Synthesis of Diastereomeric Bis(oxazoline) Ligands Derived from (*S*,*S*)-1,1'-Bis(4-isopropyloxazolin-2-yl)ferrocene

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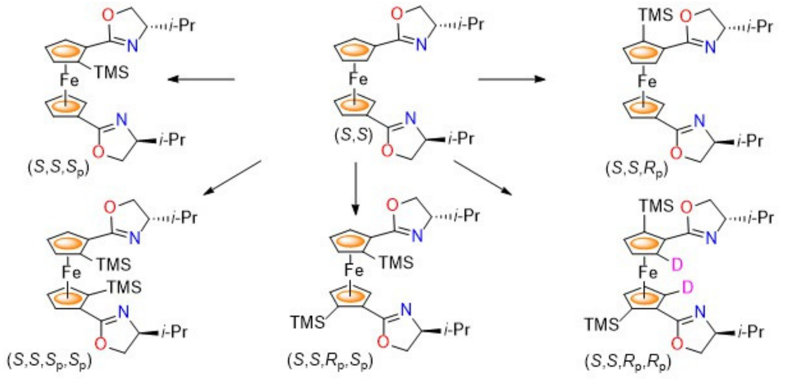

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Abstract Starting from (*S*,*S*)-1,1'-bis(4-isopropyloxazolin-2-yl)ferrocene, all possible 2-trimethylsilyl and 2,2'-di(trimethylsilyl) substituted diastereoisomers, potential bisoxazoline ligands for use in asymmetric catalysis, were synthesised by selective lithiation followed by addition of trimethylsilyl chloride. Access to the (*S*,*S*,*R*p,*R*p)-diastereoisomer was achieved following diastereoselective introduction of two deuterium blocking groups and utilisation of the high k_H/k_D value for lithiation, methodology that was also applied to the synthesis of a related 2,2'-di(diphenylmethanol)bisoxazoline ligand.

Key words Bisoxazoline, ligands, ferrocene, lithiation, deuterium, kinetic isotope effect, diastereoisomers

Ligands employed in metal-catalysed asymmetric reactions frequently contain more than one element of chirality, such that matched and mismatched diastereoisomers can be identified with respect to product enantioselectivity.[1] In addition, the introduction of an element of chirality to an existing chiral non-racemic ligand will typically result in an increase in the enantioselectivity of a given metal-catalysed reaction for one of the resulting diastereoisomers.[2] Thus synthetic methods that enable the diastereoselective modification of an existing chiral non-racemic ligand are of significant value, especially where all possible resulting diastereoisomers can be accessed with good stereocontrol.

Bisoxazolines have been employed extensively in metal-catalysed asymmetric transformations, a represenative example being (*S*)-valine derived methylene-linked ligand **1**.[3] In contrast, 1,1'-ferrocene-linked bisoxazolines, exemplifed by ligand **2**, have not been studied to nearly the same extent.[4] Notwithstanding that **1** and **2** may result in different metal-coordinating modes, the ferrocene-based bisoxazoline offers significant scope for chirality element introduction by replacement of one or two hydrogens at the positions indicated by exploitation of oxazoline mediated α (*ortho*)-lithiation (Figure 1). Two planar chiral diastereoisomers will result from the introduction of a single substituent [R_p and S_p], and three diastereoisomers from the introduction of the same substituent twice [S_p,S_p, R_p,S_p and R_p,R_p). Although there are several reports on the diastereoselective lithiation and subsequent functionalisation of ferrocene-based bisoxazolines such as **2**,[5] principally with the goal of generating 2-diphenylphosphino and 2,2'-di(diphenylphosphino) ligands, the selective generation of all five possible diastereoisomers from **2** has not proven possible. In this Letter we describe the synthesis of all five trimethylsilyl substituted diastereoisomers. Access to the most challenging (R_p,R_p)-2,2'-di(trimethylsilyl) diastereoisomer was achieved by use of deuterium blocking groups to reverse lithiation diastereoselectivity.[6]

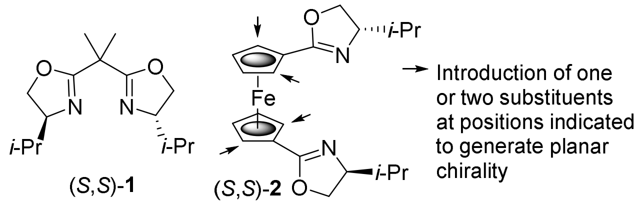
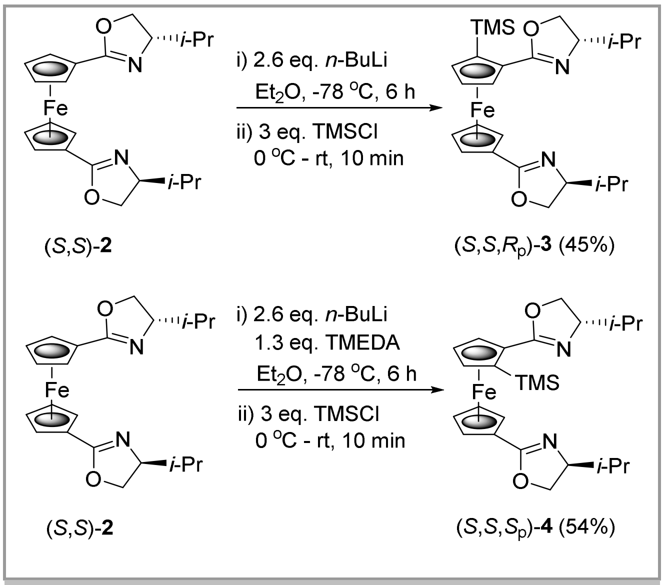


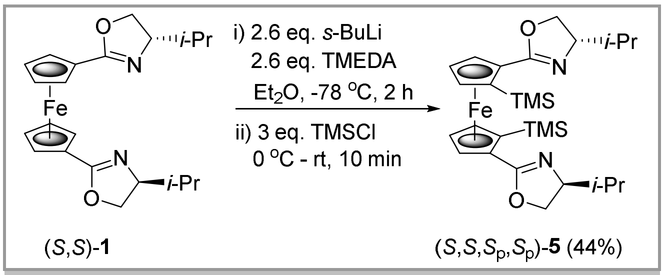
Figure 1 Representative bisoxazoline ligands **1** and **2** and positions for the functionalisation of **2**.

Previous studies on the lithiation of (*S*,*S*)-**2** have revealed that *n*-BuLi is insufficiently basic to achieve 1,1'-dilithiation, even when used in excess.[5a,b] With diethyl ether as solvent, and following the addition as electrophile of chlorodiphenylphosphine, the (R_p)-2-diphenylphosphino diastereoisomer was formed as the major product with both 1.2 and 2.2 equivalents of *n*-BuLi.[5c,7] Thus reaction of (*S*,*S*)-**2** with excess[8] *n*-BuLi in ether followed by addition of trimethylsilyl chloride was expected to give primarily a monosilylated product, and this proved to be the case to give (*S*,*S*,R_p)-**3** with the configuration of the new element of planar chirality assigned by comparison (Scheme 1).[9]



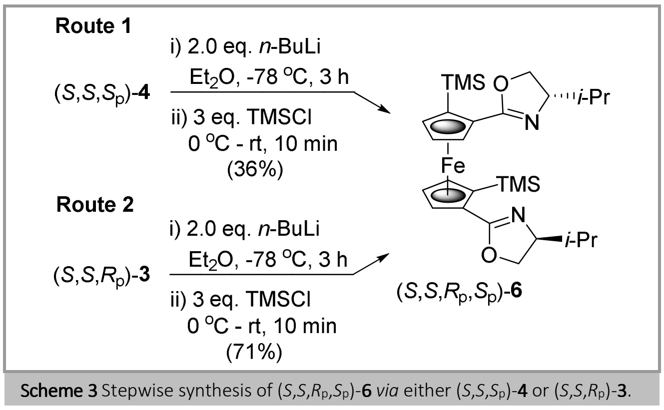
Scheme 1 Synthesis of (S,S,R_{p})-**3** and (S,S,S_{p})-**4** *via* the diastereoselective monolithiation of (S,S)-**1**.

The diastereoselectivity of monolithiation was reversed simply by addition as additive of TMEDA. Similar conditions to those used (2.3 eq. *n*-BuLi, Et$_2$O, TMEDA, -78 °C) have been employed previously for the highly diastereoselective lithiation of (*S*)-1-(4-isopropyloxazolin-2-yl)ferrocene to give the (S,S_{p})-diastereoisomer following addition of trimethylsilyl choride (dr > 100: 1).[10] A similar outcome was achieved with bisoxazoline (S,S)-**2** enabling the isolation of (S,S,S_{p})-**4** (Scheme 1). That the same outcome is observed on lithiation in the presence of TMEDA of (S,S)-**2** and its mono-oxazoline congener is in contrast to the outcomes observed in the absence of TMEDA. Lithiation of the mono-oxazoline with *n*-BuLi in Et$_2$O gives the opposite sense of diastereoselectivity to that observed with the bisoxazoline.[11] Thus under these conditions the second oxazoline group of (S,S)-**2** influences the outcome, presumably *via* nitrogen-lithium coordination.[12] This interaction is likely prevented in the presence of TMEDA which has been shown to alter significantly the nature of a lithiating species as a result of lithium chelation.[13,14]

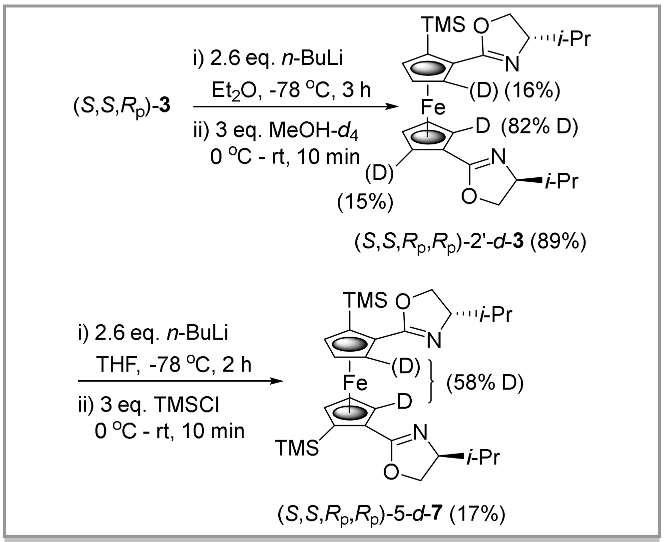


Scheme 2 Synthesis of $(S,S,S_{\mathrm{p}},S_{\mathrm{p}})$-**5** *via* the diastereoselective dilithiation of (S,S)-**1**.

Previous investigations into the diastereoselective dilithiation of (S,S)-**2** have established conditions, following addition of an electrophile,[15] for the generation of $S_{\mathrm{p}},S_{\mathrm{p}}$ (2.6 eq. *s*-BuLi, Et$_2$O, TMEDA, 10 : 1 dr)[5d,16] and $S_{\mathrm{p}},R_{\mathrm{p}}$ (2.2 eq. *t*-BuLi, Et$_2$O, >20 : 1 dr)[5a,c] products. In contrast the $R_{\mathrm{p}},R_{\mathrm{p}}$ diastereoisomer was, at best, obtained in low yield as a 1:1 mixture with the corresponding $S_{\mathrm{p}},R_{\mathrm{p}}$ product.[5c] Thus the first of these sets of conditions was employed for the synthesis of $(S,S,S_{\mathrm{p}},S_{\mathrm{p}})$-**5** (Scheme 2). Then, with (S,S,S_{p})-**4** and (S,S,R_{p})-**3** already in hand, we chose to investigate if these could be transformed, respectively, into $(S,S,R_{\mathrm{p}},S_{\mathrm{p}})$-**6** and $(S,S,R_{\mathrm{p}},R_{\mathrm{p}})$-**7**. Application of the conditions used for the synthesis of (S,S,R_{p})-**3** (*n*-BuLi/Et$_2$O) with (S,S,S_{p})-**4** gave $(S,S,R_{\mathrm{p}},S_{\mathrm{p}})$-**6** as anticipated (Scheme 3). However, on application of the same conditions to (S,S,R_{p})-**3** the diastereoisomer $(S,S,S_{\mathrm{p}},R_{\mathrm{p}})$-**6** was again formed. These two stepwise procedures reveal that competitive formation of (S,S)-2,5-di(trimethylsilyl)-1,1'-bis(4-isopropyloxazolin-2-yl)ferrocene is not a significant issue, and that the contrasting diastereoselectivities may again be due to the differential involment, via lithium coordination, of a second oxazoline substituent.



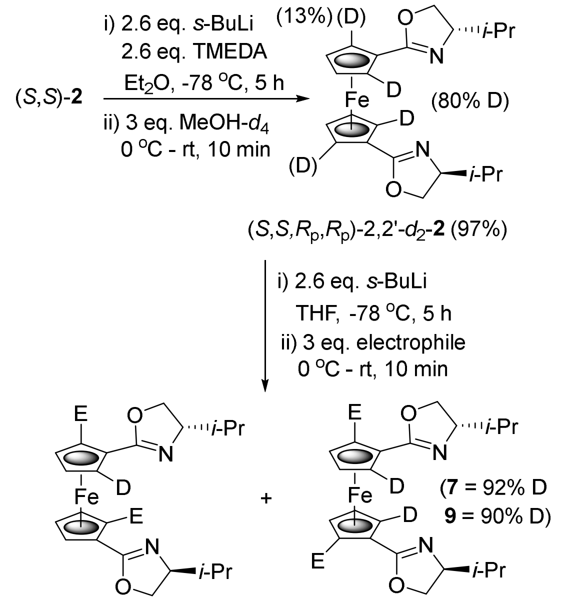
Scheme 3 Stepwise synthesis of $(S,S,R_{\mathrm{p}},S_{\mathrm{p}})$-**6** *via* either (S,S,S_{p})-**4** or (S,S,R_{p})-**3**.



Scheme 4 Stepwise synthesis of $(S,S,R_{\mathrm{p}},R_{\mathrm{p}})$-5-*d*-**7** *via* (S,S,R_{p})-2'-*d*-**3** incorporating a single deuterium blocking group.

As an alternative method to access the $R_{\mathrm{p}},R_{\mathrm{p}}$ diastereoisomer we then chose to use a deuterium blocking group. This is an approach we recently employed for the synthesis of ligand diastereoisomers derived from (*S*)-1-(4-isopropyloxazolin-2-yl)ferrocene, a substrate for which the lithiation diastereoselectivity can be altered from being very high to very low. Use of conditions that give high diastereoselectivity, followed by addition of a deutero acid and recovery of the deuterated starting material, was followed by the use of conditions that give poor diastereoselectivity, followed by the addition of the electrophile. The diastereoselectivity of the second lithiation was controlled primarily by the high value[17] for $k_{\rm H}/k_{\rm D}$ to give an overall reversal in lithiation diastereoselectivity.[6]

Accordingly, repetition of the lithiation of $(S,S,R_{\rm p})$-**3** as before, followed by the addition of methanol-d_4, gave $(S,S,R_{\rm p},R_{\rm p})$-2'-$d$-**3**[18] with 82% deuterium incorporation at the position requiring a blocking group (Scheme 4). Subjecting this to lithiation using conditions that previously had resulted in low diastereoselectivity,[6] followed by addition of TMSCl, resulted in a modest yield of $(S,S,R_{\rm p},R_{\rm p})$-5-$d$-**7** together with other doubly or triply silylated products.[8]



$(S,S,R_{\rm p},S_{\rm p})$-5-$d$-**6**
E = TMS (36% yield)
$(S,S,R_{\rm p},S_{\rm p})$-5-$d$-**8**
E = CPh$_2$OH (31% yield)

$(S,S,R_{\rm p},R_{\rm p})$-5,5'-$d_2$-**7**
E = TMS (41% yield)
$(S,S,S_{\rm p},S_{\rm p})$-5,5'-$d_2$-**9**
E = CPh$_2$OH (33% yield)

Scheme 5 Conversion of (S,S)-**2** into predominantly $(S,S,R_{\rm p},R_{\rm p})$-2.2'-$d_2$-**7** followed by the generation of $(S,S,R_{\rm p},R_{\rm p})$-5.5'-$d_2$-**7** and $(S,S,S_{\rm p},S_{\rm p})$-5.5'-$d_2$-**9**.

As a more direct two-step approach to the $R_{\rm p},R_{\rm p}$ di(trimethylsilyl) diastereoisomer, (S,S)-**2** was dilithiated using the same conditions that led to predominantly $(S,S,S_{\rm p},S_{\rm p})$-**5** (Scheme 2), with methanol-d_4 rather than TMSCl added in the second step of the reaction. By analogy with the result of silylation, the product of this reaction contained predominantly $(S,S,R_{\rm p},R_{\rm p})$-2,2'-$d_2$-**2** (Scheme 5). Consistent with this outcome was the percentage deuterium incorporation at the two diastereotopic α–positions of 80% and 13%, as determined by ^{1}H NMR spectroscopy. Dilithiation in turn of $(S,S,R_{\rm p},R_{\rm p})$-2,2'-$d_2$-**2** under less selective conditions,[19] followed by addition of excess TMSCl, gave a moderate but usable quantity of $(S,S,R_{\rm p},R_{\rm p})$-5,5'-$d_2$-**7** together with $(S,S,R_{\rm p},S_{\rm p})$-5-$d$-**6**. This overall two-step methodology was repeated using benzophenone as an alternative electrophile to give $(S,S,R_{\rm p},S_{\rm p})$-5-$d$-**8** and $(S,S,S_{\rm p},S_{\rm p})$-5,5'-$d_2$-**9** , formation of the latter completing the series of all three possible diastereoisomers.[16] The new ligands were obtained diastereomerically pure from both reactions following column chromatography.

In conclusion, all five diastereoisomers resulting from substitution of the title compound with a 2-trimethylsilyl group, or 2,2'-di(trimethylsilyl) groups, were synthesised readily using diastereoselective mono or dilithiation. Access to previously unavailable compounds was achieved by exploiting the high kinetic isotope effect for C-H *vs.* C-D lithiation. The application of these bisoxazoline ligands in asymmetric catalysis will be reported in due course.

Acknowledgment

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Supporting Information

YES (this text will be updated with links prior to publication)

Primary Data

NO (this text will be deleted prior to publication)

References and Notes

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(7) The configuration of this monophosphine was initially incorrectly assigned as $(S,S,S_{\rm p})$: see reference 5a.
(8) In our hands the use of 1.3 equivalents of n-BuLi resulted only in the recovery of starting material such that 2.6 equivalents were required to give product.
(9) For all lithiation/silylation reactions the identity and ratio (where possible) of the by-products is given in the supporting information. All silylated bisoxazolines were obtained diastereomerically pure by colum chromatography.
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(14) The diastereoselectivity of monolithiation of (S,S)-**2** with n-BuLi can also be reversed by use of THF as solvent. See reference 5c.
(15) The electrophiles used in these studies are MeI, C_2Cl_6 and $C_2Br_2Cl_4$ and ClPPh$_2$. The discussion of the resulting planar chiral configurations ($R_{\rm p}$ or $S_{\rm p}$) is on the basis that the priority of the group introduced is higher than that of the oxazoline substituent (which is the case for Cl, Br, PPh$_2$ and SiMe$_3$, with CPh$_2$OH having a lower priority).
(16) Lithiation under these conditions followed by the addition of benzophenone has been reported to result in a 3.5 : 1 ratio of $(S,S,R_{\rm p},R_{\rm p})$ and $(S,S,R_{\rm p},S_{\rm p})$ diastereoisomers respectively. See: Zhang, W.; Yoshinaga, H.; Imai, Y.; Kida, T.; Nakatsuji, Y.; Ikeda, I. *Synlett* **2000**, 1512.
(17) Values for $k_{\rm H}/k_{\rm D}$ in excess of 50 are known, see: (a) Hoppe, D.; Paetow, M.; Hintze, F. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 394. (b) Clayden, J.; Pink, J. H.; Westlund, N.; Wilson, F. X. *Tetrahedron Lett.* **1998**, *39*, 8377.

(18) Compounds that differ only by the presence or absence of deuterium have the same number. In all cases, position 1 of the substituted cyclopentadienyl ring is attached to the oxazoline substituent. A compound is designated deuterated if it contains >50% D incorporation at the position indicated [*i.e.* D rather than (D)].

(19) Lithiation of (*S*,*S*)-**2** with *s*-BuLi (2.2 eq.) in THF followed by the addition of PPh_2Cl has previoulsy been reported to result in 2.9 : 1 ratio of (*S*,*S*,S_p,S_p) and (*S*,*S*,R_p,S_p) diastereoisomers.[5c] An attempt to use ether as the reaction solvent in place of THF with (*S*,*S*,R_p,R_p)-2,2'-d_2-**2** resulted in only mono-silylation.