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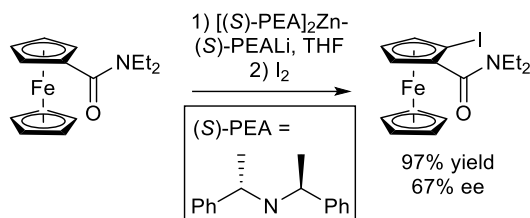
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Our attempts to deprotometalate *N,N*-dialkyl ferrocenecarboxamides enantioselectively by using chiral lithium or lithium-zinc dialkylamides are reported.

## Enantioselective deprotometalation of *N,N*-dialkyl ferrocenecarboxamides using metal amides†

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## Abstract:

*N,N*-Diisopropylferrocenecarboxamide can be enantioselectively deprotometalated by combining butyllithium with (–)-sparteine in diethyl ether at low temperature. It is of interest to identify conditions that could allow substrates bearing more reactive functional groups (such as esters and ketones) to be similarly converted. We here report our efforts to use different chiral lithium-zinc bases, made from a simple chiral lithium amide, (*R,R*)- or (*S,S*)-lithium bis(1-phenylethyl)amide (PEALi), for the enantioselective deprotonation of *N,N*-diisopropylferrocenecarboxamide. First, different zinc-based *in situ* traps were employed to intercept the formed ferrocenyllithium; optimization using enantiopure lithium bis[1-(*S*)-phenylethyl]amide ((*S*)-PEALi) led to the 2-iodo derivative in 96% yield and 69% ee in favor of the *R<sub>p</sub>* enantiomer. The method was extended to *N,N*-dimethylferrocenecarboxamide, morpholinoferrrocenecarboxamide and *N,N*-diethylferrocenecarboxamide; for the latter, similar yield and enantioselectivity were recorded. DFT calculations on a model reaction showed very small differences between the activation energies leading to (*R<sub>p</sub>*)- and (*S<sub>p</sub>*)-2-lithioferrocenecarboxamides. Next, the behavior of various mixed amino-alkyl lithium zincates of the types  $R_2[(S)\text{-PEA}]\text{ZnLi}$  and  $R_2[(S)\text{-PEA}]_2\text{ZnLi}_2$  (R = alkyl) was studied, notably by varying the reaction temperature and time, and the amount of base. The best results were obtained with  $\text{Me}_2[(S)\text{-PEA}]_2\text{ZnLi}_2$ , affording the 2-iodo derivative in 97% yield and 86% ee in favor of the *S<sub>p</sub>* enantiomer.

## Introduction

Ferrocene-containing compounds have been used in different fields such as catalysis, material sciences and medicinal chemistry; thus, many efforts have been devoted to the development of efficient syntheses to produce these important substrates.<sup>1</sup> Among the existing ways to achieve ferrocene C-H bond functionalization, transition metal-catalyzed reactions have recently emerged,<sup>2-3</sup> with possible extensions to enantioselective versions.<sup>4</sup> However, the most efficient methods imply the use of expensive catalytic sources (e.g. palladium salts) and, while approaches using first-row transition

metals are investigated,<sup>5-6</sup> there is still a need for progress in the use of main-group metals such as lithium.

The stereoselective synthesis of 1,2-disubstituted ferrocenes can be achieved by deprotometalation of a ferrocene suitably substituted by a chiral directing group.<sup>7-10</sup> However, the introduction of chiral groups on ferrocene requires additional reaction steps before investigating the asymmetric process. Thus, looking for alternative chiral substituent-free routes is highly welcome, and employing chiral bases to deprotometalate prochiral monosubstituted ferrocenes is a promising one. In this vein, Uemura and co-workers reported in 1996 non-racemic 1,2-disubstituted derivatives, prepared upon treatment by butyllithium-(*R,R*)-*N,N,N',N'*-tetramethylcyclohexane-1,2-diamine in diethyl ether at 0 °C, from different (aminomethyl)ferrocenes (e.g. 80% ee for the *R<sub>P</sub>*-formylated derivative of Fc-CH<sub>2</sub>NMe<sub>2</sub>; Fc = ferrocenyl).<sup>11</sup> At almost the same time, Snieckus and co-workers showed that butyllithium can be combined with (-)-sparteine in diethyl ether at low temperature to deprotolithiate *N,N*-diisopropylferrocenecarboxamide in a highly enantioselective way (e.g. 96% ee in favor of the *R<sub>P</sub>* derivative after interception with iodine).<sup>12-13</sup> Alkylolithium-diamine chelates still have a place for enantioselective deprotonation of *N*-cumyl-*N*-ethylferrocenecarboxamide (using butyllithium-(-)-sparteine<sup>14</sup> and -(+)-sparteine surrogate<sup>15</sup> allows either one enantiomer or its antipode to be obtained) as well as boron trifluoride-activated aminoferrocenes (e.g. 82% ee for the *S<sub>P</sub>*-formylated derivative of Fc-NMe<sub>2</sub> by using isopropylolithium-(*S,S*)-*N,N'*-dimethyl-*N,N'*-dibutylcyclohexane-1,2-diamine in methyl *tert*-butyl ether at low temperature),<sup>16</sup> and (aminomethyl)ferrocenes (e.g. 90% ee for the *R<sub>P</sub>* carbinol derivative of Fc-CH<sub>2</sub>NMe<sub>2</sub> by using isopropylolithium-(*R,R*)-*N,N,N',N'*-tetramethylcyclohexane-1,2-diamine in pentane-diethyl ether at low temperature).<sup>17</sup> However, they can hardly be used in the case of other monosubstituted ferrocenes such as sulfonates.<sup>18</sup>

Lithium amides have barely been used for ferrocene enantioselective deprotonation. In 1995, Price and Simpkins reported the only significant example; upon treatment by lithium bis[(*S*)-1-phenylethyl]amide in THF (THF = tetrahydrofuran) containing an excess of chlorotrimethylsilane at -78

°C, ferrocene diphenylphosphine oxide was converted to its 2-silyl derivative in a non-racemic way (54% ee for the  $R_P$  enantiomer; 95% yield). In contrast, the ferrocenes substituted by  $\text{CH}_2\text{OH}$ ,  $\text{CH}_2\text{OMe}$ ,  $\text{CH}_2\text{OCH}_2\text{OMe}$ ,  $\text{PPh}_2$  or  $\text{SPh}$  did not react under these conditions while those substituted by  $\text{SO}_2\text{Ph}$  and  $\text{CONiPr}_2$  only gave racemic mixtures.<sup>19</sup> The poor reactivity of monosubstituted ferrocenes toward chiral lithium amides seems to have prevented the development of this approach.

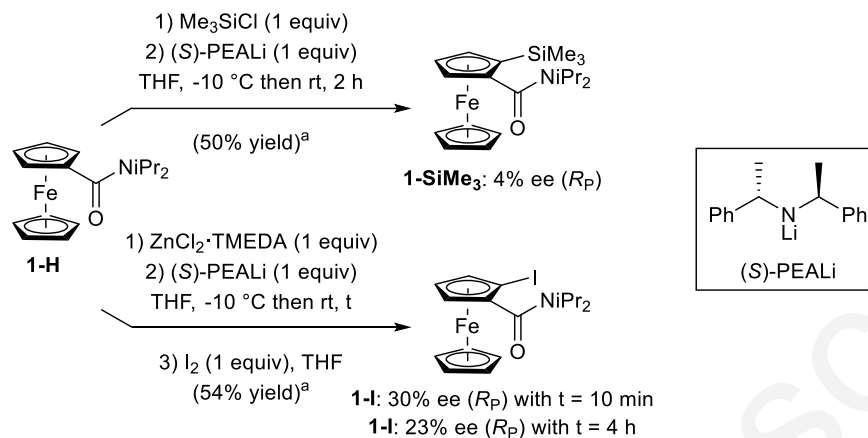
About ten years ago, we embarked in a study dedicated to the use of mixed lithium-zinc bases to enantioselectively deprotometalate  $N,N$ -diisopropylferrocenecarboxamide. In this context, we showed that bis[( $S$ )-1-phenylethyl]amino (( $S$ )-PEA) can be incorporated into lithium aminodialkylzincates or dilithium diaminodialkylzincates to generally furnish the  $S_P$  as major enantiomer after subsequent iodolysis while the  $R_P$  is favored after treatment of the monometal lithium bis[( $S$ )-1-phenylethyl]amide.<sup>20</sup> At this period, the understanding of such results was poor since only little was known on mixed lithium-zinc amides. In addition to providing more insight into this study, the last few years have witnessed the emergence of new metallic *in situ* traps by which lithium amide-mediated deprotonation can be moved forward.<sup>21</sup> This approach opened the way to the deprotonation of monosubstituted ferrocenes that were not reactive enough otherwise with chiral lithium amides. Our goal in the present paper is to disclose our latest findings on the subject.

## Results and discussion

### *Study using chiral lithium amides*

Price and Simpkins reported a deprotometalation-trapping sequence of  $N,N$ -diisopropylferrocenecarboxamide (**1-H**). The treatment at  $-78$  °C of a THF solution of **1-H** and chlorotrimethylsilane by lithium bis[( $S$ )-1-phenylethyl]amide (( $S$ )-PEALi) gave **1-SiMe<sub>3</sub>** as a racemic mixture.<sup>19</sup> Performing the same reaction at  $-10$  °C gave a similar result in our hands (Scheme 1, top). Interestingly, replacing chlorotrimethylsilane by  $\text{ZnCl}_2 \cdot \text{TMEDA}$  (TMEDA =  $N,N,N',N'$ -tetramethylethylenediamine) as *in situ* trap led to an enantiomeric mixture of iodides in which the  $R_P$  enantiomer predominates (Scheme 1, bottom). Even if lower under *in situ* trapping conditions, lithium

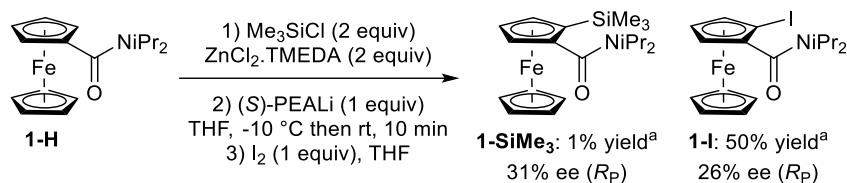
chloride has in general an impact on LiTMP-mediated deprotometalations.<sup>22</sup> In the present case, additional lithium chloride (1 equiv) had no effect on the course of the latter reaction.



**Scheme 1.** Effect of the *in situ* trap on the enantioselectivity.

<sup>a</sup> The rest is starting material and, in the case of  $\text{Me}_3\text{SiCl}$ , traces of a disilylated product (probably formed from **1-SiMe<sub>3</sub>** by a further deprotometalation-trapping sequence).<sup>12</sup>

At this stage, we suspected a different ability to intercept the generated lithio compound between chlorotrimethylsilane and  $\text{ZnCl}_2\cdot\text{TMEDA}$ . This prompted us to perform a competitive experiment by adding (S)-PEALi at  $-10\text{ }^\circ\text{C}$  to **1-H** in the presence of equimolar amounts of both chlorotrimethylsilane and  $\text{ZnCl}_2\cdot\text{TMEDA}$ . While aryl silanes are only converted to the corresponding aryl iodides under specific conditions, all arylzinc or zincate compounds (even in the presence of lithium salts) are spontaneously iodolyzed when treated by a THF solution of iodine.<sup>21</sup> Thus, after subsequent iodolysis, we expected silane **1-SiMe<sub>3</sub>** to remain unchanged and the organozincs to be converted to iodide **1-I**. The results showed that  $\text{ZnCl}_2\cdot\text{TMEDA}$  is capable of trapping the lithio compound more efficiently than chlorotrimethylsilane since iodide **1-I** was isolated in 50% yield (26% ee) while only traces of silane **1-SiMe<sub>3</sub>** (31% ee) were detected (Scheme 2).



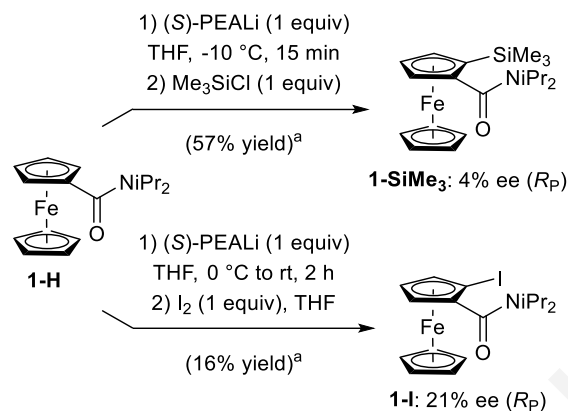
**Scheme 2.** Competitive experiment to identify the best *in situ* trap. <sup>a</sup> The rest is starting material.

Thus, the lower efficiency of chlorotrimethylsilane to act as *in situ* trap could result in the low enantioselectivities recorded in the case of silane **1-SiMe<sub>3</sub>** (Scheme 1, top). That it was obtained in 31% ee in our competitive experiment is not inconsistent with this statement; indeed, these traces of **1-SiMe<sub>3</sub>** were formed at the same time as iodide **1-I**. This experiment tends to show that the difference observed by using two different electrophiles depends on their ability to rapidly intercept the ferrocenyllithium.

It is of interest to draw a parallel between these results and those reported by Simpkins and co-workers on tricarbonyl( $\eta^6$ -arene)chromiums. From 1994, these authors have shown that discrimination by deprotolithiation is possible between the two enantiotopic adjacent hydrogens of such monosubstituted complexes under certain conditions.<sup>23-25</sup> By using chlorotrimethylsilane as *in situ* quench and lithium bis[(*R*)-1-phenylethyl]amide [(*R*)-PEALi] as base in THF at -78 °C, the silanes were obtained in yields and selectivities depending on the substituent (OiPr: 65% yield, 90% ee in favor of the *S<sub>P</sub>* enantiomer; OMe: 83%, 84%; OEt: 82%, 81%; OCH<sub>2</sub>OMe: 76%, 80%; CH(OCH<sub>2</sub>CH<sub>2</sub>O): 36%, 84%; Cl: 27%, 51%; CONiPr<sub>2</sub>: 87%, 48%; N(Me)CO*t*Bu: 65%, 44%; F: 57%, 16%).<sup>23,25</sup> That the discrimination was kinetically controlled was later evidenced by these authors, with a racemization of the lithio derivatives occurring for most of the substrates in the presence of proton donors such as the starting complex and, to a lesser extent, the amine formed upon the deprotometalation.<sup>24-25</sup>

In an effort to know whether or not such a racemization could take place in the case of **1-H**, we investigated the accumulation of its lithio derivative before the trapping step. When chlorotrimethylsilane was added after 15 min contact in THF at -10 °C between **1-H** and (*S*)-PEALi (1 equiv), silane **1-SiMe<sub>3</sub>** was isolated in 57% yield as a racemic mixture (Scheme 3), probably because the reaction actually starts after addition of chlorotrimethylsilane (as in Scheme 1, top). A different result was recorded when iodine was introduced after 2 h contact in THF at room temperature between **1-H** and (*S*)-PEALi. The moderate 16% yield noticed in the latter case can be easily rationalized by the absence of either *in situ* trap<sup>21</sup> or LiCl<sup>22</sup> which are both known to accelerate lithium amide-mediated deprotometalations. As to the racemization of the lithio compound, an enantioselectivity in favor of the

$R_P$  enantiomer is still observed after 2 h at room temperature (21% ee; Scheme 3); it is lower than the one obtained after 10 min (30% ee) but seems to be faster than observed for the corresponding organozincs (23% ee after 4 h) (Scheme 1, bottom).



**Scheme 3.** Effect of the trapping conditions on the enantioselectivity.

<sup>a</sup> The rest is starting material and, in the case of  $\text{Me}_3\text{SiCl}$ , traces of a disilylated product (probably formed from **1-SiMe<sub>3</sub>** by a further deprotonation-trapping sequence).<sup>12</sup>

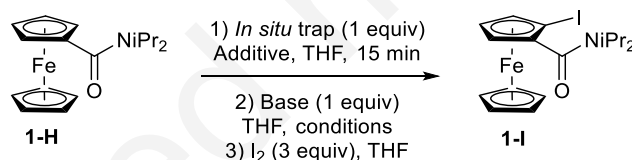
In a previous study dedicated to the diastereoselective deprotonation of sugar-based ferrocene esters, we identified the *in situ* trap-base pair  $[(R)$ -PEA]<sub>2</sub>Zn (*in situ* prepared from  $\text{ZnCl}_2 \cdot \text{TMEDA}$  and  $(R)$ -PEALi in a 1:2 ratio) -  $(R)$ -PEALi as efficient for this purpose.<sup>26</sup> The best results being so far observed by using  $\text{ZnCl}_2 \cdot \text{TMEDA}$ , we decided to turn to bisaminozincs as *in situ* traps (Table 1).

The results recorded under various conditions allow some conclusions to be drawn. First, the yields are now nearly quantitative while they were around 50% by using chlorotrimethylsilane or  $\text{ZnCl}_2 \cdot \text{TMEDA}$  as *in situ* trap; this could be due to competitive trapping of the lithium amide by the *in situ* trap (Schemes 1 and 2). At temperatures between  $-20^\circ\text{C}$  and  $0^\circ\text{C}$ , the enantioselectivities were found similar to those obtained by using  $\text{ZnCl}_2 \cdot \text{TMEDA}$  as *in situ* trap (see Scheme 1), and do not change by varying the contact time before iodolysis (entries 1-3). In addition, the presence of an additional equivalent of TMEDA has no effect on the course of the reaction. The use of either achiral  $(\text{TMP})_2\text{Zn}$  (TMP = 2,2,6,6-tetramethylpiperidino; *in situ* prepared from  $\text{ZnCl}_2 \cdot \text{TMEDA}$  and  $\text{TMPLi}$  in a 1:2 ratio) as *in situ* trap, or achiral  $\text{TMPLi}$  as base leads to a partial or complete loss of enantioselectivity, a result that can be explained by both the higher propensity of  $\text{TMPLi}$  to deprotonate



than PEALi and rapid ligand exchanges (entries 4 and 5). Interestingly, decreasing the reaction temperature led to higher enantioselectivities, and the best result was obtained by introducing the base at -70 °C before a slow warming to -10 °C (69% ee), temperature at which iodolysis of the zinc species was performed (entries 6-8). The enantioselectivity noticed is not complete; this could be partly due to competitive deprotonation by an amido of the formed R[(S)-PEA]<sub>2</sub>ZnLi (R = deprotonated *N,N*-diisopropylferrocenecarboxamide **1**). Indeed, reaction of **1-H** with R[(S)-PEA]<sub>2</sub>ZnLi (R = Me or Et or Bu) in THF at 0 °C for 2 h followed by iodolysis led to **1-I** in good yields (81, 95 and 95%, respectively), but in enantioselectivities that depend on the R group (37% in favor of the *S<sub>P</sub>* enantiomer for Me, 26% in favor of the *R<sub>P</sub>* for Et and 13% in favor of the *S<sub>P</sub>* enantiomer for Bu). The use of *in situ* traps containing unreactive amido could be attempted in order to avoid such competitive zincate-mediated deprotometalation.

**Table 1.** Use of (R<sub>2</sub>N)<sub>2</sub>Zn-R<sub>2</sub>NLi *in situ* trap-base pairs to attempt the enantioselective functionalization of **1-H**.

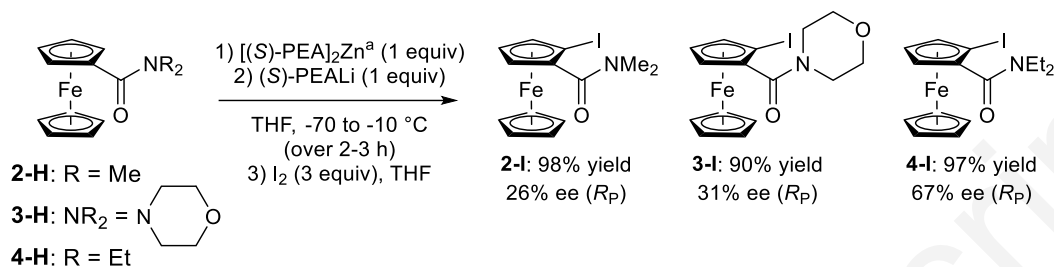


Entry	<i>In situ</i> trap	Base	Conditions	Yield of <b>1-I</b> (%) <sup>a</sup>	ee (%) <sup>b</sup>
1	[( <i>R</i> )-PEA] <sub>2</sub> Zn <sup>c</sup>	( <i>R</i> )-PEALi	0 °C, 0.5 h	96	35 ( <i>S<sub>P</sub></i> )
2	[( <i>R</i> )-PEA] <sub>2</sub> Zn <sup>c</sup>	( <i>R</i> )-PEALi	-20 °C, 10 min	97	32 ( <i>S<sub>P</sub></i> )
3	[( <i>R</i> )-PEA] <sub>2</sub> Zn <sup>c</sup>	( <i>R</i> )-PEALi	-20 °C, 4 h	98	32 ( <i>S<sub>P</sub></i> ) <sup>d</sup>
4	(TMP) <sub>2</sub> Zn <sup>c</sup>	( <i>R</i> )-PEALi	-20 °C, 0.5 h	97	10 ( <i>S<sub>P</sub></i> )
5	[( <i>S</i> )-PEA] <sub>2</sub> Zn <sup>c</sup>	TMPLi	-10 °C then rt, 0.5 h	97	1 ( <i>R<sub>P</sub></i> )
6	[( <i>S</i> )-PEA] <sub>2</sub> Zn <sup>c</sup>	( <i>S</i> )-PEALi	-10 °C then rt, 0.5 h	98	36 ( <i>R<sub>P</sub></i> )
7	[( <i>S</i> )-PEA] <sub>2</sub> Zn <sup>c</sup>	( <i>S</i> )-PEALi	-50 °C to -10 °C <sup>e</sup>	97	60 ( <i>R<sub>P</sub></i> ) <sup>f</sup>
8	[( <i>S</i> )-PEA] <sub>2</sub> Zn <sup>c</sup>	( <i>S</i> )-PEALi	-70 °C to -10 °C <sup>e</sup>	96	69 ( <i>R<sub>P</sub></i> )

<sup>a</sup> After purification (see experimental part). <sup>b</sup> Concerning the ee determination, see the experimental part and supporting information. <sup>c</sup> *In situ* prepared from ZnCl<sub>2</sub>·TMEDA and the lithium amide in a 1:2 ratio. <sup>d</sup> 33 (*S<sub>P</sub>*) (95% yield) when the reaction was carried out in the presence of an additional equivalent of TMEDA. <sup>e</sup> Slow warming (2-3 h). <sup>f</sup> 19 (*R<sub>P</sub>*) (68% yield) when only 0.5 equiv of *in situ* trap was used.

Next we examined the effect of the size of the ferrocene substituent on the discrimination control between the two enantiotopic adjacent hydrogens by deprotolithiation (Scheme 4). While *N,N*-

dimethylferrocenecarboxamide (**2-H**) and morpholinoferrrocenecarboxamide (**3-H**) are deprotonated with moderate enantioselectivities, *N,N*-diethylferrocenecarboxamide (**4-H**) led to 2-iodo **4-I** in both high yield and selectivity close to the one observed for **1-I**.



**Scheme 4.** Extension to other ferrocenecarboxamides.

<sup>a</sup> *In situ* prepared from ZnCl<sub>2</sub>·TMEDA and (S)-PEALi in a 1:2 ratio.

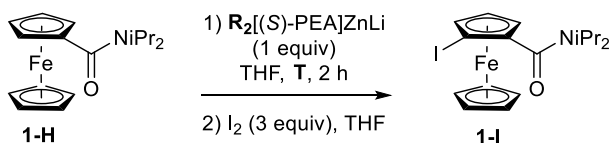
In order to have a more accurate idea about the origin of the lower enantioselectivities observed in the case of the less hindered carboxamides, the activation energies leading to (*R<sub>P</sub>*)- and (*S<sub>P</sub>*)-2-lithioferrocenecarboxamides were estimated and compared. DFT calculations at B3LYP/6-31+G\*\* (B3LYP/LanI2DZ for Fe) (without solvent or with dimethyl ether) level of theory were conducted on reactions involving *N,N*-dimethylferrocenecarboxamide (**2-H**) and monomeric LiTMP.<sup>22</sup> TMEDA and LiCl were neglected since these species have shown a low impact on LiTMP-mediated deprotonations in the presence of *in situ* traps.<sup>22</sup> The data given in Electronic supplementary information show very small differences between the activation energies leading to the (*R<sub>P</sub>*) and the (*S<sub>P</sub>*) lithio derivatives. As a consequence, racemization would not be at the origin of the lower enantioselectivities noticed in the case of **2-H** and **3-H**, but rather the smaller size of the carboxamide group.

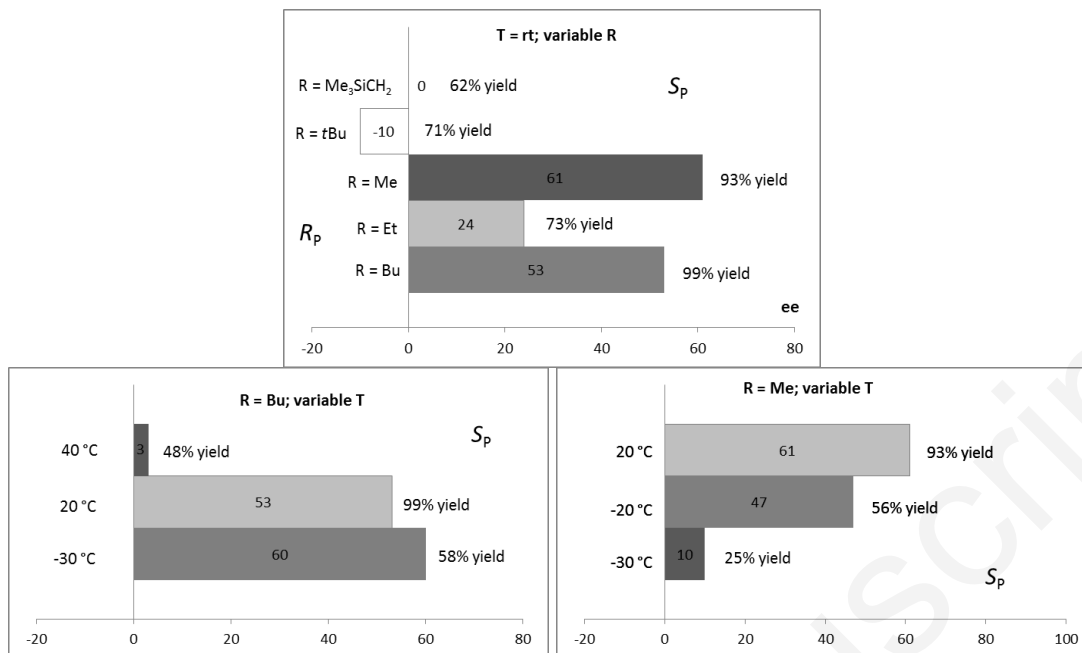
#### **Study using chiral lithium zincates**

Besides lithium amides, lithium aminozincates are alternative bases in which chiral amino groups can be incorporated.<sup>27-32</sup> We prepared different putative<sup>33-34</sup> R<sub>2</sub>[(S)-PEA]ZnLi (R = alkyl) in THF by reacting (S)-PEALi (1 equiv) with ZnCl<sub>2</sub>·TMEDA (15 min at 0 °C) before addition of RLi (R = Bu, Et, Me, *t*Bu, Me<sub>3</sub>SiCH<sub>2</sub>; 2 equiv) and stirring for 15 min at 0 °C. We first compared the ability of these

chiral zincates (1 equiv) to deprotonate **1-H** efficiently and chemoselectively at room temperature (Scheme 5, top). Trapping with iodine after 2 h showed that both yields and enantioselectivities depend on the alkyl group present in the zincate base.<sup>35-37</sup> The best results were recorded for R = Bu (99% yield and 53% ee in favor of the *S<sub>P</sub>* enantiomer) and R = Me (93% yield and 61% ee in favor of the *S<sub>P</sub>* enantiomer). The yields are lower (between 62 and 73%) for the other alkyl groups; a racemic mixture was obtained in the case of R = Me<sub>3</sub>SiCH<sub>2</sub> while moderate enantioselectivities were noticed for R = Et (still in favor of the *S<sub>P</sub>* enantiomer) and above all R = *t*Bu (the only result in favor of the *R<sub>P</sub>* enantiomer). A few data are available in the literature on arene deprotonations using the corresponding R<sub>2</sub>[TMP]ZnLi bases. With R = Et<sup>38</sup> and *t*Bu,<sup>34,39</sup> the reactions seem to proceed in two steps: (i) TMP-mediated proton abstraction, and (ii) alkyl-mediated TMPH consumption. In the case of R = Me<sup>40</sup> and *t*Bu,<sup>39</sup> reactions of the deprotonated arenes with the formed TMPH are not excluded. Because of the complexity of the present reactions, it is difficult to draw conclusions about the results obtained. However, one can mention that the enantioselectivity generally observed by using these lithium aminodialkylzincates made from (*S*)-PEALi (in favor of the *S<sub>P</sub>* enantiomer) is in general opposite to that recorded with (*S*)-PEALi (in favor of the *R<sub>P</sub>* enantiomer).

By employing PEALi with **1-H**, lowering the temperature had a positive effect on the enantioselectivity (Table 1, entries 6-8). Thus, with the most promising lithium aminozincates (R = Bu and R = Me), we repeated a few reactions at different temperatures (Scheme 5, bottom). These lithium zincates proved to be less reactive than the (*S*)-PEALi-*in situ* trap tandems at low temperatures (-30 °C) while higher temperatures (40 °C) did not give better results. As observed above, these lower yields in general (except in one case) matched with lower enantioselectivities.



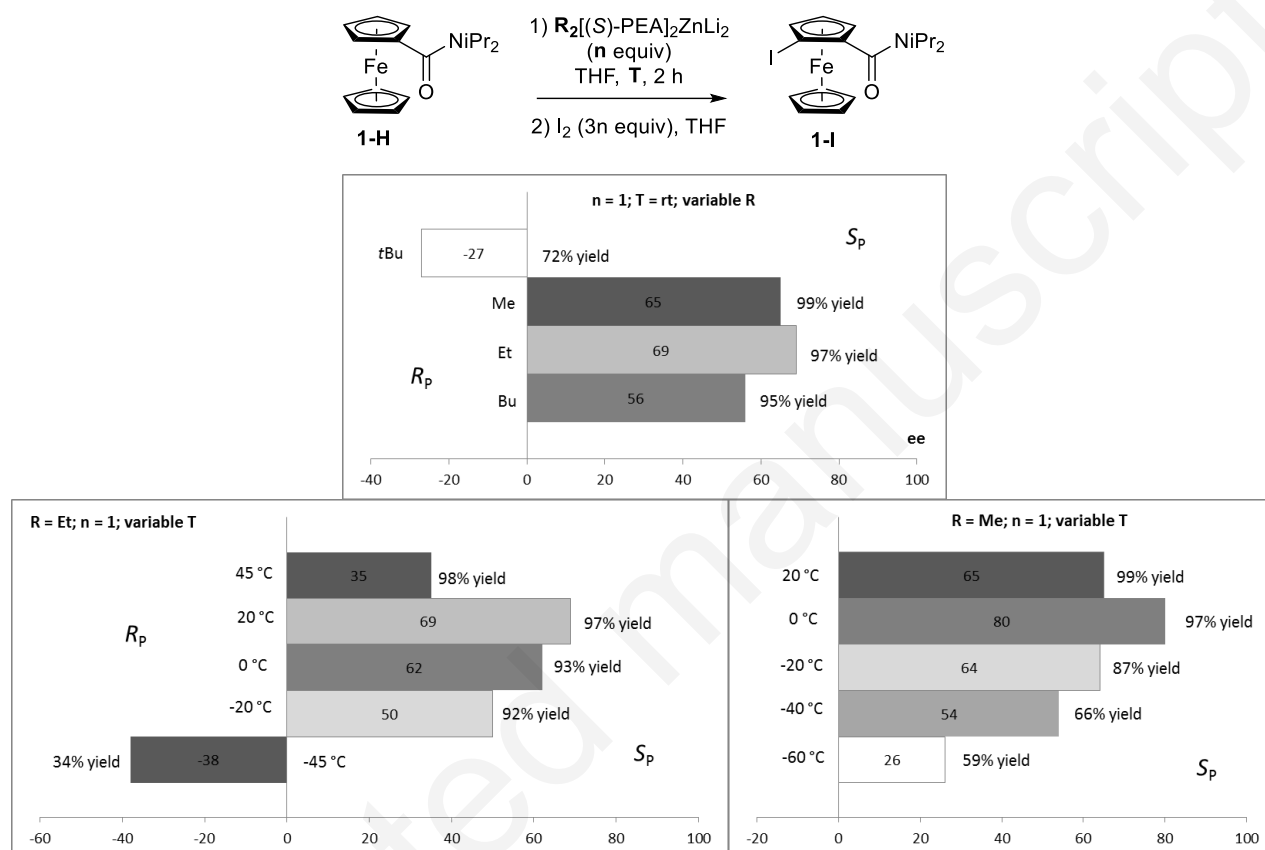


**Scheme 5.** Enantioselective functionalization of **1-H** using lower order lithium zincates.  
*Top:* Use of different R<sub>2</sub>[(S)-PEA]ZnLi at rt (ee are given for the different R groups tested).  
*Bottom:* Use of R<sub>2</sub>[(S)-PEA]ZnLi at different temperatures (*left:* R = Bu; *right:* R = Me).

We next turned to the corresponding higher order mixed dialkyl-diamino dilithium zincates,<sup>41</sup> which are generally more reactive than the lower order ones,<sup>27-32</sup> in order to compare them with lithium aminodialkylzincates used before. To this purpose, new putative<sup>20</sup> R<sub>2</sub>[(S)-PEA]<sub>2</sub>ZnLi<sub>2</sub> (R = alkyl) were prepared in THF by reacting (S)-PEALi (2 equiv) with ZnCl<sub>2</sub>·TMEDA (15 min at 0 °C) before addition of RLi (R = Bu, Et, Me, tBu; 2 equiv) and stirring for 15 min at 0 °C. As before, the substrate **1-H** was added at 0 °C before warming at room temperature for 2 h and subsequent iodolysis (Scheme 6, top). Under these conditions, the S<sub>P</sub> enantiomer also predominated in the case of R = Bu (95% yield; 56% ee), R = Et (97% yield; 69% ee) and R = Me (99% yield; 65% ee) while it was rather the R<sub>P</sub> enantiomer with R = tBu (72% yield; 27% ee).

Solvents other than THF were tested; using dimethoxymethane or 1,2-dimethoxyethane for the reaction of **1-H** with Bu<sub>2</sub>[(S)-PEA]<sub>2</sub>ZnLi<sub>2</sub> at -25 °C gave the expected iodide in similar yields but lower enantioselectivities (21 and 30% ee, respectively). As above, we repeated the reactions involving the most promising higher order dilithium diaminozincates (R = Et, Me) at different temperatures (Scheme 6, bottom). As expected, a higher reactivity was observed at lower temperatures (about 90% yield at -20

°C against 55-60% for the lower order lithium zincates); in addition to remaining **1-H**, *N,N*-diisopropyl-1'-iodoferrocenecarboxamide was also detected in the crudes when these higher order zincates were used. The temperature has a high impact on the enantioselectivity, with the best results noticed at 0-20 °C (80% ee for R = Me at 0 °C).



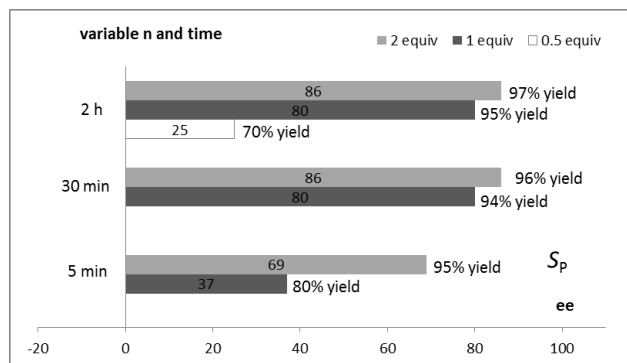
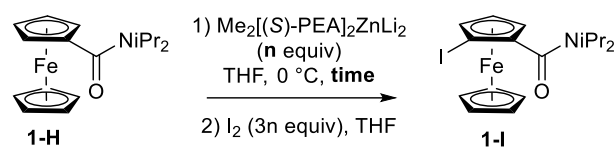
**Scheme 6.** Enantioselective functionalization of **1-H** using higher order lithium zincates.

*Top:* Use of different  $\text{R}_2[(\text{S})\text{-PEA}]_2\text{ZnLi}_2$  at rt (ee are given).

*Bottom:* Use of  $\text{R}_2[(\text{S})\text{-PEA}]\text{ZnLi}$  at different temperatures (*left:* R = Et; *right:* R = Me).

Note that the  $R_P$  enantiomer was also obtained by using  $\text{Et}[(\text{S})\text{-PEA}]_2\text{ZnLi}$  at 0 °C.

It was also of interest to see the impact of the amount of base and reaction time on the course of the reaction using putative<sup>20</sup>  $\text{Me}_2[(\text{S})\text{-PEA}]_2\text{ZnLi}_2$  (Scheme 7). In the previous experiments, a contact time of 2 h between the zincate base (1 equiv) and **1-H** was used before iodolysis; it was found that 0.5 h was enough to ensure a similar result, but 5 min reaction time led to a lower yield together with a drop on the enantioselectivity. Interestingly, increasing the amount of base (from 0.5 to 2 equiv), by increasing the yield, favors the formation of the  $S_P$  enantiomer.



**Scheme 7.** Impact of the amount of base and reaction time on the enantioselective functionalization of **1-H** using higher order lithium zincates.

In an attempt to simplify the possible pathways, putative<sup>20</sup>  $\text{Me}_2[(S)\text{-PEA}]_2\text{ZnLi}_2$  was replaced by putative<sup>20</sup>  $\text{Me}_3[(S)\text{-PEA}]\text{ZnLi}_2$ ; however, if good yields were obtained (>90%), the enantioselectivities were lowered to about 50% after 2 h reaction times at 0 or 20 °C. Different amounts of methyllithium (1, 2 or 3 equiv) were also added to a mixture of **1-H** and  $[(S)\text{-PEA}]_2\text{Zn}$  in THF at 0 °C; high yields were obtained for the three quantities, but a significant enantioselectivity was only observed for 2 equivalents (65% ee), confirming the efficiency of putative<sup>20</sup>  $\text{Me}_2[(S)\text{-PEA}]_2\text{ZnLi}_2$ . Finally, using putative<sup>29</sup>  $\text{Me}[(S)\text{-PEA}]_2\text{ZnLi}$  led to the iodide in 81% yield and 37% ee.

## Conclusions

Our goal was to find a way to deprotonate *N,N*-diisopropylferrocenecarboxamide in an enantioselective way with recourse to chiral lithium amides. The best results were obtained by using a putative higher order dialkyl-diamino dilithium zincate,  $\text{Me}_2[(S)\text{-PEA}]_2\text{ZnLi}_2$ . However, these results proved quite difficult to rationalize due to the numerous possible ways by which the starting ferrocene can be deprotonated/reprotonated, and the numerous zinc compounds in which the deprotonated ferrocene can be incorporated (not to mention the disproportionation by which  $\text{LiR}(\text{Fc})\text{ZnNR}_2$  could also be converted into  $\text{Fc}_2\text{Zn}$  and  $\text{Li}_2\text{R}_2\text{Zn}(\text{NR}_2)_2$ ).<sup>39</sup> As a consequence, it is not obvious to explain why,

for a great majority of the reactions, remaining starting material in the crude goes hand in hand with loss of enantioselectivity. In contrast, the use of PEALi-*in situ* trap tandems appears as being easier to understand, and promising results were obtained on *N,N*-diethylferrocenecarboxamide. Studies on substrates not compatible with chiral chelates such as BuLi-(–)-sparteine are underway in the group.

## Experimental

### General details

All the reactions were carried out in Schlenk tubes under an argon atmosphere. THF was distilled from sodium-benzophenone. Column chromatography separations were achieved on silica gel (40-63  $\mu\text{m}$ ). Melting points were measured on a Kofler apparatus. IR spectra were taken on a Perkin-Elmer Spectrum 100 spectrometer.  $^1\text{H}$  and  $^{13}\text{C}$  Nuclear Magnetic Resonance (NMR) spectra were recorded on a Bruker Avance III spectrometer at 300 MHz and 75 MHz respectively.  $^1\text{H}$  chemical shifts ( $\delta$ ) are given in ppm relative to the solvent residual peak and  $^{13}\text{C}$  chemical shifts are relative to the central peak of the solvent signal.<sup>42</sup>  $\text{ZnCl}_2\cdot\text{TMEDA}$ ,<sup>29</sup> *N,N*-diisopropylferrocenecarboxamide (**1-H**),<sup>43</sup> *N,N*-dimethylferrocenecarboxamide (**2-H**),<sup>43</sup> morpholinoferrrocenecarboxamide (**3-H**)<sup>43</sup> and *N,N*-diethylferrocenecarboxamide (**4-H**)<sup>43</sup> were prepared as described previously.

### Deprotonation with PEALi using chlorotrimethylsilane as *in situ* trap

To a stirred, cooled ( $-10\text{ }^\circ\text{C}$ ) solution of bis[(*S*)-1-phenylethyl]amine [(*S*)-PEAH; 0.23 mL, 1.0 mmol] in THF (6 mL) was added BuLi (1.6 M in hexanes, 1.0 mmol). After 5 min at this temperature, this solution of lithium (*S*)-PEALi was cannulated into a solution of *N,N*-diisopropylferrocenecarboxamide (**1-H**; 0.32 g, 1.0 mmol) and chlorotrimethylsilane (0.13 mL, 1.0 mmol) in THF (6 mL) at  $-10\text{ }^\circ\text{C}$ . The mixture was then stirred for 2 h at room temperature. The solvent was evaporated under reduced pressure, and purification by column chromatography over silica gel (eluent: petroleum ether-AcOEt 90:10;  $R_f = 0.61$ ) gave the silane **1-SiMe<sub>3</sub>** in 50% yield as an orange powder: mp  $113\text{-}114\text{ }^\circ\text{C}$ ; IR (ATR): 753, 807, 834, 979, 1000, 1036, 1279, 1368, 1455, 1627, 2972, 3100  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$

0.28 (s, 9H, SiMe<sub>3</sub>), 1.27 (br s, 12H, CHMe<sub>2</sub>), 3.44 (br s, 1H, CHMe<sub>2</sub>), 4.13 (dd, 1H, *J* = 2.3 and 1.2 Hz, H3), 4.18 (br s, 1H, CHMe<sub>2</sub>), 4.28 (s, 5H, Cp), 4.30 (t, 1H, *J* = 2.3 Hz, H4), 4.35 (dd, 1H, *J* = 2.3 and 1.2 Hz, H5); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 0.67 (3CH<sub>3</sub>, SiMe<sub>3</sub>), 20.9 (2CH<sub>3</sub>, CHMe<sub>2</sub>), 21.1 (2CH<sub>3</sub>, CHMe<sub>2</sub>), 46.1 (CH, CHMe<sub>2</sub>), 50.0 (CH, CHMe<sub>2</sub>), 69.4 (CH), 69.9 (5CH, Cp), 69.9 (CH), 73.5 (CH), 73.7 (C, C2), 92.3 (C, C1), 169.0 (C, C=O). The spectral data are analogous to those described previously.<sup>12</sup> The ee (4% in favor of the *R*<sub>P</sub> enantiomer) was determined by HPLC analysis on a chiral stationary phase (IC3 column; hexane-isopropanol 99.5:0.5; 0.7 mL.min<sup>-1</sup>; 20 °C; λ = 220 nm).

### Deprotonation with PEALi using ZnCl<sub>2</sub>·TMEDA as *in situ* trap

To a stirred, cooled (-10 °C) solution of bis[(*S*)-1-phenylethyl]amine [(*S*)-PEAH; 0.23 mL, 1.0 mmol] in THF (6 mL) was added BuLi (1.6 M in hexanes, 1.0 mmol). After 5 min at this temperature, this solution of lithium (*S*)-PEALi was cannulated into a solution of *N,N*-diisopropylferrocenecarboxamide (**1-H**; 0.32 g, 1.0 mmol) and ZnCl<sub>2</sub>·TMEDA (0.25 g, 1.0 mmol) in THF (6 mL) at -10 °C. The mixture was then stirred for a reaction time *t* (10 min or 4 h) at room temperature, and a solution of I<sub>2</sub> (0.25 g, 1.0 mmol) in THF (6 mL) was added. The mixture was stirred overnight before addition of an aqueous saturated solution of Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (10 mL) and extraction with AcOEt (3 x 20 mL). After drying over anhydrous Na<sub>2</sub>SO<sub>4</sub>, the solvent was evaporated under reduced pressure, and purification by column chromatography over silica gel (eluent: heptane-AcOEt 95:5; R<sub>f</sub> = 0.65) gave the iodide **1-I** in 54% yield as an orange powder. The compound was found identical to that described previously.<sup>43</sup> The ee (30% in favor of the *R*<sub>P</sub> enantiomer for *t* = 10 min; 23% in favor of the *R*<sub>P</sub> enantiomer for *t* = 4 h) was determined by HPLC analysis on a chiral stationary phase (IC3 column; hexane-isopropanol 98:2; 1.5 mL.min<sup>-1</sup>; 20 °C; λ = 220 nm).

### Competitive experiment between two *in situ* traps, chlorotrimethylsilane and ZnCl<sub>2</sub>·TMEDA

To a stirred, cooled (-10 °C) solution of bis[(*S*)-1-phenylethyl]amine [(*S*)-PEAH; 0.23 mL, 1.0 mmol] in THF (6 mL) was added BuLi (1.6 M in hexanes, 1.0 mmol). After 5 min at this temperature, this solution of lithium (*S*)-PEALi was cannulated into a solution of *N,N*-diisopropylferrocenecarboxamide



(**1-H**; 0.32 g, 1.0 mmol), chlorotrimethylsilane (0.26 mL, 2.0 mmol) and  $\text{ZnCl}_2 \cdot \text{TMEDA}$  (0.50 g, 2.0 mmol) in THF (6 mL) at  $-10\text{ }^\circ\text{C}$ . The mixture was then stirred for 10 min at room temperature, and a solution of  $\text{I}_2$  (0.25 g, 1.0 mmol) in THF (6 mL) was added. The mixture was stirred overnight before addition of an aqueous saturated solution of  $\text{Na}_2\text{S}_2\text{O}_3$  (10 mL) and extraction with AcOEt (3 x 20 mL). After drying over anhydrous  $\text{Na}_2\text{SO}_4$ , the solvent was evaporated under reduced pressure, and purification by column chromatography over silica gel (eluent: heptane-AcOEt 95:5) gave the iodide **1-I** in 50% yield and the silane **1-SiMe<sub>3</sub>** in 1% yield. The ee (26% in favor of the  $R_P$  enantiomer) of **1-I** was determined by HPLC analysis on a chiral stationary phase (IC3 column; hexane-isopropanol 99:1; 1 mL.min<sup>-1</sup>; 20 °C;  $\lambda = 220\text{ nm}$ ). The ee (31% in favor of the  $R_P$  enantiomer) of **1-SiMe<sub>3</sub>** was determined by HPLC analysis on a chiral stationary phase (IC3 column; hexane-isopropanol 99.5:0.5; 0.7 mL.min<sup>-1</sup>; 20 °C;  $\lambda = 220\text{ nm}$ ).

#### **Deprotonation with PEALi followed by trapping using chlorotrimethylsilane**

To a stirred, cooled ( $-10\text{ }^\circ\text{C}$ ) solution of bis[(*S*)-1-phenylethyl]amine [(*S*)-PEAH; 0.23 mL, 1.0 mmol] in THF (6 mL) was added BuLi (1.6 M in hexanes, 1.0 mmol). After 5 min at this temperature, this solution of lithium (*S*)-PEALi was cannulated into a solution of *N,N*-diisopropylferrocenecarboxamide (**1-H**; 0.32 g, 1.0 mmol) in THF (6 mL) at  $-10\text{ }^\circ\text{C}$ . The mixture was then stirred for 15 min at this temperature before trapping with chlorotrimethylsilane (0.13 mL, 1.0 mmol). The solvent was evaporated under reduced pressure, and purification by column chromatography over silica gel (eluent: petroleum ether-AcOEt 90:10;  $R_f = 0.61$ ) gave the silane **1-SiMe<sub>3</sub>** in 57% yield. The ee (4% in favor of the  $R_P$  enantiomer) was determined by HPLC analysis on a chiral stationary phase (IC3 column; hexane-isopropanol 99.5:0.5; 0.7 mL.min<sup>-1</sup>; 20 °C;  $\lambda = 220\text{ nm}$ ).

#### **Deprotonation with PEALi followed by trapping using iodine**

To a stirred, cooled ( $-10\text{ }^\circ\text{C}$ ) solution of bis[(*S*)-1-phenylethyl]amine [(*S*)-PEAH; 0.23 mL, 1.0 mmol] in THF (6 mL) was added BuLi (1.6 M in hexanes, 1.0 mmol). After 5 min at this temperature, this solution of lithium (*S*)-PEALi was treated by *N,N*-diisopropylferrocenecarboxamide (**1-H**; 0.32 g, 1.0

mmol). The mixture was then stirred for 2 h at room temperature, and a solution of I<sub>2</sub> (0.25 g, 1.0 mmol) in THF (6 mL) was added. The mixture was stirred overnight before addition of an aqueous saturated solution of Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (10 mL) and extraction with AcOEt (3 x 20 mL). After drying over anhydrous Na<sub>2</sub>SO<sub>4</sub>, the solvent was evaporated under reduced pressure, and purification by column chromatography over silica gel (eluent: heptane-AcOEt 95:5; R<sub>f</sub> = 0.65) gave the iodide **1-I** in 16% yield. The ee (21% in favor of the R<sub>P</sub> enantiomer) was determined by HPLC analysis on a chiral stationary phase (IC3 column; hexane-isopropanol 98:2; 1.5 mL.min<sup>-1</sup>; 20 °C; λ = 220 nm).

#### **General procedure for the deprotonation with PEALi using (PEA)<sub>2</sub>Zn as *in situ* trap**

To a stirred, cooled (-10 °C) solution of bis[(*S*)-1-phenylethyl]amine [(*S*)-PEAH; 0.46 mL, 2.0 mmol] in THF (6 mL) was added BuLi (1.6 M in hexanes, 2.0 mmol). After 5 min at this temperature, ZnCl<sub>2</sub>·TMEDA (0.25 g, 1.0 mmol) was quickly introduced and, after 15 min stirring at -10 °C the starting ferrocene (1.0 mmol). After 15 min, this mixture was cooled at -70 °C before slow cannulation of a solution of lithium (*S*)-PEALi (1.0 mmol; prepared as before in THF and cooled at -70 °C). The bath was slowly warmed to -10 °C (it takes 2-3 h), and a solution of I<sub>2</sub> (0.76 g, 3.0 mmol) in THF (10 mL) was added. The mixture was stirred overnight before addition of an aqueous saturated solution of Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (10 mL) and extraction with AcOEt (3 x 20 mL). After drying over anhydrous Na<sub>2</sub>SO<sub>4</sub>, the solvent was evaporated under reduced pressure, and the iodide was purified by column chromatography over silica gel (the eluent is given in the product description).

*N,N*-Diisopropyl-2-iodoferrocenecarboxamide (**1-I**). The general procedure applied to *N,N*-diisopropylferrocenecarboxamide (**1-H**; 0.32 g, 1.0 mmol) gave the iodide **1-I** in 96% yield (eluent: heptane-AcOEt 95:5; R<sub>f</sub> = 0.65) as an orange powder. The compound was found identical to that described previously.<sup>43</sup> The ee (69% in favor of the R<sub>P</sub> enantiomer) was determined by HPLC analysis on a chiral stationary phase (IC3 column; hexane-isopropanol 99:1; 1 mL.min<sup>-1</sup>; 20 °C; λ = 220 nm).

*N,N*-Dimethyl-2-iodoferrocenecarboxamide (**2-I**). The general procedure applied to *N,N*-dimethylferrocenecarboxamide (**2-H**; 0.26 g, 1.0 mmol) gave the iodide **2-I** in 98% yield (eluent:

petroleum ether-AcOEt 70:30;  $R_f = 0.33$ ) as an orange powder. The compound was found identical to that described previously.<sup>43</sup> The ee (26% in favor of the  $R_P$  enantiomer) was determined by HPLC analysis on a chiral stationary phase (IC3 column; hexane-isopropanol 85:15; 1.5 mL.min<sup>-1</sup>; 20 °C;  $\lambda = 220$  nm).

*1-Iodo-2-(4-morpholinocarbonyl)ferrocene (3-I)*. The general procedure applied to morpholinoferrrocenecarboxamide (**3-H**; 0.30 g, 1.0 mmol) gave the iodide **3-I** in 90% yield (eluent: petroleum ether-AcOEt 60:40;  $R_f = 0.37$ ) as a yellowish powder. The compound was found identical to that described previously.<sup>43</sup> The ee (31% in favor of the  $R_P$  enantiomer) was determined by HPLC analysis on a chiral stationary phase (IC3 column; hexane-isopropanol 90:10; 1.5 mL.min<sup>-1</sup>; 20 °C;  $\lambda = 220$  nm).

*N,N-Diethyl-2-iodoferrrocenecarboxamide (4-I)*. The general procedure applied to *N,N*-diethylferrrocenecarboxamide (**4-H**; 0.285 g, 1.0 mmol) gave the iodide **4-I** in 97% yield (eluent: petroleum ether-AcOEt 80:20;  $R_f = 0.43$ ) as an orange powder. The compound was found identical to that described previously.<sup>43</sup> The ee (67% in favor of the  $R_P$  enantiomer) was determined by HPLC analysis on a chiral stationary phase (IC3 column; hexane-isopropanol 96:4; 1.5 mL.min<sup>-1</sup>; 20 °C;  $\lambda = 220$  nm).

#### **Typical procedure for the deprotonation with lower order lithium zincates**

To a stirred, cooled (0 °C) solution of bis[(*S*)-1-phenylethyl]amine [(*S*)-PEAH; 0.23 mL, 1.0 mmol] in THF (5 mL) were successively added BuLi (1.6 M in hexanes, 1.0 mmol) and, 5 min later, ZnCl<sub>2</sub>·TMEDA (0.25 g, 1.0 mmol). The mixture was stirred for 15 min at 0 °C before introduction of MeLi (1.6 M in Et<sub>2</sub>O, 2.0 mmol) and, 15 min later, *N,N*-diisopropylferrrocenecarboxamide (**1-H**; 0.32 g, 1.0 mmol). After 2 h at room temperature, a solution of I<sub>2</sub> (0.76 g, 3.0 mmol) in THF (10 mL) was added. The mixture was stirred overnight before addition of an aqueous saturated solution of Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (10 mL) and extraction with AcOEt (3 x 20 mL). After drying over anhydrous Na<sub>2</sub>SO<sub>4</sub>, the solvent was evaporated under reduced pressure, and purification by column chromatography over silica gel (eluent:

heptane-AcOEt 95:5;  $R_f = 0.65$ ) gave the iodide **1-I** in 93% yield. The ee (61% in favor of the  $S_P$  enantiomer) was determined by HPLC analysis on a chiral stationary phase (IC3 column; hexane-isopropanol 98:2; 1.5 mL.min<sup>-1</sup>; 20 °C;  $\lambda = 220$  nm).

#### **Typical procedure for the deprotonation with higher order lithium zincates**

To a stirred, cooled (0 °C) solution of bis[(*S*)-1-phenylethyl]amine [(*S*)-PEAH; 0.46 mL, 2.0 mmol] in THF (5 mL) were successively added BuLi (1.6 M in hexanes, 2.0 mmol) and, 5 min later, ZnCl<sub>2</sub>·TMEDA (0.25 g, 1.0 mmol). The mixture was stirred for 15 min at 0 °C before introduction of MeLi (1.6 M in Et<sub>2</sub>O, 2.0 mmol) and, 15 min later, *N,N*-diisopropylferrocenecarboxamide (**1-H**; 0.32 g, 1.0 mmol). After 2 h at room temperature, a solution of I<sub>2</sub> (1.0 g, 4.0 mmol) in THF (10 mL) was added. The mixture was stirred overnight before addition of an aqueous saturated solution of Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (10 mL) and extraction with AcOEt (3 x 20 mL). After drying over anhydrous Na<sub>2</sub>SO<sub>4</sub>, the solvent was evaporated under reduced pressure, and purification by column chromatography over silica gel (eluent: heptane-AcOEt 95:5;  $R_f = 0.65$ ) gave the iodide **1-I** in 97% yield. The ee (80% in favor of the  $S_P$  enantiomer) was determined by HPLC analysis on a chiral stationary phase (IC3 column; hexane-isopropanol 98:2; 1.5 mL.min<sup>-1</sup>; 20 °C;  $\lambda = 220$  nm).

**Conflicts of interest.** There are no conflicts of interest to declare.

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**Electronic Supplementary Information (ESI) available:** HPLC chromatograms, and computational details. See: DOI: 10.1039/xx.

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