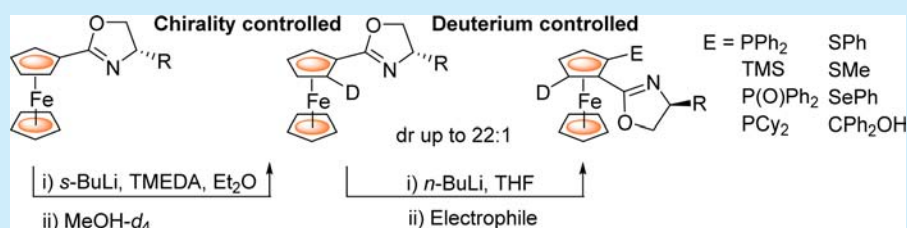


Deuterium as a Stereochemically Invisible Blocking Group for Chiral Ligand Synthesis

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Supporting Information



ABSTRACT: Highly diastereoselective lithiation (*s*-BuLi/TMEDA in Et₂O, −78 °C, 2 h) of (*S*)-2-ferrocenyl-4-(substituted)-oxazolines followed by addition of MeOH-*d*₄ gave up to 95% D incorporation. Subsequent application of alternative lithiation conditions (*n*-BuLi in THF, −78 °C, 2 h), followed by addition of an electrophile, resulted in a reversal of diastereoselectivity controlled primarily by the high *k*_H/*k*_D value for lithiation (isomer ratio typically between 10:1 and 20:1).

Many nonracemic ligands employed in metal-catalyzed asymmetric reactions contain more than one element of chirality. For a C₁-symmetric ligand containing two such elements, diastereoisomers are possible which may result in different reaction product enantioselectivities, and there are a number of examples where the identification of matched and mismatched chirality pairings has been established.¹ In most cases, however, ligand diastereoisomers are not explored in catalysis, not least because they are commercially unavailable and/or are difficult to synthesize.

For example, *i*-Pr- and *t*-Bu-containing (*S*,*S*_p)-**1a/b** are two frequently used and commercially available ferrocene-based P–N ligands (Figure 1).² Both are generated by highly

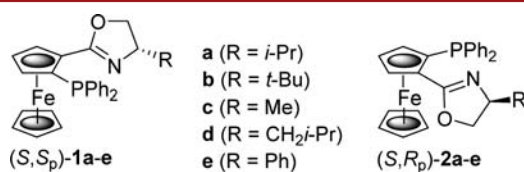


Figure 1. Phosphinoferrocenyloxazoline ligand diastereoisomers **1** and **2**.

diastereoselective lithiation of a ferrocenyloxazoline precursor³ followed by introduction of the diphenylphosphine moiety using Ph₂PCl, methodology that has been applied also to the synthesis of (*S*,*S*_p)-**1c–e**. The diastereoisomers (*S*,*R*_p)-**2a–c** have been synthesized by use of a removable TMS blocking group, with lithiation and phosphine introduction then occurring at the other α -position.^{2c} There are a small number of reports on the use of ligands **2a/b** in catalysis,⁴ including instances where these are the matched diastereoisomer.^{4g}

An alternative to the use of a TMS blocking group is to employ the additive di-*tert*-butyldiglyme [(*t*-Bu)₂-DGME],

which reverses the selectivity of lithiation (dr up to 6:1 in a study which employed MeSSMe as the electrophile, R = *i*-Pr, Me).⁵ This methodology should permit the direct synthesis of **2a** and **2c** by use of Ph₂PCl as the electrophile. The practicality of this procedure is, however, restricted by the low yield (28%) reported for the synthesis of commercially unavailable (*t*-Bu)₂-DGME. In addition, no diastereoselectivity resulted with (*t*-Bu)₂-DGME on lithiation of the *t*-Bu oxazoline precursor to **1b/2b**, and the application of this procedure to the CH₂*i*-Pr and Ph oxazoline precursors to **1d/2d** and **1e/2e**, respectively, has not been reported.

In this paper, we describe an alternative approach to access these largely unexplored ligand diastereoisomers in just two steps. This exploits the very high primary kinetic isotope effect reported for C–D vs C–H lithiation for which values of *k*_H/*k*_D in excess of 50 are known.⁶ This effect has been exploited to aid the control of reaction selectively (chemoselectivity, regioselectivity, and enantioselectivity),⁷ but examples of changes in diastereoselectivity appear to be rare.⁸ Herein, we report on the reversal of lithiation selectivity for diastereoisomer ligand synthesis, following introduction of deuterium, by exploitation of high values of *k*_H/*K*_D.

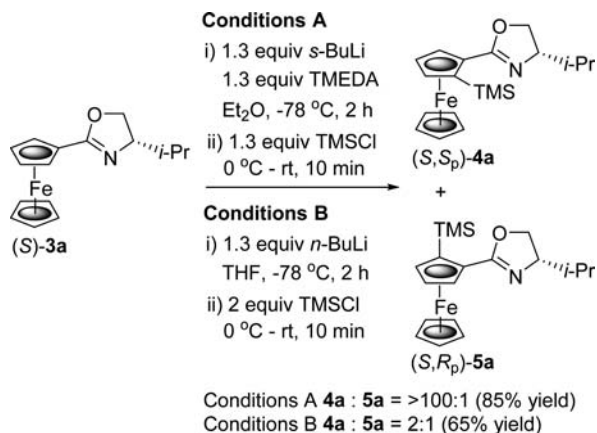
The application of a deuterium blocking group to the selective generation of a diastereoisomer requires that conditions exist for both the highly selective and poorly/nonselective lithiation of the starting substrate. Then in the first instance lithiation followed by the addition of a deuterio acid will result in the highly selective introduction of deuterium. In the second instance, the deuterium will principally control the position of lithiation to give the alternative diastereoisomer with high

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selectivity, following addition of the electrophile. As already inferred, (*S*)-valinol-derived ferrocenyloxazoline (*S*)-**3a** meets these requirements, as lithiation selectivity is highly dependent upon the solvent and additive employed. High diastereoselectivity results when a diethyl ether solution is treated at low temperature with *s*-BuLi in the presence of TMEDA.³ Repetition of these conditions (conditions A) followed by the addition of trimethylsilyl chloride resulted in the essentially exclusive (>100:1) formation of (*S,S*_p)-**4a** (Scheme 1). In contrast,

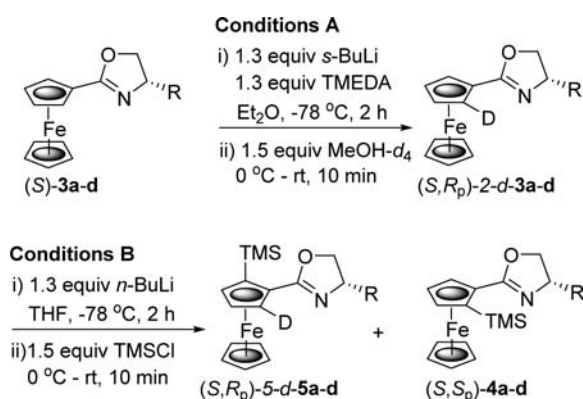
Scheme 1. High and Low Selectivity for the Lithiation and Subsequent Trimethylsilylation of (*S*)-3a****



use of *n*-BuLi in THF at low temperature (conditions B), followed by addition of trimethylsilyl chloride, resulted in a 2:1 ratio of diastereoisomeric products due to the significant formation of (*S,R*_p)-**5a**.

These high and low lithiation stereoselectivities, together with the use of deuterium, were used to bring about an overall reversal in the stereochemistry of α -silylation (Scheme 2).

Scheme 2. Synthesis of (*S,R*_p)-5-*d*-5a-d** by Deuterium-Directed Reversal of Diastereoselectivity**



Lithiation under conditions A, followed by the addition of methanol-*d*₄, gave (*S,R*_p)-2-*d*-**3a**⁹ in which only a single cyclopentadienyl α -hydrogen was deuterated, with a percentage incorporation of 94% as determined by ¹H NMR spectroscopy (Table 1, entry 1). Subsequent application of lithiation conditions B to (*S,R*_p)-2-*d*-**3a**, followed by addition of trimethylsilyl chloride, resulted in the formation of (*S,R*_p)-5-*d*-**5a** as the major diastereoisomer in a ratio of 10:1 (Figure 2). Using the

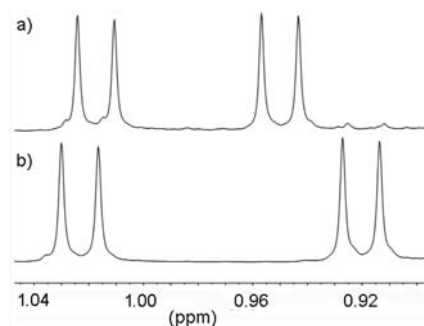


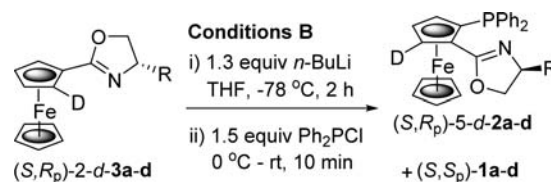
Figure 2. Reversal of diastereoselectivity. Part of the 500 MHz ¹H NMR spectrum (CDCl₃, CH(CH₃)₃) of the unpurified product mixture arising from the reaction illustrated by (a) Scheme 2, conditions B (R = *i*-Pr), and (b) Scheme 1, conditions A.

lithiation ratios determined from conditions B with both non-deuterated (*S*)-**3a** (2:1) and deuterated (*S,R*_p)-2-*d*-**3a** (1:10), together with the percentage deuterium incorporation (94%), gave a calculated value for k_H/k_D of ~20.

This sequence of reactions was also applied to oxazolines **3b-d** (Table 1, entries 2–4) resulting in high overall diastereoselectivity for the methyl (**3c**) and isobutyl (**3d**) substituted oxazolines but in a reduced yield and modest diastereoselectivity for the *tert*-butyl derivative (**3b**). The latter result is likely due to the higher lithiation selectivity of this nondeuterated oxazoline under conditions B.¹⁰

The reversal in diastereoselectivity with deuterated ferrocenyloxazolines was extended to the synthesis of P–N ligands (*S,R*_p)-5-*d*-**2a-d** (Scheme 3, Table 2). These were formed as

Scheme 3. Deuterium-Directed Synthesis of (*S,R*_p)-5-*d*-2a-d****



the major isomer when chlorodiphenylphosphine was used as the electrophile following lithiation under conditions B, albeit in modest yield.¹¹ Obtaining diastereomerically pure ligands by

Table 1. Synthesis of (*S,R*_p)-5-*d*-5a-d** by Deuterium-Directed Reversal of Diastereoselectivity**

entry	substrate (R)	yield of (<i>S,R</i> _p)-2- <i>d</i> - 3a-d (%) (% D ^a)	ratio of 5a-d / 4a-d ^b	yield ^c (%) (% D ^{a,d})
1	3a (<i>i</i> -Pr)	95 (94)	10:1	78 ^c (98)
2	3b (<i>t</i> -Bu)	95 (90)	2.3:1	41 (94)
3	3c (Me)	85 (95)	21:1	59 ^c (92)
4	3d (CH ₂ <i>i</i> -Pr)	93 (95)	17:1	49 (94)

^aDetermined by ¹H NMR spectroscopy (500 MHz, CDCl₃). ^bDetermined before column chromatography. ^cDetermined after column chromatography (SiO₂). ^dOf major isomer. ^eIsolated as a single diastereoisomer.

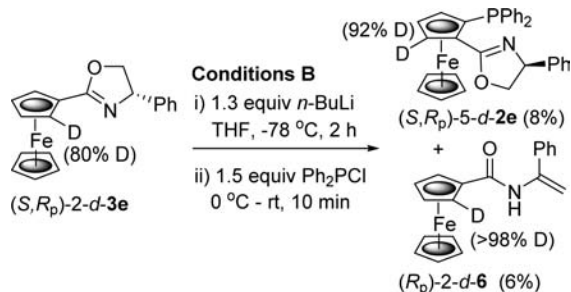
Table 2. Deuterium-Directed Synthesis of (*S,R_p*)-5-*d*-2a–d

entry	substrate (<i>S,R_p</i>)-2- <i>d</i> -3a–d (R)	substrate (% D ^a)	ratio of (<i>S,R_p</i>)-5- <i>d</i> -2:(<i>S,S_p</i>)-1 ^{a,b}	% yield ^b (% D ^{a,c})
1	3a (R = <i>i</i> -Pr)	92	21:1	49 ^d (98)
2	3b (R = <i>t</i> -Bu)	90	2.5:1	50 (98)
3	3c (R = Me)	85	5:1	39 ^e (92)
4	3d (R = CH ₂ <i>i</i> -Pr)	95	17:1	20 (94)

^aDetermined by ¹H NMR spectroscopy (500 MHz, CDCl₃). ^bDetermined after column chromatography (SiO₂). ^cOf major isomer. ^dIsolated diastereomerically pure in 29% yield after recrystallization. ^eIsolated diastereomerically pure in 36% yield after recrystallization.

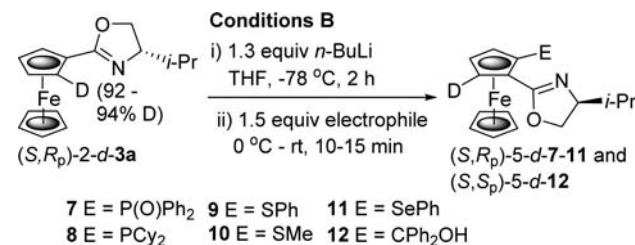
chromatographic separation proved challenging for these products (*vide infra*), but purification was readily achieved for (*S,R_p*)-5-*d*-2a and (*S,R_p*)-5-*d*-2c by recrystallization.

This methodology was also applied to the phenyl-substituted ferrocenyloxazoline 3e. Application of lithiation conditions A followed by addition of methanol-*d*₄ resulted in (*S,R_p*)-2-*d*-3e in 45% yield with a reasonable (80%) level of deuterium incorporation. Subsequent application of the conditions B/PPh₂Cl protocol resulted in a mixture of products from which were isolated by column chromatography diastereomerically pure (*S,R_p*)-5-*d*-2e and enamide (*R_p*)-2-*d*-6 (Scheme 4). The latter

Scheme 4. Reaction of (*S,R_p*)-2-*d*-3e

likely arises from lithiation at position 4 of the oxazoline followed by ring-opening and nitrogen protonation on workup, a process reported previously with another phenyl-substituted oxazoline substrate.¹² Thus, prevention of the favored lithiation pathway by deuterium introduction can lead to an undesirable reaction pathway in addition to the formation of the alternative diastereoisomer.

The facility with which *i*-Pr-containing ferrocenyloxazolines (*S*)-3a/(*S,R_p*)-2-*d*-3a undergo lithiation led us to extend this methodology to the synthesis of a range of bidentate ligand diastereoisomers (Scheme 5, Table 3). Use of diphenylphosphinic

Scheme 5. Deuterium-Directed Synthesis of (*S,R_p*)-5-*d*-7–11 and (*S,S_p*)-5-*d*-12

chloride (entry 1), chlorodicyclohexylphosphine (entry 2), phenyl and methyl disulfides (entries 3 and 4), diphenyl selenide (entry 5), and benzophenone (entry 6) as electrophiles all resulted in high diastereoselectivity. In almost all cases, the major

Table 3. Synthesis of (*S,R_p*)-5-*d*-7–11 and (*S,S_p*)-5-*d*-12

entry	electrophile	product	isomer ratio ^{a,b}	yield ^{c,d} (%) (% D ^{a,e})
1	CIP(O)Ph ₂	7	22:1	23 (92)
2	CIPCy ₂	8	17:1 ^c	86 ^f (94)
3	PhSSPh	9	12:1	85 (98)
4	MeSSMe	10	13:1	50 (96)
5	PhSeSePh	11	13:1	61 (96)
6	PhCOPh	12	11:1	68 ^g (94)

^aDetermined by ¹H NMR spectroscopy (500 MHz, CDCl₃).

^bDetermined before column chromatography unless otherwise stated.

^cDetermined after column chromatography (SiO₂).

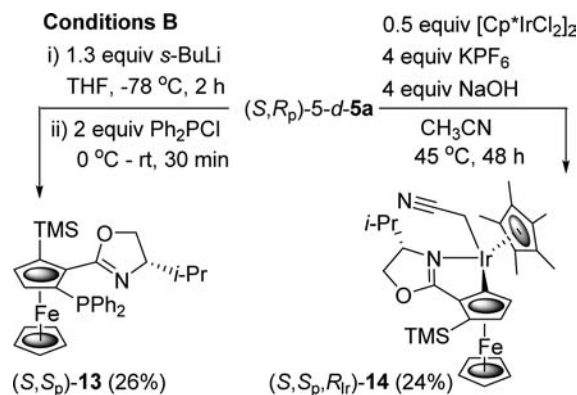
^dDiastereomerically pure unless otherwise stated. ^eOf major isomer. ^fObtained as a mixture of diastereoisomers ^gYield determined after recrystallization.

isomer was obtained readily as a single diastereoisomer following SiO₂ column chromatography or recrystallization.

The diastereomeric bidentate ligands listed in Tables 2 and 3 have the potential to be applied in many metal-catalyzed asymmetric reactions. For such applications, the incorporated deuterium blocking group may be regarded as being stereochemically invisible. When not broken as part of a reaction, the similarity between a C–D and a C–H bond is illustrated by the former being only ca. 0.4 pm shorter than the latter.¹³ Furthermore, the five-bond separation between deuterium and a metal coordinated by one of the bidentate ligands listed in Tables 2 and 3 would appear to rule out the possibility of secondary isotope effects influencing catalyst activity and selectivity.^{14,15}

Finally, that deuterium can be replaced in a subsequent reaction was illustrated by two procedures starting with (*S,R_p*)-5-*d*-5a that display C–D vs C–Si selectivity (Scheme 6).

Scheme 6. Selective C–D vs C–Si Lithiation and Cycloiridation



Lithiation using conditions B, with *s*-BuLi substituted for *n*-BuLi, followed by addition of chlorodiphenylphosphine led to the isolation of silylated N–P ligand (*S,S_p*)-13.¹¹ Also displaying this selectivity was cycloiridation with [Cp*IrCl₂]₂ which resulted in iridacycle (*S,S_p*,*R_{Ir}*)-14 being formed as a

single diastereoisomer.¹⁶ These uses of deuterium as a removable blocking group illustrate how this methodology enables the rapid stereoselective synthesis of multiple substituted ferrocene derivatives.

In conclusion, the combination of high and low diastereoselectivity resulting from C–H lithiation and the use of the high value of the primary kinetic isotope effect observed for C–D vs C–H lithiation provide the basis for largely reversing the diastereoselectivity of lithiation. This was exploited for the practical two-step synthesis of a series of ferrocenyloxazoline-based ligands and extended to the synthesis of trisubstituted ferrocene derivatives.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: [10.1021/acs.orglett.6b03874](https://doi.org/10.1021/acs.orglett.6b03874).

Experimental procedures and compound characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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