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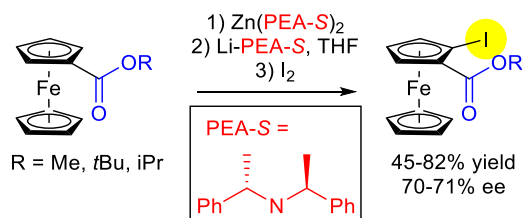
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Our attempts to deprotometalate alkyl ferrocenecarboxylates enantioselectively by using chiral lithium-zinc or lithium-cadmium bases are reported.

## Enantioselective deprotometalation of alkyl ferrocenecarboxylates using bimetallic bases†

Gandrath Dayaker,<sup>¶a</sup> William Erb,<sup>a,\*</sup> Madani Hedidi,<sup>‡a,b</sup> Floris Chevallier,<sup>§a,\*</sup> Marielle Blot,<sup>a</sup>  
Philippe C. Gros,<sup>c</sup> Göran Hilmersson,<sup>d</sup> Thierry Roisnel,<sup>a</sup> Vincent Dorcet,<sup>a</sup>  
Ghenia Bentabed-Ababsa<sup>b</sup> and Florence Mongin<sup>a,\*</sup>

<sup>a</sup> Univ Rennes, CNRS, ISCR (Institut des Sciences Chimiques de Rennes) - UMR 6226, F-35000 Rennes, France. E-mails: [william.erb@univ-rennes1.fr](mailto:william.erb@univ-rennes1.fr), [floris.chevallier@ens-lyon.fr](mailto:floris.chevallier@ens-lyon.fr), [florence.mongin@univ-rennes1.fr](mailto:florence.mongin@univ-rennes1.fr)

<sup>b</sup> Laboratoire de Synthèse Organique Appliquée, Faculté des Sciences Exactes et Appliquées, Université Oran1 Ahmed Ben Bella, BP 1524 El M'Naouer, 31000 Oran, Algeria

<sup>c</sup> Université de Lorraine, CNRS, L2CM, F-54000 Nancy, France

<sup>d</sup> Department of Chemistry and Molecular Biology, Göteborg University, 412 96 Göteborg, Sweden

<sup>¶</sup> Current address: Department of Chemistry, McGill University, FRQNT Centre for Green Chemistry and Catalysis (CCVC/CGCC), 801 Sherbrooke St. W. H31 0B8, Montreal, Canada

<sup>§</sup> Current address: Univ Lyon, ENS de Lyon, CNRS UMR 5182, Laboratoire de Chimie, F69342 Lyon, France

<sup>‡</sup> Current address: Département Chimie, Faculté des Sciences Exactes et Informatique, Université Hassiba Benbouali de Chlef, Hay Es-salam RN 19, 02000 Chlef, Algeria

**Keywords:** ferrocene; ester; deprotometalation; chiral bases; lithium; zinc

**Abstract:**

The enantioselective deprotometalation of alkyl ferrocenecarboxylates ( $\text{FcCO}_2\text{R}$ ) using mixed lithium-zinc or lithium-cadmium bases is described. By using  $\text{FcCO}_2\text{Me}$  as the substrate, chiral lithium alkyl-amidozincates prepared from *exo*-( $\alpha R$ )- or *endo*-( $\alpha S$ )-*N*-( $\alpha$ -phenylethyl)bornylamine (**H-exo-born-R** or **H-endo-born-S**) were tested; the best results (27% yield and 62% ee in favor of the  $R_P$  enantiomer) were obtained by using  $\text{Bu}_2(\text{endo-born-S})\text{ZnLi}$  in tetrahydrofuran (THF) at  $-30\text{ }^\circ\text{C}$  before iodolysis. Due to the low compatibility of  $\text{FcCO}_2\text{Me}$  with alkyl-containing lithium zincates, 1:1 mixtures of lithium and zinc amides were tested. Chiral (**H-exo-born-R** or **H-endo-born-S**) or/and achiral (lithium 2,2,6,6-tetramethylpiperidide or lithium diisopropylamide) secondary amines gave good results, the best (81% yield and 44% ee in favor of the  $R_P$  enantiomer) being obtained by using  $(\text{endo-born-S})_3\text{ZnLi}$  in THF at room temperature. Among other secondary amines also prepared and/or tested, commercial (*S,S*)-bis( $\alpha$ -phenylethyl)amine (**H-PEA-S**) proved promising. After optimization of the reaction conditions, the best enantioselectivity (26% yield and 80% ee in favor of the  $R_P$  enantiomer)) was observed by treating a THF solution of  $\text{FcCO}_2\text{Me}$  and  $\text{Zn}(\text{PEA-S})_2$  with Li-PEA-S at  $-80\text{ }^\circ\text{C}$  before iodolysis. That no reaction took place with cadmium instead of zinc suggests the formation of ‘ate complexes upon treatment of  $\text{Cd}(\text{PEA-S})_2$  by Li-PEA-S while  $\text{Zn}(\text{PEA-S})_2$  and Li-PEA-S would rather work in tandem (Li-PEA-S as the base and  $\text{Zn}(\text{PEA-S})_2$  as the *in situ* trap for the formed ferrocenyllithium). While  $\text{FcCO}_2\text{Me}$ ,  $\text{FcCO}_2t\text{Bu}$  and  $\text{FcCO}_2i\text{Pr}$  could be converted into their racemic 2-iodinated derivatives with a yield of 84 to 87% by employing LiTMP (2 equiv) in the presence of  $\text{ZnCl}_2\cdot\text{TMEDA}$  (1 equiv) as an *in situ* trap, their enantioselective deprotometalation rather required Li-PEA-S together with  $\text{Zn}(\text{PEA-S})_2$  to produce the enantio-enriched derivatives with yields of 45-82% and 71% ee.

## Introduction

Since the discovery of their parent compound,<sup>1, 2</sup> ferrocenes including enantiopure derivatives have been developed for applications in different fields such as catalysis, materials science and medicinal chemistry.<sup>3-5</sup> In addition, monosubstituted ferrocenes being prochiral substrates,<sup>6, 7</sup> their conversion into 1,2-disubstituted derivatives raises the question of enantioselective functionalization, which remains a significant issue. Among the existing routes to achieve this objective, mention may be made of enantioselective C-H bond functionalization reactions, catalyzed by noble transition metals (*e.g.* palladium).<sup>8-13</sup> If approaches using first-row transition metals (*e.g.* copper) have been investigated for C-H functionalization,<sup>14-16</sup> they are however far from efficient to achieve these reactions enantioselectively. There is therefore a need for the development of such protocols, able to deliver enantiopure 1,2-disubstituted ferrocenes, and our approach is part of the efforts aimed at using main-group metals (and notably lithium) at this end.

Even today, the diastereoselective deprotometalation of a ferrocene substituted by a chiral directing group is the most general way to synthesize 1,2-disubstituted ferrocenes.<sup>7, 17-19</sup> However, this involves additional steps to introduce and remove the required substituent. In comparison, employing chiral bases to deprotometalate prochiral monosubstituted ferrocenes appears to be a promising alternative.<sup>19</sup>

In this vein, different (aminomethyl)ferrocenes were converted to non-racemic 2-substituted derivatives by employing alkyllithium-*(R,R)*-*N,N,N',N'*-tetramethylcyclohexane-1,2-diamine chelates (ee up to 98%).<sup>20, 21</sup> Alkyllithium-diamine chelates still have a place for the enantioselective deprotonation of boron trifluoride-activated aminoferrocenes (ee up to 82% in the case of (dimethylamino)ferrocene by using isopropyllithium-*(S,S)*-*N,N'*-dimethyl-*N,N'*-dibutylcyclohexane-1,2-diamine).<sup>22</sup> However, the most successful achievement is probably the enantioselective deprotolithiation of tertiary carboxamides, namely *N,N*-diisopropylferrocenecarboxamide and *N*-cumyl-*N*-ethylferrocenecarboxamide, using butyllithium-(-)-sparteine (ee up to 99%)<sup>23, 24</sup> or butyllithium-(+)-sparteine surrogate (ee up to 92%).<sup>25, 26</sup> However, these chelates can hardly be used

for other monosubstituted ferrocenes such as *O*-isopropylferrocenesulfonate (ee not exceeding 58%).<sup>27</sup>,  
<sup>28</sup> In addition, they are not compatible with the presence of functional groups such as esters. Thus, the development of other bases capable of delivering enantiopure 1,2-disubstituted ferrocenes is necessary.

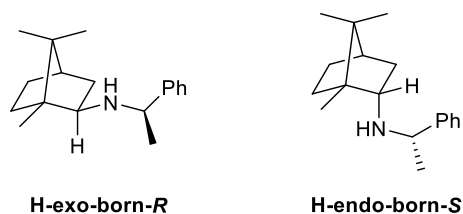
Alternative pathways to lithium bases (alkyllithiums and hindered lithium dialkylamides)<sup>29-33</sup> have gradually emerged in aromatic deprotometalation to address the issue of the low compatibility between organolithiums and substrates sensitive to nucleophilic attacks.<sup>34-39</sup> In this vein, *O*-alkylferrocenecarboxylates can be deprotometalated by using the Turbo base TMPMgCl·LiCl (TMP = 2,2,6,6-tetramethylpiperidino),<sup>40</sup> the base formed by mixing LiTMP and ZnCl<sub>2</sub>·TMEDA (or CdCl<sub>2</sub>·TMEDA) in a 3:1 ratio,<sup>41</sup> or the aluminate base iBu<sub>3</sub>Al(TMP)Li.<sup>42</sup>

More than ten years ago, we launched a study dedicated to the enantioselective deprotometalation of monosubstituted ferrocenes by mixed lithium-zinc bases.<sup>43</sup> We recently disclosed a complete study dedicated to tertiary carboxamides in which we showed that the chiral lithium amide Li-PEA-*S* (PEA = bis( $\alpha$ -phenylethyl)amino) could, when combined with zinc-based *in situ* traps, result in asymmetric deprotometalation<sup>44</sup> with enantioselectivities up to 69% ee;<sup>43</sup> in contrast, the higher-order lithium zincate Me<sub>2</sub>(PEA-*S*)<sub>2</sub>ZnLi<sub>2</sub> was found to promote the formation of the other enantiomer (up to 86% ee). Due to their ability to tolerate sensitive substrates, lithium-zinc bases seem promising for the enantioselective functionalization of ferrocene esters. While we published our very preliminary results in 2012,<sup>43</sup> we here report the full study in light of the latest developments in the field.

## Results and discussion

***Study using chiral lithium alkyl-amidozincates prepared from exo-(1R)- or endo-(1S)-N-( $\alpha$ -phenylethyl)bornylamine (H-exo-born-R or H-endo-born-S)***

*Exo*-(1*R*)-*N*-( $\alpha$ -phenylethyl)bornylamine (**H-exo-born-R**) and *endo*-(1*S*)-*N*-( $\alpha$ -phenylethyl)bornylamine (**H-endo-born-S**) are chiral secondary amines (Figure 1) easily synthesized by reductive amination from (+)-camphor and (*R*)- or (*S*)- $\alpha$ -methylbenzylamine, respectively.<sup>45</sup>



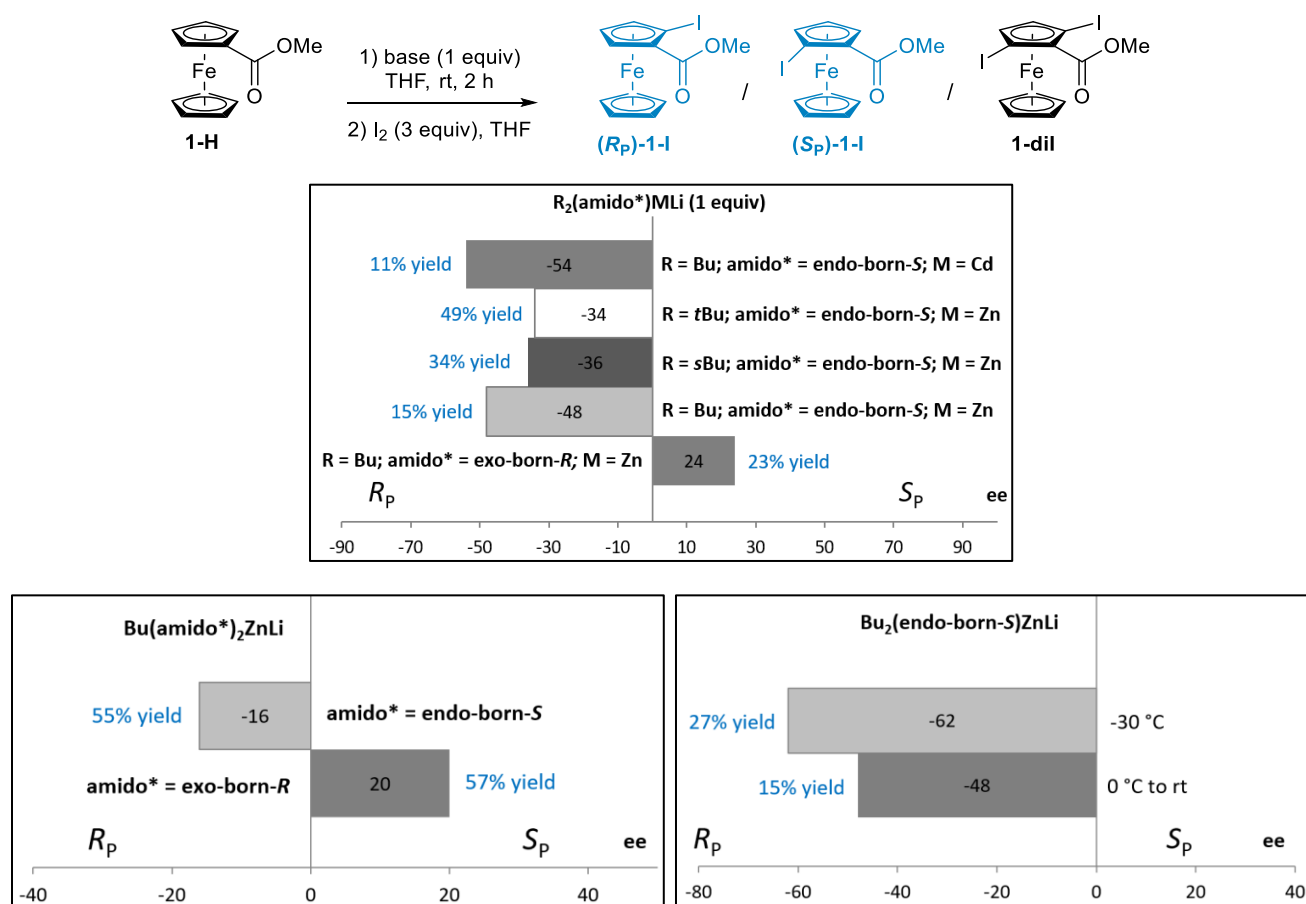
**Figure 1.** *Exo-(αR)-N-(α-phenylethyl)bornylamine (H-exo-born-R)* and *endo-(αS)-N-(α-phenylethyl)bornylamine (H-endo-born-S)*.

Lithium amidozincates are an alternative to lithium bases making it possible to incorporate chiral amino groups to obtain chiral bases. Since lower-order lithium zincates<sup>34, 37, 38, 46-48</sup> are generally less reactive than higher-order ones<sup>49</sup> and more compatible with functional groups,<sup>43</sup> we first decided to evaluate them in the enantioselective deprotometalation of *O*-methylferrocenecarboxylate (**1-H**).

To this end, putative<sup>50, 51</sup> chiral dibutyl-amidozincates incorporating either **exo-born-R** or **endo-born-S** were prepared by reacting **Li-exo-born-R** or **Li-endo-born-S** (1 equiv) with ZnCl<sub>2</sub>·TMEDA (1 equiv; TMEDA = *N,N,N',N'*-tetramethylethylenediamine) in THF (15 min at 0 °C) before adding butyllithium (2 equiv) and stirring for 15 min at 0 °C. *O*-Methylferrocenecarboxylate (**1-H**) was allowed to react with these bases for 2 h at room temperature (rt) before quenching with iodine. Moderate yields of **1-I** (23 or 15%, respectively), due to significant degradation (only 5% or 6% of the starting material recovered), and moderate to medium enantioselectivities (24% ee in favor of the *S<sub>P</sub>* enantiomer, or 48% ee in favor of the *R<sub>P</sub>*) were recorded under these conditions (Scheme 1, top).

The behavior of a mixed alkyl-amido zincate also depends on the nature of the alkyl group(s).<sup>52, 53</sup> Here, the replacement of butyl by methyl gave a complex mixture from which **1-I** could not even be isolated (**1-H** recovered in 10-15% yield). While the replacement of butyl by more hindered *sec*-butyl and *tert*-butyl groups led to more chemoselective reactions, with **1-I** isolated with respective yields of 34% (9% of recovered **1-H**) and 49% (20% of recovered **1-H**), the enantioselectivities were not improved. On the other hand, replacing the zinc in the dibutyl-amidozincate with cadmium<sup>54</sup> did not improve the result of the reaction.

The corresponding chiral butyl-diamidozincates were similarly prepared and tested. Their use in the **1-H** deprotometalation-trapping sequence provided **1-I** with higher yields but lower enantioselectivities (Scheme 1, bottom left). Finally, by repeating the reaction using putative Bu<sub>2</sub>(endo-*S*)ZnLi at -30 °C instead of rt, **1-I** was obtained both with improved yield (27%; 54% of recovered **1-H**) and enantioselectivity (62% ee in favor of the *R<sub>P</sub>*; Scheme 1, bottom right).



**Scheme 1.** Investigation of lithium alkyl-amidozincates coming from **H-exo-born-*R*** and **H-endo-born-*S*** in enantioselective deprotometalation.

*Study using lithium-zinc amides prepared from chiral exo-(α*R*)- or endo-(α*S*)-N-(α-phenylethyl)bornylamine (H-exo-born-*R* or H-endo-born-*S*)*

Because the 1:1 LiTMP-Zn(TMP)<sub>2</sub> (TMP = 2,2,6,6-tetramethylpiperidino) mixture of amides, formed by mixing LiTMP and ZnCl<sub>2</sub>·TMEDA in a 3:1 ratio,<sup>55-57</sup> is a powerful base for obtaining aromatic deprotometalation,<sup>44</sup> we then decided to explore the use of chiral versions to attempt

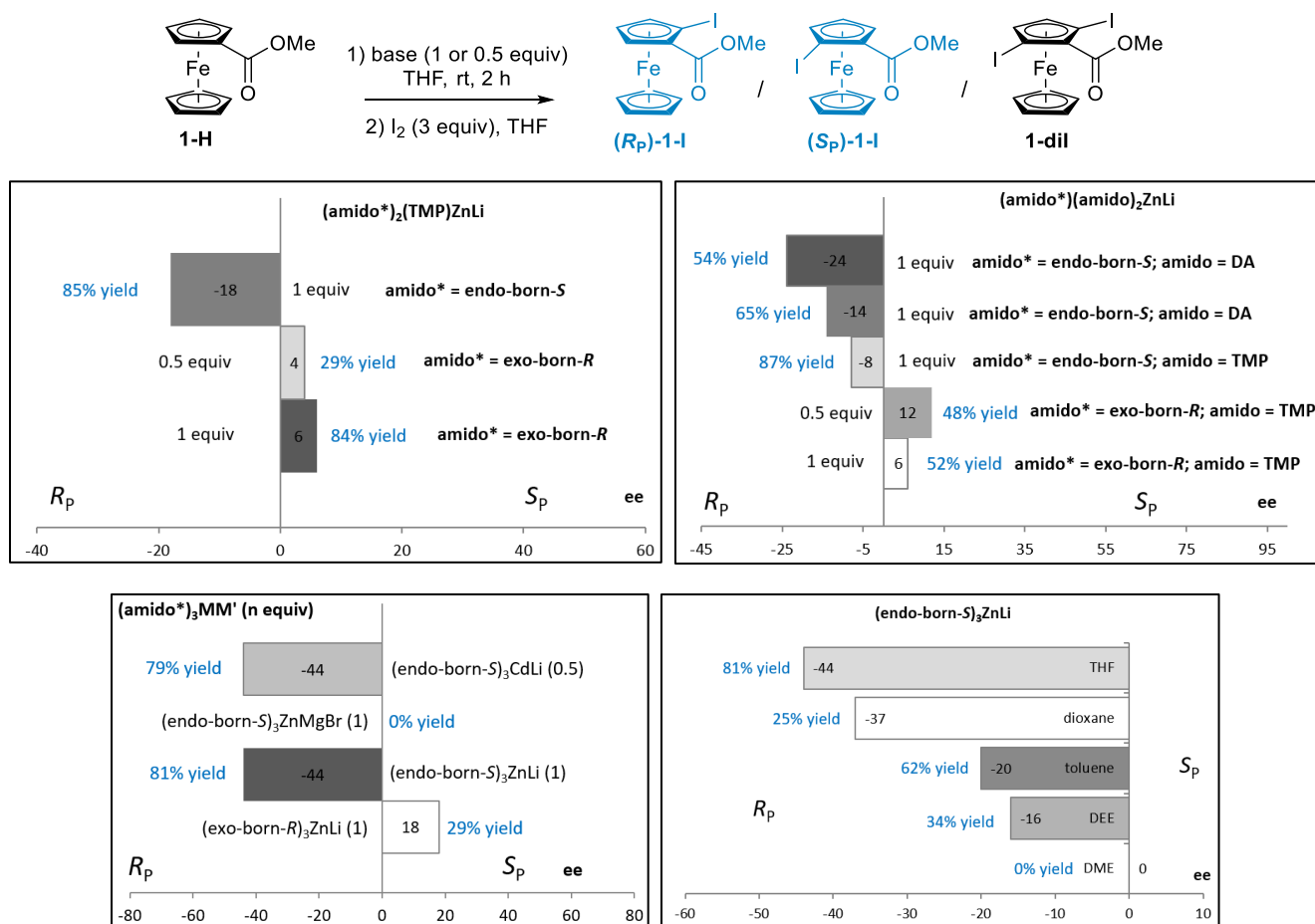
enantioselective reactions. To do this, we replaced the TMP groups of 1:1 LiTMP-Zn(TMP)<sub>2</sub> with chiral amino groups coming from **H-exo-born-R** and **H-endo-born-S** (Scheme 2).

To prepare the first base, we treated a solution of **H-exo-born-R** (2 equiv) and H-TMP (1 equiv) in THF at 0 °C with butyllithium (3 equiv) for 5 min in order to generate the corresponding 2:1 mixture of the lithium amides **Li-exo-born-R** and LiTMP; the ZnCl<sub>2</sub>·TMEDA chelate (1 equiv) was then added, and the solution was stirred at the same temperature for 15 min. *O*-Methylferrocenecarboxylate (**1-H**) was introduced at 0 °C, and the reaction mixture was stirred at rt for 2 h before iodolysis. Under these conditions, the 2-iodinated derivative **1-I** was obtained with a good yield of 84%, but a very low ee of 6% in favor of the *S<sub>P</sub>* enantiomer (Scheme 2, top left). The use of 0.5 equivalent of each of the two amides LiTMP and Zn(TMP)<sub>2</sub> is often sufficient to deprotometalate with good yield; however, with TMP replaced by **exo-R**, a moderate 29% yield of **1-I** was recorded (55% **1-H** recovered). By repeating the first reaction with **H-endo-born-S** (2 equiv) and H-TMP (1 equiv), the 2-iodinated derivative **1-I** was obtained with a good yield of 85%, but higher ee (18%) in favor of the *R<sub>P</sub>* enantiomer.

Next, we tested two bases prepared in a similar way from 1 equivalent of chiral amine (**H-exo-born-R** or **H-endo-born-S**) and 2 equivalents of H-TMP (Scheme 2, top right). When it comes to conversions, these bases have proved to be stronger than the previous ones. Indeed, by using that prepared from **H-exo-born-R** (1 equiv) and H-TMP (2 equiv), the 52% yield was limited only by the concomitant formation of the diiodide **1-diI**, isolated in 36% yield. In addition, by reducing the amount of base, **1-I** was still formed in a yield of 48%. Regarding the enantioselectivities, the base change did not have a significant effect, with enantiomeric excesses (ee) between 6 and 12%, quite similar to those recorded by using 2 equivalents of the chiral amine (**H-exo-born-R** or **H-endo-born-S**) and 1 equivalent of H-TMP (between 4 and 18%). As already noted from anisole,<sup>45</sup> these results tend to show that the chiral amino groups employed are less capable of deprotonating than TMP (in accordance, treating **1-H** sequentially with Zn(TMP)<sub>2</sub> and **Li-endo-born-S** under the same conditions before iodolysis similarly furnished **1-I** with a high 94% yield and a low 12% ee). To confirm this hypothesis,



we replaced H-TMP ( $pK_a = 37.3$ ) with diisopropylamine (H-DA;  $pK_a = 35.7$ ), which is a slightly weaker base;<sup>58</sup> as expected, the enantioselectivity remained unchanged, but the efficiency logically fell to 65% due to the competitive formation of 2-iodo-*N,N*-diisopropylferrocenecarboxamide (isolated in 25% yield; 8% ee). The ee of the iodoester could be slightly improved to 24% by preparing the base differently (**Li-endo-born-S** (1 equiv) was treated with the  $ZnCl_2 \cdot TMEDA$  chelate (1 equiv) for 15 min at 0 °C before addition of LiDA (2 equiv)), but not enough to be satisfactory.



**Scheme 2.** Investigation of mixtures of lithium and zinc amides coming from **H-exo-born-R** and **H-endo-born-S** in enantioselective deprotometalation.

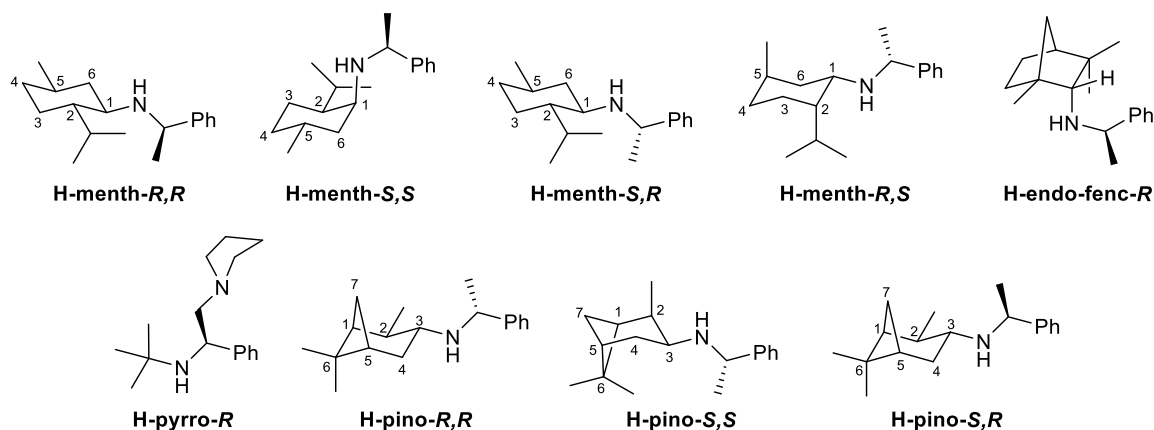
We therefore decided to use bases containing 3 identical chiral amino groups (Scheme 2, bottom left). The first two bases were prepared by reacting the corresponding lithium amide (3 equiv) in THF with  $ZnCl_2 \cdot TMEDA$  (1 equiv) at 0 °C for 15 min. Interestingly, the bases prepared from **H-exo-born-R** and **H-endo-born-S** did not give the same results: unlike  $(exo-R)_3ZnLi$ ,<sup>59-61</sup> which afforded **1-I** with

moderate 29% yield (27% of **1-H** recovered) and enantioselectivity (18% ee in favor of the  $S_P$ ), the corresponding *endo-S* base gave **1-I** with a satisfactory yield of 81% (2% of **1-diI** also isolated) and higher enantioselectivity (44% ee in favor of the  $R_P$ ). When other solvents (dioxane, toluene, diethyl ether (DEE) and 1,2-dimethoxyethane (DME)) were tested, the yield and enantioselectivity dropped (Scheme 2, bottom right). It is also interesting to note that the reactions carried out in the absence of lithium chloride<sup>57</sup> or TMEDA proceeded without significant changes.

(*Endo-S*)<sub>3</sub>ZnMgBr,<sup>59-61</sup> prepared from **BrMg-endo-born-S** (obtained by reacting **H-endo-born-S** (3 equiv) with isopropylmagnesium bromide (3 equiv) in THF at 50 °C for 3 h) and ZnCl<sub>2</sub>·TMEDA (1 equiv) at 0 °C for 15 min, did not react at all with **1-H**; this result is as expected given the low reactivity as bases of already reported magnesium zincates.<sup>45</sup> While the use of 1 equivalent of (*endo-S*)<sub>3</sub>CdLi<sup>59-61</sup> led to the diiodide **1-diI** with a 75% yield, reducing the amount to 0.5 equivalent provided **1-I** with 79% yield (8% of **1-H** also recovered) and 44% ee (in favor of the  $R_P$ ). As already documented,<sup>41, 62-64</sup> the replacement of zinc by cadmium in mixed lithium-metal amides (or mixture of amides) generally led to an increased reactivity (Scheme 2, bottom left).

### ***Study using lithium-zinc amides prepared from a chiral amine among those shown in Figure 2***

The encouraging results obtained so far by using **H-exo-born-R** and **H-endo-born-S** have led us to evaluate another set of chiral secondary amines (Figure 2; Scheme 3).

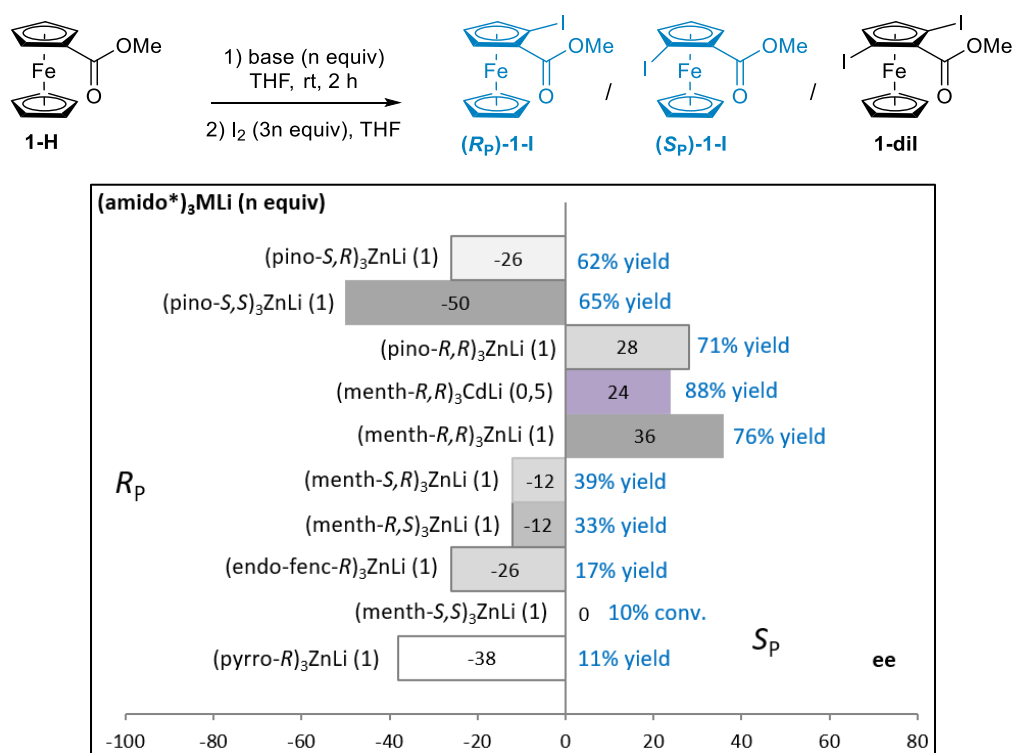


**Figure 2.** Second set of secondary amines used to attempt the enantioselective deprotometalation of **1-H**.

Because the synthesis of ( $\alpha R$ )-*N*-(*tert*-butyl)- $\alpha$ -phenyl- $\beta$ -(*N*-pyrrolidyl)ethylamine (**H-pyrro-R**) is well-described,<sup>65</sup> we first tested the derived lithium-zinc base; however, it failed to efficiently deprotometalate *O*-methylferrocenecarboxylate (**1-H**) (11% yield of **1-I** and 25-30% **1-H** recovered).

( $\alpha S$  Or  $\alpha R$ )- $\alpha$ -methyl-*N*-[(1*S* or 1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl]benzylamines (**H-menth-R,R**, **H-menth-S,S**, **H-menth-S,R** and **H-menth-R,S**) and *endo*-(+)-( $\alpha R$ )-*N*-( $\alpha$ -phenylethyl)fenchylamine (**H-endo-fenc-R**) were obtained by reductive amination<sup>45</sup> using (–)-menthone or (–)-fenchone and (*S*)- or (*R*)- $\alpha$ -methylbenzylamine (see ESI). As before, the bases were prepared by treating the corresponding lithium amides (3 equiv) in THF with ZnCl<sub>2</sub>·TMEDA (1 equiv) at 0 °C for 15 min before introducing **1-H**; iodolysis was carried out after 2 h of contact at rt. Probably due to steric hindrance, the bases prepared from **H-menth-S,S** and **H-endo-fenc-R** were the less reactive (10-20% conversion). While (menth-*R,S*)<sub>3</sub>ZnLi<sup>59-61</sup> and (menth-*S,R*)<sub>3</sub>ZnLi<sup>59-61</sup> provided **1-I** with moderate 33 and 39% yields (33 and 16% of **1-H** recovered, respectively) and low enantioselectivities (12% ee for both in favor of the *R<sub>P</sub>*), a more satisfactory yield of 76% as well as a 36% ee (this time in favor of the *S<sub>P</sub>*) was obtained with (menth-*R,R*)<sub>3</sub>ZnLi.<sup>59-61</sup> The replacement of zinc by cadmium in the latter base resulted in an improved yield of 88% (the remainder was recovered **1-H**), but a lower ee of 24%.

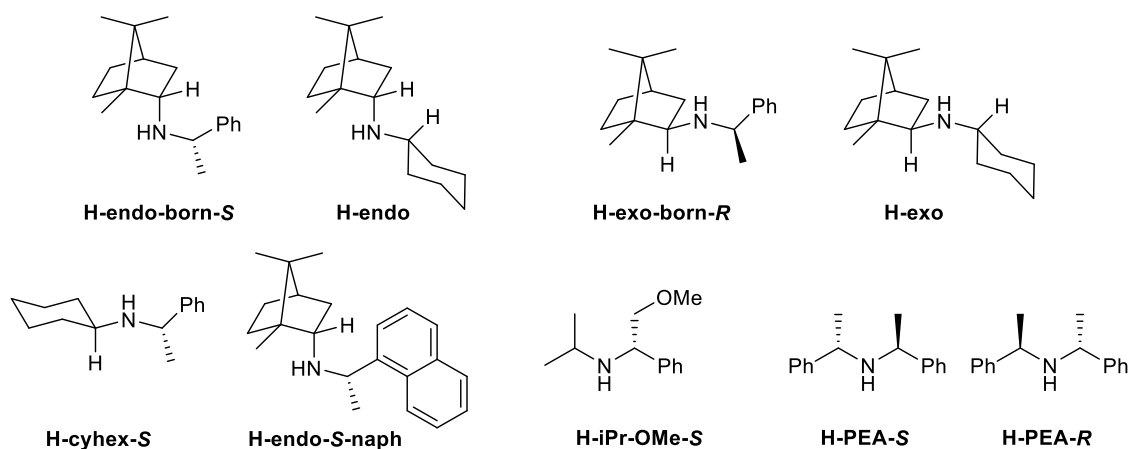
It is known that (–)-isopinocampone epimerizes easily (C2-position);<sup>66</sup> consequently, the thermodynamically more favorable (–)-pinocampone derivatives (1*S*,2*R*,3*R* or 3*S*,5*R*)-2,6,6-trimethyl-*N*-[( $\alpha R$  or  $\alpha S$ )- $\alpha$ -phenylethyl]bicyclo[3.1.1]heptan-3-amines (**H-pino-R,R**, **H-pino-S,S** and **H-pino-S,R**) were instead obtained when the imine formation reactions using (*R*)- and (*S*)- $\alpha$ -methylbenzylamine were carried out in order to get new secondary amines after subsequent reduction (see ESI). The corresponding lithium-zinc bases delivered **1-I** with yields ranging from 62 to 71% (the remainder being **1-H**, recovered with a yield of 10-20%, and **1-diI**, formed with a yield of approximately 10%), and enantioselectivities between 28% (in favor of the *S<sub>P</sub>*) with putative (pino-*R,R*)<sub>3</sub>ZnLi<sup>59-61</sup> and 50% (in favor of the *R<sub>P</sub>*) with putative (pino-*S,S*)<sub>3</sub>ZnLi<sup>59-61</sup> (Scheme 3).



**Scheme 3.** Investigation of mixtures of lithium and zinc amides coming from **H-pyrro-*R***, **H-menth-*S,S***, **H-endo-fenc-*R***, **H-menth-*R,S***, **H-menth-*S,R***, **H-menth-*R,R***, **H-pino-*R,R***, **H-pino-*S,S*** and **H-pino-*S,R*** in enantioselective deprotometalation.

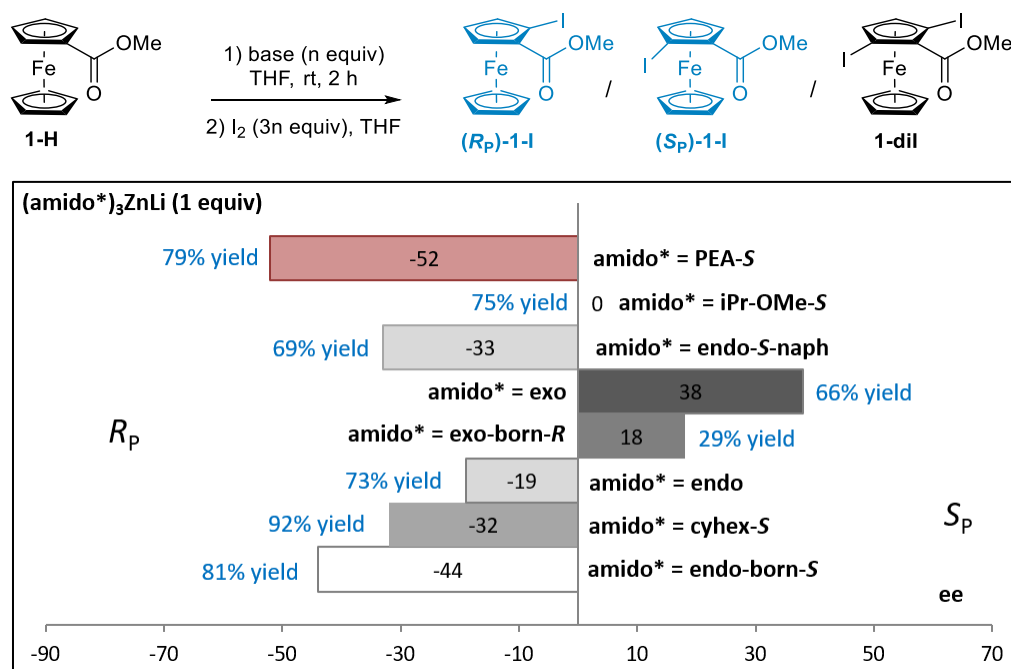
*Study using lithium-zinc amides prepared from a chiral amine among those shown in Figure 3*

Since the amines displayed in Figure 2 are less obvious to prepare than the bornylamines shown in Figure 1, without improving the deprotometalation-trapping results, we decided to bring structural changes to the promising *endo-S* base (Figure 3; Scheme 4).



**Figure 3.** Third set of secondary amines used to attempt the enantioselective deprotometalation of **1-H**.

For this purpose, we have replaced one of the nitrogen substituents of the bornylamines with an achiral group. This was done by using either ((*S*)- $\alpha$ -phenylethyl)cyclohexylamine<sup>67</sup> (**H-cyhex-S**) or *endo*-*N*-cyclohexylbornylamine (**H-endo**) instead of **H-endo-born-S** to prepare the lithium-zinc base; in this way, **1-I** was isolated with a 92 or 73% yield, respectively, and a moderate 32 or 19% ee in favor of the *R<sub>P</sub>* enantiomer. Further, the use of *exo*-*N*-cyclohexylbornylamine (**H-exo**) instead of **H-exo-born-R** gave **1-I** with a yield of 66% and an improved ee of 38% in favor of the *S<sub>P</sub>* enantiomer (Scheme 4, bottom).



**Scheme 4.** Investigation of mixtures of lithium and zinc amides coming from **H-endo-born-S**, **H-cyhex-S**, **H-endo**, **H-exo-born-R**, **H-exo**, **H-endo-S-naph**, **H-iPr-OMe-S** and **H-PEA-S** in enantioselective deprotonation.

The phenyl group of **H-endo-born-S** was also modified to a more hindered 1-naphthyl group toward *endo*-( $\alpha$ *S*)-*N*-( $\alpha$ -( $\alpha$ -naphthyl)ethyl)bornylamine (**H-endo-S-naph**); however, while a good yield of 69% was recorded (the remainder being **1-H**), the enantioselectivity (33% ee in favor of the *R<sub>P</sub>*) was not improved. Besides, a racemic mixture was obtained by using (*S*)-*N*-isopropyl-*O*-methylphenylglycinol<sup>68, 69</sup> (**H-iPr-OMe-S**) as the source of amido.

These unsatisfactory results led us to consider the use of chiral secondary amines possessing a C2-symmetry. The most widely used chiral lithium amides for enantioselective deprotonations in the tricarbonyl( $\eta$ 6-arene)chromium<sup>70, 71</sup> and ferrocene<sup>72</sup> series are probably lithium bis[ $\alpha$ -phenylethyl]amides, and in particular Li-PEA-*R* and -*S* available commercially. Thus, (PEA-*S*)<sub>3</sub>ZnLi<sup>59-61</sup> was prepared by treating the corresponding lithium amide (3 equiv) in THF with ZnCl<sub>2</sub>·TMEDA (1 equiv) at 0 °C for 15 min before successively introducing **1-H** and, after 2 h at rt, iodine. Under these conditions, an encouraging 52% ee was recorded while **1-I** and **1-diI** were both isolated with 79% and 6% yield, respectively (Scheme 4, top); the presence of lithium chloride<sup>57</sup> (3 equiv) did not have a significant impact on the outcome of this reaction (**1-I** obtained in 84% yield and 50% ee), which also worked in dimethoxymethane (71% yield and 41% ee).

Mixed amido/organo lithium zincates are generally less reactive bases than lithium amide-zinc trap combinations.<sup>43, 73</sup> Nevertheless, in order to reduce competitive deprotonation by the chiral ferrocenyl-diamidozincates formed during these reactions, we tested lower temperatures. However, by using (*endo-S*)<sub>3</sub>ZnLi<sup>59-61</sup> at -30 °C, **1-I** was formed with a yield of 77% and an ee of 39% in favor of the *R<sub>p</sub>* enantiomer, a result similar to that obtained at rt. In another attempt to improve results, testing a higher dilution (3 times) had no effect on the course of the reaction. The enantioselectivity also did not change with the reaction time (from 5 min to 24 h); however, long contacts with the base favored the formation of **1-diI**, as indicated by the TLC control (results not shown).

A slight improvement was nevertheless seen when **Li-endo-born-S** (1 equiv) was added slowly at -40 °C to a solution of **1-H** and zinc diamide (the latter being prepared from ZnCl<sub>2</sub>·TMEDA (1 equiv) and **Li-endo-born-S** (2 equiv) in THF) before slow rise to rt and iodolysis; thus, under these conditions, **1-I** was isolated only with a yield of 55% (due to the formation of 23% of **1-diI**) but with an improved ee of 52% (results not shown). We therefore decided to turn again to (PEA-*S*)<sub>3</sub>ZnLi<sup>59-61</sup> and carefully investigate the impact of temperature (Table 1); under the above conditions, except for the temperature which was only raised to -20 °C before iodolysis in order to reduce dimetalation, **1-I**

was isolated with a good 81% yield (95% in the presence of lithium chloride)<sup>57</sup> and an improved 67% ee (entries 1 and 2).

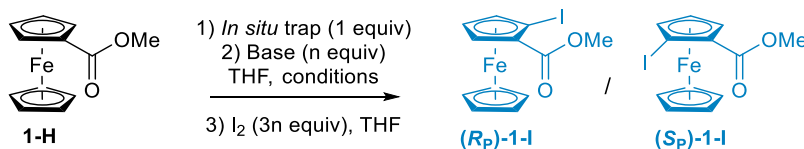
Maintaining a low contact temperature of -50 °C between base and **1-H** for 1 h resulted in **1-I** with a 52% yield and a slightly improved 74% ee (entry 3). Under the same reaction conditions, the use of (PEA-*R*)<sub>3</sub>ZnLi<sup>59-61</sup> led to **1-I** with similar enantioselectivity, this time in favor of the *S<sub>P</sub>* enantiomer (entry 4). We have therefore reduced this contact temperature to -80 °C; however, if an 80% ee was recorded, **1-I** was obtained with a moderate 26% yield (entry 5). This problem could not be ruled out by using the base in excess and a contact time extended to 14 h (entry 6). Furthermore, no change was observed by introducing **1-H** into a solution of the *in situ* trap and the base (entry 7), even if this solution already contains 0.5 equivalent of **1-H** (entry 8). Finally, when an even lower temperature of -90 °C was maintained during the contact time between the base and **1-H**, a conversion of less than 20% was recorded while the ee was not improved (entry 9).

Rapid exchanges of ligands at the NMR timescale are generally observed for mixed lithium-zinc compounds; however, as our deprotometalation reaction starts as early as -80 °C, we decided to try using NMR spectroscopy, as previously reported,<sup>43</sup> to learn more about the species present in solution. The <sup>1</sup>H and <sup>13</sup>C NMR spectra recorded at this temperature for a 1:1 **1-H**-Zn(PEA-*S*)<sub>2</sub><sup>43</sup> (the latter being prepared from ZnCl<sub>2</sub>·TMEDA (1 equiv) and Li-PEA-*S* (2 equiv)) d<sup>8</sup>-THF solution indicated the absence of interaction between the two species. After subsequent addition of Li-PEA-*S* (1 equiv) at the same temperature, monitoring by NMR recording after 12 h and 60 h contact made it possible to demonstrate the formation of a ferrocenylmetal, in accordance with the results already obtained above. While the NOESY experiments allowed us to establish proximities between the PEA methyl and both the ferrocene free cyclopentadienyl and the ester methyl, and therefore the existence of a ferrocenyl-Zn-PEA pattern, it proved impossible to demonstrate the formation of a lithium zincate.

These NMR studies tend to show that Zn(PEA-*S*)<sub>2</sub> is not involved in the deprotolithiation event. The enantioselectivity seems to be the result of a more favorable complexation of the ester C=O of the

substrate to the metalating lithium amide.<sup>74-76</sup> A low temperature would therefore seem preferable for better discrimination between the two enantiotopic hydrogens.

**Table 1.** Investigation of  $M(NR_2)_2$ -LiNR<sub>2</sub> *in situ* trap-base pairs coming from (*S,S*)- or (*R,R*)-bis( $\alpha$ -phenylethyl)amine (**H-PEA-S** or **H-PEA-R**) in the enantioselective functionalization of **1-H**.



Entry	<i>In situ</i> trap	Base (n equiv)	Conditions	<b>1-I</b> yield <sup>a</sup> and ee <sup>b</sup>	<b>1-H</b> yield <sup>a</sup>
1	Zn(PEA- <i>S</i> ) <sub>2</sub> <sup>c</sup>	Li-PEA- <i>S</i> <sup>d</sup> (1)	-50 °C to -10 °C <sup>e</sup>	81%, 67% ( <i>R</i> <sub>P</sub> )	16%
2 <sup>f</sup>	Zn(PEA- <i>S</i> ) <sub>2</sub> <sup>c</sup>	Li-PEA- <i>S</i> <sup>d</sup> (1)	-50 °C to -10 °C <sup>e</sup>	95%, 68% ( <i>R</i> <sub>P</sub> )	0%
3	Zn(PEA- <i>S</i> ) <sub>2</sub> <sup>c</sup>	Li-PEA- <i>S</i> <sup>d</sup> (1)	-50 °C, 1 h	52%, 74% ( <i>R</i> <sub>P</sub> )	46%
4	Zn(PEA- <i>S</i> ) <sub>2</sub> <sup>c</sup>	Li-PEA- <i>S</i> <sup>d</sup> (1)	-50 °C, 1 h	40%, 72% ( <i>S</i> <sub>P</sub> )	55%
5	Zn(PEA- <i>S</i> ) <sub>2</sub> <sup>c</sup>	Li-PEA- <i>S</i> <sup>d</sup> (1)	-80 °C, 2 h	26%, 80% ( <i>R</i> <sub>P</sub> )	74%
6	Zn(PEA- <i>S</i> ) <sub>2</sub> <sup>c</sup>	Li-PEA- <i>S</i> <sup>d</sup> (3)	-80 °C, 14 h	28%, 75% ( <i>R</i> <sub>P</sub> )	66%
7 <sup>g</sup>	Zn(PEA- <i>S</i> ) <sub>2</sub> <sup>c</sup>	Li-PEA- <i>S</i> (3)	-80 °C, 14 h	25%, 76% ( <i>R</i> <sub>P</sub> )	72%
8 <sup>h</sup>	Zn(PEA- <i>S</i> ) <sub>2</sub> <sup>c</sup>	Li-PEA- <i>S</i> <sup>d</sup> (1)	-80 °C, 14 h	21%, 76% ( <i>R</i> <sub>P</sub> )	75%
9	Zn(PEA- <i>S</i> ) <sub>2</sub> <sup>c</sup>	Li-PEA- <i>S</i> <sup>d</sup> (1)	-90 °C, 14 h	<20%, <sup>i</sup> 68% ( <i>R</i> <sub>P</sub> )	80% <sup>i</sup>
10	Zn(PEA- <i>S</i> ) <sub>2</sub> <sup>c</sup>	Li-PEA- <i>S</i> <sup>d</sup> (1)	-50 °C to -20 °C <sup>e</sup>	79%, 70% ( <i>R</i> <sub>P</sub> )	20%
11	Zn(PEA- <i>S</i> ) <sub>2</sub> <sup>c</sup>	Li-PEA- <i>S</i> <sup>d</sup> (1)	-60 °C to -20 °C <sup>e</sup>	85%, 65% ( <i>R</i> <sub>P</sub> )	3%
12	Zn(PEA- <i>S</i> ) <sub>2</sub> <sup>c</sup>	Li-PEA- <i>S</i> <sup>d</sup> (1)	-80 °C to -20 °C <sup>e</sup>	77%, 71% ( <i>R</i> <sub>P</sub> )	13%
13	Zn(PEA- <i>S</i> ) <sub>2</sub> <sup>c</sup>	Li-PEA- <i>S</i> <sup>d</sup> (3)	-80 °C to -20 °C <sup>e</sup>	68.5%, 68% ( <i>R</i> <sub>P</sub> )	<sup>j</sup>
14 <sup>k</sup>	Zn(PEA- <i>S</i> ) <sub>2</sub> <sup>c</sup>	Li-PEA- <i>S</i> <sup>d</sup> (1)	-80 °C to -20 °C <sup>e</sup>	35%, 66% ( <i>R</i> <sub>P</sub> )	31%
15	Zn(PEA- <i>R</i> ) <sub>2</sub> <sup>c</sup>	Li-PEA- <i>R</i> <sup>d</sup> (1)	-80 °C to -20 °C <sup>e</sup>	13%, 72% ( <i>S</i> <sub>P</sub> )	76%
16	Cd(PEA- <i>S</i> ) <sub>2</sub> <sup>c</sup>	Li-PEA- <i>S</i> <sup>d</sup> (1)	-80 °C, 14 h	0%	93%
17 <sup>g</sup>	Cd(PEA- <i>S</i> ) <sub>2</sub> <sup>c</sup>	Li-PEA- <i>S</i> (1)	-80 °C, 5 h	0%	<sup>j</sup>
18	Cd(PEA- <i>S</i> ) <sub>2</sub> <sup>c</sup>	Li-PEA- <i>S</i> <sup>d</sup> (2)	-80 °C, 14 h	0%	94%
19	Cd(PEA- <i>S</i> ) <sub>2</sub> <sup>c</sup>	Li-PEA- <i>S</i> <sup>d</sup> (1)	-50 °C, 1 h	58%, 20% ( <i>R</i> <sub>P</sub> )	6%
20	Cd(PEA- <i>R</i> ) <sub>2</sub> <sup>c</sup>	Li-PEA- <i>R</i> <sup>d</sup> (1)	-50 °C, 1 h	63%, 31% ( <i>S</i> <sub>P</sub> )	30%

<sup>a</sup> Yield after purification (see experimental part). <sup>b</sup> Concerning the ee determination, see the experimental part and ESI. <sup>c</sup> *In situ* prepared from ZnCl<sub>2</sub>·TMEDA or CdCl<sub>2</sub>·TMEDA and the lithium amide in a 1:2 ratio.

<sup>d</sup> The solution was cooled to the same temperature before transfer. <sup>e</sup> Slow warming (~ 8 h). <sup>f</sup> In the presence of LiCl (3 equiv). <sup>g</sup> **1-H** was added to the solution containing the *in situ* trap and the base. <sup>h</sup> In the presence of additional **1-H** (0.5 equiv). <sup>i</sup> Conversion determined by NMR. <sup>j</sup> Not determined. <sup>k</sup> In the presence of additional **1-H** (1 equiv).

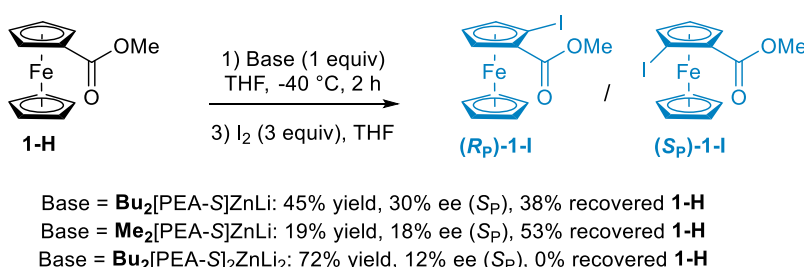
As a last attempt to optimize the reaction (keep a good yield and maintain the enantioselectivity), we applied a slow warming to -20 °C after adding the lithium amide to the reaction mixture at three



different low temperatures, -50 °C, -60 °C and -80 °C; only insignificant differences were noted (entries 10-12). In addition, the result obtained by applying a temperature gradient from -80 to -20 °C (77% yield and 71% ee; entry 12) was not modified by the use of an excess of base (entry 13). An excess of **1-H** caused a drop in yield but did not change the enantioselectivity (entry 14); this suggests that the chiral lithiated ferrocene does not racemize through the reaction with **1-H**. As already noticed in entry 4, the replacement of PEA-*S* by PEA-*R* in the M(NR<sub>2</sub>)<sub>2</sub>-LiNR<sub>2</sub> *in situ* trap-base pair led to **1-I** with lower efficiency but with similar enantioselectivity (entry 15).

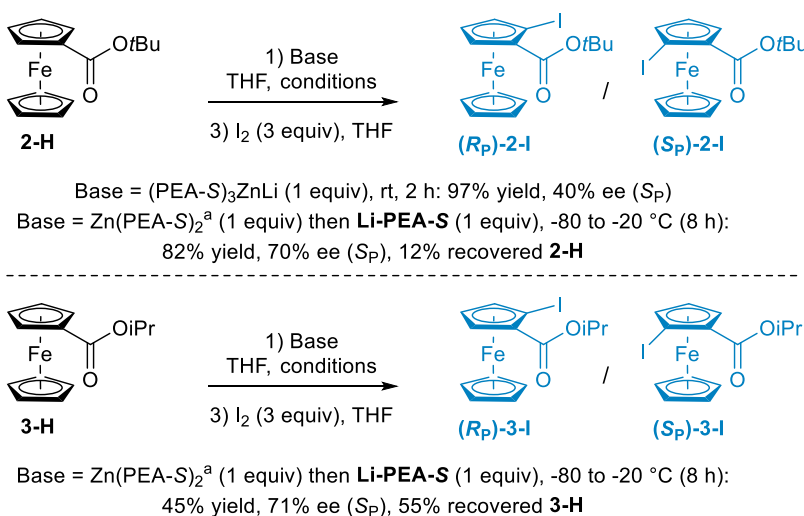
For reasons of curiosity, despite the toxicity of organocadmium compounds, we carried out some additional reactions by replacing zinc with cadmium. At -80 °C, the lithium-cadmium base turned out to be less reactive than the corresponding lithium-zinc base (entries 16-18). At -50 °C, the two lithium-cadmium bases derived from **H-PEA-S** (entry 19) and **H-PEA-R** (entry 20) led to the expected product **1-I** with correct yields of 58% and 63%, respectively, but with disappointing enantioselectivities (20% and 31%). Such results may reflect a less efficient interception of the formed ferrocenyllithium by cadmium *in situ* traps; however, this is not consistent with the good tolerance of this type of deprotonations toward substrates sensitive to organolithiums such as azines,<sup>77, 78</sup> diazines<sup>79, 80</sup> and aromatic esters.<sup>81, 82</sup> A higher capacity of the cadmium traps than those with zinc to intercept lithium amides could rather be put forward to explain the different results of the reactions, ‘ate’ complexes being more likely with cadmium than with zinc.<sup>63</sup>

Some putative<sup>50, 51</sup> (di)lithium dialkyl-(di)amidozincates incorporating PEA-*S* have also been prepared by reacting Li-PEA-*S* (1 or 2 equiv) with ZnCl<sub>2</sub>·TMEDA (1 equiv) in THF (15 min at 0 °C) before addition of the alkyllithium (2 equiv) and stirring for 15 min at 0 °C. When **1-H** was allowed to react with these bases for 2 h at -40 °C before being quenched with iodine, **1-I** was obtained with varying yields and moderate enantioselectivities in favor this time of the *S<sub>p</sub>* enantiomer (Scheme 5). In the light of these results, it can be argued that competitive deprotonations by ‘ate’ complexes formed during the reaction can be deleterious for its enantioselectivity.



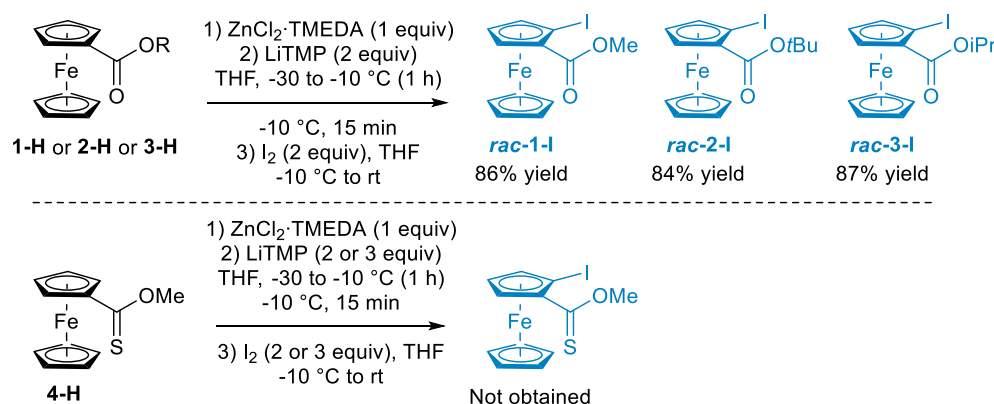
**Scheme 5.** Investigation of lithium alkyl-amidozincates coming from **H-PEA-S** in enantioselective deprotometalation.

With these optimized conditions in hand, we turned to *O*-*tert*-butylferrocenecarboxylate (**2-H**) (Scheme 6, top). When successively treated with (PEA-*S*)<sub>3</sub>ZnLi<sup>59-61</sup> (rt, 2 h) and iodine, the iodide **2-I** was obtained in almost quantitative yield; the ee (40%; *R<sub>P</sub>* enantiomer) could only be determined after reduction to 2-iodoferrocenemethanol.<sup>83</sup> A better result was observed with the optimized sequential addition to **2-H** of the zinc diamide and, 15 min later, the lithium amide at -80 °C before slowly warming to -20 °C; under these conditions, **2-I** was isolated after iodolysis with 82% yield and 70% ee. Thus, the hindered alkyl group of the ester did not alter the course of the reaction which took place with results quite close to those obtained from **1-H** (77% yield and 71% ee). These conditions were also found to be suitable for the enantioselective deprotometalation of *O*-isopropylferrocenecarboxylate (**3-H**), affording **3-I** with a similar ee of 71% but a lower yield of 45% (Scheme 6, bottom).



**Scheme 6.** Investigation of chiral lithium-zinc bases coming from (*S,S*)-bis( $\alpha$ -phenylethyl)amine (**H-PEA-S**) in the enantioselective functionalization of **2-H** and **3-H**. <sup>a</sup> *In situ* prepared from ZnCl<sub>2</sub>·TMEDA and Li-PEA-*S* in a 1:2 ratio.

Regarding the yields, the results throughout this paper show that Li-PEA bases are less apt to deprotonate than LiTMP. This was further demonstrated from the esters **1-H**, **2-H** and **3-H**: by simply using  $\text{ZnCl}_2\cdot\text{TMEDA}$  (1 equiv) as the *in situ* trap and LiTMP (2 equiv) as the base in THF at  $-30\text{ }^\circ\text{C}$ , the iodides **1-I**, **2-I** and **3-I** were isolated with yields ranging from 84 to 87%. However, in the case of the thionoester **4-H**, which can be functionalized next to the function by palladium-catalyzed C-H bond activation,<sup>84</sup> no reaction was found possible by using LiTMP (2 or 3 equiv) in the presence of  $\text{ZnCl}_2\cdot\text{TMEDA}$  (1 equiv) and either starting material or degradation was observed; this could be due to the lower ability of sulfur (compared to oxygen) to coordinate lithium (Scheme 7).



**Scheme 7.** Investigation of  $\text{ZnCl}_2\cdot\text{TMEDA}$  (1 equiv) as the *in situ* trap and LiTMP as the base for the functionalization of **1-H**, **2-H**, **3-H** and **4-H**.

The enantioselective reactions we developed in the second part of the present study may appear comparable to those reported by Price and Simpkins in 1995. Indeed, these authors tested chlorotrimethylsilane as an *in situ* trap to intercept lithiated derivatives obtained by treating monosubstituted ferrocenes with Li-PEA-S; this worked with limited success since only ferrocene diphenylphosphine oxide could lead to a clearly enantioenriched derivative (54% ee).<sup>72</sup> Simpkins and co-workers demonstrated on monosubstituted tricarbonyl( $\eta^6$ -arene)chromiums that a such discrimination between the two enantiotopic hydrogens of such complexes is kinetically controlled, with racemization of the lithio derivatives occurring in the presence of proton donors (*e.g.* starting compound and, to a lesser extent, the amine formed upon the deprotometalation).<sup>85, 86</sup> We realized in

2019 that, while chlorotrimethylsilane is often used as an *in situ* trap in deprotolithiation reactions using hindered lithium amides,<sup>44</sup> its ability to intercept lithium species is low compared to other traps such as  $\text{ZnCl}_2 \cdot \text{TMEDA}$  and  $\text{Zn}(\text{TMP})_2$ .<sup>73</sup> As a consequence, this was no surprise when we tested chlorotrimethylsilane as an *in situ* trap in the reaction between **1-H** and LiTMP in THF at -30 °C: poor results were obtained due to the degradation before trapping of the ferrocenyllithiums formed (not shown).

The development of *in situ* traps capable of intercepting rapidly and selectively<sup>87</sup> (organolithium vs. lithium amide) formed ferrocenyllithiums is therefore crucial if we want to improve this enantioselective deprotometalation using lithium amides.

## Conclusions

Our objective was to find a way to use lithium-metal (zinc or cadmium) bases to enantioselectively functionalize the alkyl ferrocenecarboxylates. Although we could not find a suitable lithium alkyl-amidozincate for this purpose, examining the use of different chiral secondary amines to access all-amido bases led us to consider commercial, enantiopure bis( $\alpha$ -phenylethyl)amines as a good start. In particular, the use of enantiopure Li-PEA together with an efficient *in situ* trap,  $\text{Zn}(\text{PEA})_2$ , has made it possible to convert different alkyl ferrocenecarboxylates into their 2-iodinated derivatives with good yields and high enantioselectivities (ee up to 71%).

## Experimental

### General details

All reactions were carried out in Schlenk tubes under an argon atmosphere. THF was freshly distilled from sodium-benzophenone. All alkylolithiums were titrated before use.<sup>88</sup> The secondary amines were stored over KOH pellets.  $\text{ZnCl}_2 \cdot \text{TMEDA}$ ,<sup>47</sup>  $\text{CdCl}_2 \cdot \text{TMEDA}$ ,<sup>63, 89</sup> *O*-methylferrocenecarboxylate (**1-H**),<sup>90</sup> **H-pyrro-R**,<sup>65</sup> *O*-*tert*-butylferrocenecarboxylate (**2-H**),<sup>40</sup> *O*-isopropylferrocenecarboxylate (**3-H**)<sup>91</sup> and *O*-methylferrocenethiocarboxylate (**4-H**)<sup>92</sup> were prepared as previously described. The other

commercially available starting materials were used without further purification. 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. Optical rotations were determined on a Perkin Elmer 341 polarimeter (589 nm, 20  $^{\circ}\text{C}$ ); the concentrations (c) are given in g/100 mL  $\text{CHCl}_3$ .  $^1\text{H}$  and  $^{13}\text{C}\{^1\text{H}\}$  Nuclear Magnetic Resonance (NMR) spectra were recorded either on a Bruker Avance III spectrometer at 300 MHz and 75.4 MHz respectively, or on a Bruker Avance III HD at 500 MHz and 126 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>93</sup> High resolution mass spectra measurements were performed at the CRMPO in Rennes (Centre Régional de Mesures Physiques de l'Ouest). **Safety considerations:** Due to its high pyrophoric character, *tert*-butyllithium has to be used only by well-trained people under anhydrous conditions and nitrogen or argon atmosphere.

#### **Typical procedure for the deprotonation with a lithium zincate (here, $\text{Bu}_2(\text{endo-}S)\text{ZnLi}$ )**

To a stirred, cooled (0  $^{\circ}\text{C}$ ) solution of *endo*-( $\alpha S$ )-*N*-( $\alpha$ -phenylethyl)bornylamine (**H-endo-born-S**; 0.26 g, 1.0 mmol) in THF (5 mL) were successively added *n*BuLi (1.6 M in hexanes, 1.0 mmol) and, 5 min later,  $\text{ZnCl}_2\cdot\text{TMEDA}$  (0.25 g, 1.0 mmol). The mixture was stirred for 15 min at 0  $^{\circ}\text{C}$  before introduction of *n*BuLi (1.6 M in hexanes, 2.0 mmol). After 15 min later, the reaction mixture was cooled to -30  $^{\circ}\text{C}$  before introduction of *O*-methylferrocenecarboxylate (**1-H**; 0.24 g, 1.0 mmol). After 2 h at this temperature, a solution of  $\text{I}_2$  (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  $\text{Na}_2\text{S}_2\text{O}_3$  (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 27% yield as an orange solid:  $R_f$  (petroleum ether-AcOEt 90:10) = 0.48; mp < 45  $^{\circ}\text{C}$ ; IR (ATR)  $\nu$  771, 791, 832, 848, 887, 909, 992, 1034, 1050, 1064, 1106, 1152, 1196, 1254, 1326, 1349, 1372, 1409, 1420, 1448, 1707, 2954, 3101  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  3.85 (s,

3H, OMe), 4.22 (s, 5H, Cp), 4.44 (t, 1H,  $J = 2.6$  Hz, H4), 4.70 (dd, 1H,  $J = 2.4$  and 1.5 Hz, H3), 4.84 (dd, 1H,  $J = 2.7$  and 1.5 Hz, H5);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 126 MHz)  $\delta$  39.8 (C, C-I, C2), 51.7 ( $\text{CH}_3$ , OMe), 70.3 (CH, C5), 71.2 (C, C-CO<sub>2</sub>Me, C1), 72.4 (CH, C4), 72.9 (5CH, Cp), 79.8 (CH, C3), 170.9 (C, C=O). These data are as reported.<sup>41</sup> The ee (62% in favor of the  $R_P$  enantiomer) was determined by HPLC analysis on a chiral stationary phase (OD-H column, eluent: hexane-isopropanol 90:10; 1 mL min<sup>-1</sup>; 20 °C;  $\lambda = 220$  nm;  $R_P$  enantiomer at 7.2 min and  $S_P$  enantiomer at 9.5 min).

**General procedure for the deprotonation with LiTMP using ZnCl<sub>2</sub>·TMEDA as *in situ* trap**<sup>94, 95</sup>

To a stirred, cooled (-15 °C) solution of 2,2,6,6-tetramethylpiperidine (H-TMP; 0.51 mL, 3.0 mmol) in THF (2.5 mL) was added dropwise *n*BuLi (1.4 M in hexanes, 3.0 mmol). After 5 min, this solution of LiTMP was cooled to -30 °C and slowly cannulated to a solution of ZnCl<sub>2</sub>·TMEDA (0.375 g, 1.5 mmol) and the starting ferrocene (1.5 mmol) in THF (2.5 mL) cooled at the same temperature. The reaction mixture was allowed to warm from -30 to -10 °C. After 15 min at -10 °C, a solution of I<sub>2</sub> (0.765 g, 3.0 mmol) in THF (3 mL) was added and the reaction mixture was warmed to rt. An aqueous saturated solution of Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (10 mL) was added, and the product was extracted with AcOEt (2 x 10 mL). After drying the combined organic layers over anhydrous MgSO<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).

*O*-Methyl-2-iodoferrocenecarboxylate (**1-I**). The general procedure, applied to *O*-methylferrocenecarboxylate (**1-H**; 1.2 g, 5.0 mmol), gave (eluent: petroleum ether-AcOEt 95:5) the desired iodide **1-I** (see above) in 86% yield.

*O*-tert-Butyl-2-iodoferrocenecarboxylate (**2-I**). The general procedure, applied to *O*-tert-butylferrocenecarboxylate (**2-H**; 0.43 g, 1.5 mmol), gave (eluent: petroleum ether-AcOEt 95:5) the desired iodide **2-I** in 84% yield as an orange powder:  $R_f$  (petroleum ether-AcOEt 90:10) = 0.70; mp 70-71 °C; IR (ATR): 744, 772, 816, 845, 952, 1002, 1028, 1057, 1107, 1139, 1253, 1280, 1329, 1366, 1389, 1430, 1456, 1477, 1702, 2930, 2975, 3097 cm<sup>-1</sup>;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  1.60 (s, 9H, *t*Bu),

4.22 (s, 5H, Cp), 4.39 (t, 1H,  $J = 2.5$  Hz, H4), 4.65 (dd, 1H,  $J = 2.3$  and 1.5 Hz, H3), 4.81 (dd, 1H,  $J = 2.6$  and 1.5 Hz, H5);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75.4 MHz)  $\delta$  28.6 ( $\text{CH}_3$ ,  $\text{CMe}_3$ ), 39.8 (C, C-I, C2), 70.4 (CH, C5), 72.0 (CH, C4), 72.7 (C,  $\text{C-CO}_2t\text{Bu}$ , C1), 72.8 (5CH, Cp), 79.7 (CH, C3), 81.2 (C,  $\text{CMe}_3$ ), 169.4 (C, C=O); HRMS (ESI; MeOH),  $m/z$  434.9517 (1 ppm) found (calcd for  $\text{C}_{15}\text{H}_{17}^{56}\text{FeIO}_2\text{Na}$ ,  $[\text{M}+\text{Na}]^+$ , requires 434.95204).

*O*-Isopropyl-2-iodoferrocenecarboxylate (**3-I**). The general procedure, applied to *O*-isopropylferrocenecarboxylate (**3-H**; 0.41 g, 1.5 mmol), gave (eluent: petroleum ether-AcOEt 95:5 to 90:10) the desired iodide **3-I** in 87% yield as an orange oil:  $R_f$  (petroleum ether-AcOEt 90:10) = 0.62; IR (ATR): 771, 798, 823, 908, 957, 1002, 1029, 1057, 1104, 1148, 1165, 1252, 1271, 1327, 1372, 1385, 1412, 1433, 1466, 1699, 2933, 2977, 3099, 3675  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  1.36 (d, 3H,  $J = 6.3$  Hz, Me), 1.39 (d, 3H,  $J = 6.3$  Hz, Me), 4.21 (s, 5H, Cp), 4.42 (t, 1H,  $J = 2.5$  Hz, H4), 4.67 (dd, 1H,  $J = 2.3$  and 1.6 Hz, H3), 4.85 (dd, 1H,  $J = 2.6$  and 1.6 Hz, H5), 5.22 (sept, 1H,  $J = 6.3$  Hz,  $\text{CHMe}_2$ ). The  $^1\text{H}$  NMR data correspond to those reported.<sup>42</sup>  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 126 MHz)  $\delta$  22.2 ( $\text{CH}_3$ , Me), 22.3 ( $\text{CH}_3$ , Me), 39.9 (C, C-I, C2), 68.0 (CH,  $\text{CHMe}_2$ ), 70.3 (CH, C5), 71.6 (C,  $\text{C-CO}_2i\text{Pr}$ , C1), 72.2 (CH, C4), 72.8 (5CH, Cp), 79.8 (CH, C3), 169.7 (C, C=O).

#### **General procedure for the deprotonation with Li-PEA-S using $\text{Zn}(\text{PEA-S})_2$ as *in situ* trap**<sup>73</sup>

To a stirred, cooled ( $-15\text{ }^\circ\text{C}$ ) solution of bis[(*S*)- $\alpha$ -phenylethyl]amine (**H-PEA-S**; 0.46 mL, 2.0 mmol) in THF (6 mL) was added dropwise *n*BuLi (1.4 M in hexanes, 2.0 mmol). After 5 min,  $\text{ZnCl}_2\cdot\text{TMEDA}$  (0.25 g, 1.0 mmol) was quickly introduced in one portion and the reaction mixture was stirred at this temperature for 15 min before addition of the starting ferrocene (1.0 mmol). After 15 min at  $-15\text{ }^\circ\text{C}$ , this mixture was cooled to  $-80\text{ }^\circ\text{C}$  before slow cannulation of a solution of lithium Li-PEA-S (1.0 mmol; prepared as before from **H-PEA-S** (0.23 mL, 1.0 mmol) and *n*BuLi (1.4 M in hexanes, 1.0 mmol) in THF (6 mL)) precooled at  $-80\text{ }^\circ\text{C}$ . The reaction mixture was stirred at  $-80\text{ }^\circ\text{C}$  for 1 h and then allowed to warm from  $-80$  to  $-20\text{ }^\circ\text{C}$  (8 h). A solution of  $\text{I}_2$  (0.76 g, 3.0 mmol) in THF (5 mL) was added and the reaction mixture was warmed to rt. An aqueous saturated solution of  $\text{Na}_2\text{S}_2\text{O}_3$  (10 mL)

was added, and the product was extracted with AcOEt (2 x 10 mL). After drying the combined organic layers over anhydrous MgSO<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). When no separation was observed by HPLC, the iodoester was converted to 2-iodoferrocenemethanol as described previously.<sup>83</sup>

*O-Methyl-2-iodoferrocenecarboxylate (1-I)*. The general procedure, applied to *O*-methylferrocenecarboxylate (**1-H**; 0.24 g, 1.0 mmol), gave (eluent: petroleum ether-AcOEt 90:10) a mixture (0.32 g) containing the desired iodide **1-I** (see above) in 77% yield and the starting material (13% yield). The ee (71% in favor of the *R<sub>P</sub>* enantiomer) was determined by HPLC analysis on a chiral stationary phase (OD-H column, eluent: hexane-isopropanol 90:10; 1 mL min<sup>-1</sup>; 20 °C; λ = 220 nm; *R<sub>P</sub>* enantiomer at 7.2 min and *S<sub>P</sub>* enantiomer at 9.5 min).

*O-tert-Butyl-2-iodoferrocenecarboxylate (2-I)*. The general procedure, applied to *O-tert*-butylferrocenecarboxylate (**2-H**; 0.29 g, 1.0 mmol), gave (eluent: petroleum ether-AcOEt 95:5) a mixture (0.38 g) containing the desired iodide **2-I** (see above) in 82% yield and the starting material (12% yield). The ee (70% in favor of the *R<sub>P</sub>* enantiomer) was determined, after reduction with DIBAL-H to 2-iodoferrocenemethanol,<sup>83</sup> by HPLC analysis on a chiral stationary phase (AS-H column, eluent: hexane-isopropanol 90:10; 1 mL min<sup>-1</sup>; 20 °C; λ = 220 nm; *R<sub>P</sub>* enantiomer at 15.6 min and *S<sub>P</sub>* enantiomer at 24.6 min).

*O-Isopropyl-2-iodoferrocenecarboxylate (3-I)*. The general procedure, applied to *O*-isopropylferrocenecarboxylate (**3-H**; 0.27 g, 1.0 mmol), gave (eluent: petroleum ether-AcOEt 95:5) a mixture (0.33 g) containing the desired iodide **3-I** (see above) in 45% yield and the starting material (55% yield). The ee (71% in favor of the *R<sub>P</sub>* enantiomer) was determined, after reduction with DIBAL-H to 2-iodoferrocenemethanol,<sup>83</sup> by HPLC analysis on a chiral stationary phase (AS-H column, eluent: hexane-isopropanol 90:10; 1 mL min<sup>-1</sup>; 20 °C; λ = 220 nm; *R<sub>P</sub>* enantiomer at 15.6 min and *S<sub>P</sub>* enantiomer at 24.6 min).



## Author contributions

Conceptualization, F. M., F. C., W. E., P. C. G., G. H.; funding acquisition, F. M., P. C. G.; investigation, G. D., W.E., M. H., M. B., T. R., V. D.; project administration, F. M.; supervision, F. M., G. H., F. C., W. E., G. B. A.; writing initial draft, F. M.; writing - review and editing, P. C. G., W. E., T. R., G. H., F. C., G. B. A.

## Conflicts of interest

There are no conflicts of interest to declare.

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**Electronic Supplementary Information (ESI) available:** Synthesis of the secondary amines, NMR spectra of **H-menth-*S,S***, **H-menth-*S,R***, **H-menth-*R,S***, **H-menth-*R,R***, **H-endo-fenc-*R***, **H-pino-*R,R***, **H-pino-*S,S***, **H-pino-*S,R***, **H-endo**, **H-exo**, **H-endo-*S-naph*** and **H-iPr-OMe-*S***, and HPLC chromatograms. See: DOI: 10.1039/xx.

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