub> proceed with complete retention of configuration.<sup>8</sup> We therefore believe, as suggested above, that the configuration at C<sub>1</sub> in Cp<sup>E</sup>H is *S*.<sup>10</sup>

Similarly, we attempted to prepare the analogous indene ligand, by reaction of **2b** with an excess of an indenyl alkaline salt. The special interest for this ligand arises from the fact that it will create a third stereogenic centre upon coordination to a transition metal (principle of planar chirality).



<sup>†</sup>In describing the configuration around carbon, CH(Me)NMe<sub>2</sub>, Ph, Cp, Me, and H groups have descending order of precedence.

The substitution takes place regioselective at the C<sub>3</sub> atom of indene, but unfortunately it is not stereoselective with respect to the ephedrine C<sub>1</sub> atom, producing two diastereomers.<sup>11</sup> The isomer ratio strongly depends on the alkaline metal employed (see Table I), but the outcome of the reaction can never be driven completely to one of the diastereomers. Longer reaction times do not change the isomer ratio as a possible result of base-promoted epimerization. These observations suggest a competing direct alkylating (S<sub>N</sub>2-like) pathway for this reaction. No further attempts to separate the two isomers were undertaken.

Currently, we are exploring the coordination chemistry of Cp<sup>E</sup>H, and its application in metal mediated stereoselective transformations of organic substrates.

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### Experimental:

*General procedures* - Preparations involving organometallic materials were conducted under an atmosphere of argon using carefully dried solvents. <sup>1</sup>H and <sup>13</sup>C n.m.r. spectra were obtained using a Varian Gemini instrument operating at 300 and 75.5 MHz, respectively. Chemical shifts were referenced to those of CD<sub>3</sub>OD (δ<sub>H</sub> 3.30; δ<sub>C</sub> 49.0 ppm), CDCl<sub>3</sub> (δ<sub>H</sub> 7.24; δ<sub>C</sub> 77.0 ppm) or C<sub>6</sub>D<sub>6</sub> (δ<sub>H</sub> 7.15; δ<sub>C</sub> 128.0 ppm).

*Starting Materials* - (1*R*,2*S*)- and (1*S*,2*S*)-α-[1-(dimethylamino)ethyl]benzenemethanol (*N*-methyl-ephedrine (**1a**) and -pseudoephedrine (**1b**)) were obtained by published methods from (-)-(1*R*,2*S*)-ephedrine (Janssen) and (+)-(1*S*,2*S*)-pseudoephedrine (Aldrich), respectively.<sup>5</sup>

(1*S*,2*S*)-β-Chloro-*N,N'*,α-trimethylbenzeneethan ammonium chloride hydrate (**2b**) - To an ice-cold solution of **1a** (62.7 g, 350 mmol) in chloroform (350 ml) was added SOCl<sub>2</sub> (32 ml, 440 mmol). The resulting clear, orange solution was stirred overnight at room temperature and evaporated to afford a foamy red solid. Recrystallisation from ether/ethanol (3:1 v/v) at -80 °C afforded 88 g (ca 100%) of a pale orange substance containing 85% **2b** and 15% of the (1*R*,2*S*) diastereomer **2a** by <sup>1</sup>H NMR. Several recrystallisations from acetone/ethanol (10:1 v/v) were necessary to obtain pure **2b** as white needles (39 g, 44%). (Found: C, 52.8; H, 7.9; N, 5.5. C<sub>11</sub>H<sub>19</sub>Cl<sub>2</sub>NO requires C, 52.4; H, 7.6; N, 5.5%). NMR in CD<sub>3</sub>OD: δ<sub>H</sub> 1.07 (3H, d, 6.7 Hz, CHCH<sub>3</sub>), 2.90/3.02 (both 3H, s, N(CH<sub>3</sub>)<sub>2</sub>H<sup>+</sup>), 4.14 (1H, dq, 10.9x6.7 Hz, CHCH<sub>3</sub>), 5.31 (1H, d, 10.9 Hz, CHPh), 7.39-7.53 (5H, m, Ph). δ<sub>C</sub> 10.24 (CHCH<sub>3</sub>), 36.55/43.98 (N(CH<sub>3</sub>)<sub>2</sub>H<sup>+</sup>), 62.85 (CHCH<sub>3</sub>), 67.60 (CHPh), 129.10 (Ph,*o*-C), 130.28 (Ph, *m*-C), 130.75 (Ph, *p*-C), 138.37 (*ipso*-C).

A similar reaction with (1*S*,2*S*)-*N*-methylpseudoephedrine and SOCl<sub>2</sub> in chloroform afforded a crude mixture of 50% **2a** and 50% **2b**. No attempts were made to separate the two diastereomers by recrystallisation. NMR of **2a** in CD<sub>3</sub>OD (containing **2b**): δ<sub>H</sub> 1.38 (3H, d, 6.6 Hz, CHCH<sub>3</sub>), 2.97/3.10 (both 3H, s, N(CH<sub>3</sub>)<sub>2</sub>H<sup>+</sup>), 3.92 (1H, dq, 3.7x6.6 Hz, CHCH<sub>3</sub>), 5.82 (1H, d, 3.7 Hz, CHPh), ca 7.35-7.55 (5H, m, Ph). δ<sub>C</sub> 9.77 (CHCH<sub>3</sub>), 41.66/42.57 (N(CH<sub>3</sub>)<sub>2</sub>H<sup>+</sup>), 62.48 (CHCH<sub>3</sub>), 68.13 (CHPh), 128.57 (Ph,*o*-C), 130.09 (Ph, *m*-C), 130.25 (Ph, *p*-C), 137.59 (*ipso*-C).

**Table I.** Rel. amounts of diastereomers on reaction of indenylM with **2b** in THF.<sup>11</sup>

M	1 <i>S</i> ,2 <i>S</i>	1 <i>R</i> ,2 <i>S</i>
Li	22%	78%
Na	75%	25%
K	92%	8%

(1*S*,2*S*)-(2-Dimethylamino-1-phenylpropyl)cyclopentadiene ( $\text{Cp}^{\text{E}}\text{H}$ ) - A solution of cyclopentadienyl-sodium was prepared by reacting sodium (18.6 g, 0.81 mol) and freshly cracked cyclopentadiene (85 ml, 1 mol) in THF (300 ml) overnight at room temperature. To this solution was added **2b** (36.1 g, 143 mmol) and stirring was continued for another night at room temperature. Water (20 ml) was added and volatiles were removed *in vacuo*. The residue was extracted with petrol (150 ml in total). Removal of solvent left a quantitative yield of a yellow-brownish viscous oil (34.6 g) containing almost pure **3**. This substance can be used for subsequent manipulations without further purification. It was identified by NMR ( $\text{CDCl}_3$ ) as a 1:1 mixture of 1- and 2-substituted cyclopentadienes:  $\delta_{\text{H}}$  0.67/0.68 (3H, both d, 6.3 Hz,  $\text{CHCH}_3$ ), 2.20/2.22 (6H, both s,  $\text{N}(\text{CH}_3)_2$ ), 2.91 (2H, m,  $\text{CH}_2$  of Cp ring), 3.22 (1H, m,  $\text{CHCH}_3$ ), 3.67/3.71 (1H, both d, 10.4 Hz,  $\text{CHPh}$ ), 6.08 (s), 6.19 (d, 5.2 Hz), 6.24 (s), 6.33 (m), 6.51 (d, 5.2 Hz) (these 5 signals integrate for 3H,  $\text{CH}$  of Cp ring), 7.05-7.3 (5H, m, Ph).  $\delta_{\text{C}}$  9.33/9.42 ( $\text{CHCH}_3$ ), 40.04/40.18 ( $\text{N}(\text{CH}_3)_2$ ), 40.87/41.67 ( $\text{CH}_2$  of Cp ring), 51.68/52.74 ( $\text{CHPh}$ ), 61.58/61.87 ( $\text{CHCH}_3$ ), 126.0 (Ph, *p*-C), 128.4 (br, Ph, *o,m*-C), 126.35/126.83/131.03/132.08/132.93/133.91 (CH of Cp ring), 143.68/143.91 (Ph, *ipso*-C), 148.96/151.18 (C of Cp ring).

A similar reaction of  $\text{CpNa}$  with a mixture of **2a** (60%) and **2b** (40%) yielded a mixture of 40%  $\text{Cp}^{\text{E}}\text{H}$  and 60% of the 1*R*,2*S*-analogue of  $\text{Cp}^{\text{E}}\text{H}$ . The latter was identified by NMR in  $\text{CDCl}_3$ :  $\delta_{\text{H}}$  0.86/0.88 (3H, both d, 6.4 Hz,  $\text{CHCH}_3$ ), 2.10/2.12 (6H, both s,  $\text{N}(\text{CH}_3)_2$ ), 2.73 (2H, m,  $\text{CH}_2$  of Cp ring), 3.26\* (1H, m,  $\text{CHCH}_3$ ), 3.80\* (1H, d, 10.8 Hz), 6.1-6.3\*, 6.46 (3H, m,  $\text{CH}$  of Cp ring), 7.1-7.3\* (5H, m, Ph).  $\delta_{\text{C}}$  9.58/9.71 ( $\text{CHCH}_3$ ), 39.91/40.1\* ( $\text{N}(\text{CH}_3)_2$ ), 40.82\*/41.34 ( $\text{CH}_2$  of Cp ring), 51.73/52.90 ( $\text{CHPh}$ ), 60.73/61.06 ( $\text{CHCH}_3$ ), 127.5/128.0\*/128.3\* (Ph, *o,m,p*-C), 125.65/125.75/131.17/131.95\*/133.22/133.83\* (CH of Cp ring), 143.58/144.13 (Ph, *ipso*-C), 148.59/150.88 (C of Cp ring).

\* (partly) coincides with signals of  $\text{Cp}^{\text{E}}\text{H}$ .

Reaction of **2b** with indenyl salts<sup>12</sup> - A five-fold excess of either indenyllithium (prepared by the action of *n*-butyllithium on indene for 1h at 0 °C), -sodium (prepared by refluxing sodium with a slight excess indene for 24h) or -potassium (prepared by reaction of potassium with a slight excess of indene for 2h at room temperature) in THF was reacted with **2b** at room temperature for 24h. Work-up as above yielded a mixture that was analysed by NMR in  $\text{CDCl}_3$ . Two compounds were identified: (1*S*,2*S*)-[(2-Dimethylamino-1-phenylpropyl)]-3-indene:  $\delta_{\text{H}}$  0.97 (3H, d, 6.4 Hz,  $\text{CHCH}_3$ ), 2.18 (6H, s,  $\text{N}(\text{CH}_3)_2$ ), 3.31 (2H, m,  $\text{CH}_2$  of indene), 3.45 (1H, dq, 10.4x6.4 Hz,  $\text{CHCH}_3$ ), 4.05 (1H, d, 10.4 Hz,  $\text{CHPh}$ ), 6.38 (1H, br s,  $\text{CH}$  of indene), 7.05-7.4\* (9H, m, Ph and indene).  $\delta_{\text{C}}$  9.37\* ( $\text{CHCH}_3$ ), 37.87\* ( $\text{CH}_2$  of indene), 40.40 ( $\text{N}(\text{CH}_3)_2$ ), 49.04\* ( $\text{CHPh}$ ), 61.51 ( $\text{CHCH}_3$ ), 119.45\* (indene C4), 123.47 (indene C7), 124.09 (indene C6), 125.65? (indene C5), 125.9\*? (Ph, *p*-C), 127.89\* (Ph, *o*-C), 128.38\* (Ph, *m*-C), 128.2? (indene C2), 142.18 (Ph, *ipso*-C), 144.39 (indene C8), 145.39? (indene C3), 145.95? (indene C9) (assignment of indene signals was based on those of 3-methylindene.<sup>13</sup>). (1*R*,2*S*)-[(2-Dimethylamino-1-phenylpropyl)]-3-indene:  $\delta_{\text{H}}$  0.72 (3H, d, 6.6 Hz,  $\text{CHCH}_3$ ), 2.24 (6H, s,  $\text{N}(\text{CH}_3)_2$ ), 3.35 (3H, m,  $\text{CH}_2$  of indene and  $\text{CHCH}_3$ ), 4.00 (1H, d, 10.1 Hz,  $\text{CHPh}$ ), 6.49 (1H, br s,  $\text{CH}$  of indene), 7.05-7.4\* (9H, m, Ph and indene).  $\delta_{\text{C}}$  9.37\* ( $\text{CHCH}_3$ ), 37.87\* ( $\text{CH}_2$  of indene), 40.27 ( $\text{N}(\text{CH}_3)_2$ ), 49.04\* ( $\text{CHPh}$ ), 61.77 ( $\text{CHCH}_3$ ), 119.45 (indene C4), 123.64 (indene

C7), 124.45 (indene C<sub>6</sub>), 125.81 (indene C<sub>5</sub>), 125.9\*? (Ph, *p*-C), 127.89\* (Ph, *o*-C), 128.38\* (Ph, *m*-C), 128.86 (indene C<sub>2</sub>), 142.76 (Ph, *ipso*-C), 144.26 (indene C<sub>8</sub>), 145.20 (indene C<sub>3</sub>), 146.37 (indene C<sub>9</sub>).

\*(partly) coincides with signals of the other diastereomer.

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11. The two diastereomers of the indene ligands could be discriminated by <sup>1</sup>H NMR: for the Cp ligands the signals of the Me group in the *1S, 2S* diastereomer lie 0.20 ppm upfield to those of the *1S, 2R* diastereomer, whereas the signals of the NMe<sub>2</sub> group lie 0.10 downfield (see *Experimental*). As the indene analogues also show differences of 0.20 ppm for the Me signal and -0.10 ppm for the NMe<sub>2</sub> signal, and besides have the same <sup>3</sup>J<sub>HH</sub> coupling (10 Hz) as the Cp-analogue, similar three-dimensional structures are anticipated.
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