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Synthesis of both enantiomers of ferrocene[1,2-*c*]1H-quinolin-2-one by diastereoselective deproto-zincation of sugar-derived ferrocene esters

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Diastereoselective deproto-metallation of several sugar-derived ferrocene esters using lithium-zinc bases was studied. While bis[(*R*)-1-phenylethyl]amino as ligand afforded the diacetone-D-glucose-based (*S*$_P$)-2-iodoferrocene ester in 91% de after iodination, the *R*$_P$ was synthesized from α-D-glucofuranose using 2,2,6,6-tetramethylpiperidino as ligand. Both (*R*$_P$)- and (*S*$_P$)-ferrocene[1,2-*c*]1H-quinolin-2-one were reached by subsequent cyclizing coupling, albeit their racemization was noted.

Metallocenes have been intensively studied due to their varied applications in fields such as catalysis, materials science,[1] and bioorganometallic chemistry.[2] Amongst all, planar-chiral ferrocenes have attracted the attention of chemists, in particular because of their use in homogeneous asymmetric catalysis.[3]

The presence of a heteroatom-containing substituent on ferrocenes usually directs lithiation onto the adjacent position. With the aim of obtaining enantio-enriched planar-chiral derivatives, reactions of ferrocenes bearing various chiral directing groups have been documented.[3b,c] We have recently contributed to these studies by identifying sugar-derived esters as suitable groups to induce ferrocene diastereoselective deproto-metallations using function-compatible lithium-cadmium base (TMP)$_3$CdLi (TMP = 2,2,6,6-tetramethylpiperidino) followed by iodination.[4] Herein, the use of lithium-zinc combinations as non-toxic basic alternatives to achieve chemo- and still diastereoselective syntheses of 2-iodoferrocene esters is described. In order to access targets such as ferrocene[1,2-*c*]1H-quinolinones **1** from the latter, coupling-cyclization one-pot sequences are next considered (Scheme 1).
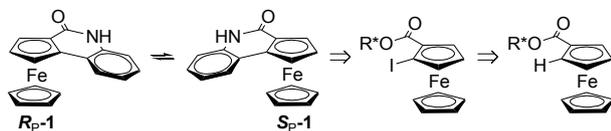
Scheme 1

We thus turned our attention to a variety of chiral ferrocene esters, prepared from ferrocenecarboxylic acid and the corresponding secondary alcohols **2a-g** depicted in Scheme 2 under classical conditions.[5] The metallation reactions were attempted in THF (tetrahydrofuran) at room temperature for 2 hours before interception with iodine (Table 1).
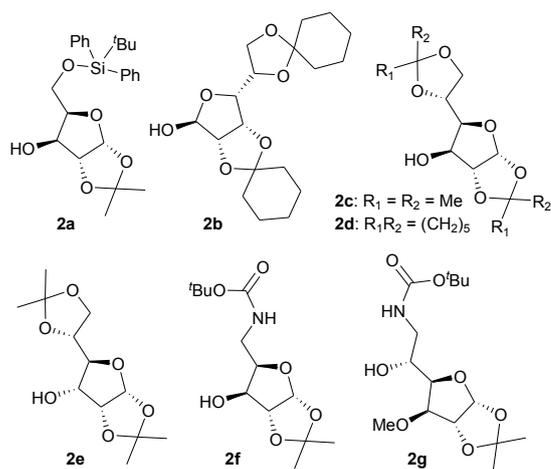
Scheme 2 Chiral alcohols used to prepare the ferrocene esters.

From the α-D-xylofuranose derivative **3a**, using the lithium-zinc base prepared in situ from ZnCl$_2$·TMEDA (1 equiv, TMEDA = *N*,*N*,*N*',*N*'-tetramethylethylenediamine) and TMPLi (3 equiv)[6] afforded **4a** in 86% yield but with a moderate 20% de. Subsequent reduction to 2-iodoferrocenemethanol (**5**) using DIBAL-H,[7] analysis by HPLC using a chiral stationary phase, and comparison with the literature showed the predominant formation of **4a** as *R*$_P$ diastereomer (Table 1, entry 1). When the α-D-mannofuranose derivative **3b** was treated similarly, the metallation proved incomplete, affording **4b** in 50% yield and a low 17% de in favor of the *S*$_P$ diastereomer (Table 1, entry 2). Under the conditions used to functionalise **3a,b**, the iodo derivatives **4c,d** were synthesized from the inexpensive α-D-glucofuranose derivatives **3c,d** in 86-87% yield and 54-56% de (major *S*$_P$ diastereomer, Table 1, entries 3,4). Involving the α-D-allofuranose derivative **3e** in the reaction, a good conversion was observed but with a disappointing 32% de in favor of the *S*$_P$ diastereomer (Table 1, entry 5). In order to evaluate more metal-coordinating groups, the α-D-xylofuranose derivative **3f** was tested using 1.5 equiv of base, giving **4f** in 70% yield and a low de (Table 1, entry 6). With the α-D-glucofuranose derivative **3g**, both diastereomers were separated and the major one, isolated in 35% yield, proved to be the *R*$_P$ (Table 1, entry 7).

Table 1 Metallation of the chiral ferrocenecarboxylates **3a-g** using the lithium-zinc base prepared from $ZnCl_2 \cdot TMEDA$ (1 equiv) and TMPLi (3 equiv) before trapping with I_2 (3 equiv).

Entry	3	4, yield (%), de[a] (%)	5, yield (%), ee[b] (%)
1	3a	4a, 86, 20	61, 22 (R)[c]
2	3b	4b, 50[d], 17	(S)[c,e]
3	3c	4c, 86, 54	(S)[c,e]
4	3d	4d, 87, 56	96, 57 (S)[c]
5	3e	4e, 64[d]	86, 32 (S)[c]
6[f]	3f	4f, 70	91, 11 (S)[c]
7[g]	3g	R_P-4g, 35 and S_P-4g, 12[d]	81, 96 (R) and 88, 92 (S)[c]

[a] Wherever possible, determined from the integration of the ^{1}H NMR spectrum of the crude mixture. [b] Determined by HPLC analysis on a chiral stationary phase (AS-H column, eluent: hexane/isopropanol 9:1, 1 mL/min, λ = 252 nm). [c] Absolute configuration assigned on the basis of reported data.[8] [d] Estimated yield, due to the presence of starting material. [e] Reduction performed on a fraction. [f] Using $ZnCl_2 \cdot TMEDA$ (1.5 equiv) and TMPLi (4.5 equiv). [g] Both diastereomers separated by column chromatography purification over silica gel.

A thorough study was then undertaken in order to evaluate the parameters responsible for the diastereoselectivity observed from promising **3c** (Table 2). In order to check the importance of the structure composition of the base, $(TMP)_2BuZnLi$[6b] was tested; similar yield and de were obtained (Table 2, entry 2). Using hexane containing TMEDA (5 equiv)[9] instead of THF still led to **4c** but in lower yield and de (Table 2, entry 3). The presence of TMEDA[10] in THF, due to the zinc source used, did not change the diastereoselectivity, as shown employing $ZnCl_2$ instead of $ZnCl_2 \cdot TMEDA$ (Table 2, entries 4,5). The addition of TMPLi (1 or 2 equiv) to a mixture of $(TMP)_2Zn$ and **3c** was attempted, and led to 87-89% yield, and 64 or 72% de, respectively (Table 2, entries 6,7), as if TMPLi (or aggregates containing LiCl)[6c] was superior to mixed ferrocenyl-TMP zincates to perform the diastereoselective reaction. Similarly, the addition of TMPLi (3 equiv) to a mixture of $ZnCl_2 \cdot TMEDA$ and **3c** led to an improved de (Table 2, entry 8). The sequential addition of $(TMP)_2Zn$ and TMPLi (2 equiv) was also attempted using 1,2-dimethoxyethane, 1,4-dioxane, and dimethoxymethane as solvents, but the reaction only proceeded with the latter, affording **4c** in 32% yield and 51% de (Table 2, entry 9). Mixing the reagents in different orders at -30 or -50 °C before warming to rt did not change significantly the diastereoselectivity (Table 2, entries 10-13).

Double asymmetric induction[11] using commercial (R)- and (S)-bis[1-phenylethyl]amine (PEAH) as ligand source instead of TMPH was next attempted. Thus, when the substrate was reacted with a base obtained from $ZnCl_2 \cdot TMEDA$ (1 equiv) and (R)- or (S)-PEALi (3 equiv), **4c** was obtained in 67 and 24% yield, and 79 and 10% de, respectively (Table 2, entries 14-15). The sequential addition of the zinc diamide (1 equiv) and lithium amide (2 equiv) to the substrate being more efficient in the case of TMPH (Table 2, entry 7), we applied a similar protocol using (R)-PEAH; under these conditions, both good yield and de were obtained (Table 2, entry 16).

Applied to the ester **3g**, the sequential addition of $(TMP)_2Zn$ (either prepared from $ZnCl_2 \cdot TMEDA$ or $ZnCl_2$) and TMPLi (2 equiv) afforded R_P-4g in 51 and 57% yield, respectively.

Table 2 Metallation of the chiral ferrocenecarboxylate **3c** using the lithium-zinc base prepared from $ZnCl_2 \cdot TMEDA$ (1 equiv), RLi (2 equiv) and R'Li (n equiv) before trapping with I_2 (3 equiv).

Entry	R	R'(n)	Solvent, conditions	Yield (%), de[a] (%)
1	TMP	TMP(1)	THF, rt, 2 h	86, 54 (S[b])
2	TMP	Bu(1)	THF, rt, 2 h	89, 55 (S[b])
3	TMP	TMP(1)	[c], rt, 2 h	50, 42 (S[b])
4[d]	TMP	TMP(1)	THF, rt, 2 h	84, 56 (S[b])
5[d,e]	TMP	TMP(1)	THF, -30 °C to rt, 2 h	46, 53 (S[b])
6[f]	TMP	TMP(1)	THF, rt, 2 h	89, 64 (S[b])
7[f]	TMP	TMP(2)	THF, rt, 2 h	87, 72 (S[b])
8	[g]	TMP(3)	THF, -30 °C to rt, 2 h	70, 68 (S[b])
9[d,f]	TMP	TMP(2)	[h], rt, 2 h	32, 51 (S[b])
10[f]	TMP	TMP(2)	THF, -30 °C to rt, 2 h	51, 52 (S[b])
11	TMP	TMP(2)	THF, -30 °C to rt, 2 h	64, 56 (S[b])
12[d]	TMP	TMP(2)	THF,[i] -30 °C to rt, 2 h	30, 56 (S[b])
13[j]	TMP	TMP(2)	THF, -50 °C to rt, 2 h	71, 56 (S[b])
14	PEA[k]	PEA[k](1)	THF, rt, 2 h	67, 79 (S[b])
15	PEA[l]	PEA[l](1)	THF, rt, 2 h	24, 10 (S[b])
16[f]	PEA[k]	PEA[k](2)	THF, rt, 2 h	85, 91 (S[b])

[a] Determined from the integration of the ^{1}H NMR spectrum of the crude mixture. [b] Determined after reduction using DIBAL-H by HPLC analysis on a chiral stationary phase (AS-H column, eluent: hexane/isopropanol 9:1, 1 mL/min, λ = 252 nm). [c] In hexane containing TMEDA (5 equiv). [d] Base prepared from $ZnCl_2$ instead of $ZnCl_2 \cdot TMEDA$. [e] TMEDA slowly added at -30 °C. [f] Sequential addition of RLi and, 10 min later, R'Li. [g] Substrate mixed with $ZnCl_2 \cdot TMEDA$ before reaction (no RLi used). [h] Using dimethoxymethane as solvent. [i] Containing TMEDA (1 equiv). [j] Base transferred to the substrate. [k] Using (R)-PEAH. [l] Using (S)-PEAH.

In order to access the quinolinones **1**, the iodides S_P-4c and R_P-4g were reacted with 2-aminophenylboronic acid. Using catalytic $Pd(dba)_2$ (dba = dibenzylidene acetone) and triphenylphosphine, dioxane as solvent, and CsF in order to avoid the use of basic reagents,[12] led to the carboxamides R_P-1 and S_P-1 through Suzuki cross-coupling and subsequent cyclization of the amino group with the ester function (Scheme 3).
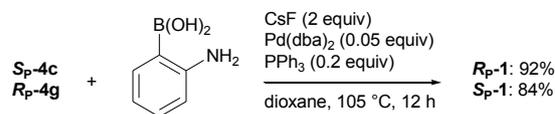
Scheme 3 Cyclizing Suzuki couplings giving **1**.

Crystals were analysed by X-ray diffraction and a structure referring to the non-chiral space group R-3 was obtained (Figure 1). This result is not sufficient to claim racemization,[13] but led us to check this possibility using HPLC on chiral phases. The interconversion (R_P-1 vs S_P-1) was noted in solution;[14] without solvent, it could be stopped at temperatures below -20 °C.

Figure 1 ORTEP diagrams (30% probability) of R_P-**1** and S_P-**1**.

Lithiation experiments on aryl carboxamides showed that the orientation of the function has an impact on the efficiency of the
5 *ortho*-metallations, which increases with the coplanarity of the oxygen and activated hydrogen with the ring.[15] A rationalization of the diastereoselectivity observed using **3c** was thus attempted by identifying more stable conformers. The geometrical (local stabilization) optimization was performed by changing the
10 dihedral angle between the upper plane of the ferrocenyl moiety and the ester carbonyl group (B3LYP/6-31G(d), structure of the ferrocenyl group fixed). The dihedral angle was fixed with 30° intervals from 0° to 330°. Two most stable structures, with dihedral angles of 0° (to give the major diastereomer) and 180°
15 (to give the minor diastereomer), were identified and calculated in greater detail (M06/LanL2DZ(Fe)&6-31G(d)) at around 0° and 180°. The conformation with the dihedral angle of -6° proved 4.6 kcal.mol^{-1} lower in energy that of 190° (Figure 2, left).[16] These calculated results are in accordance with the observed
20 diastereoselectivity in the deproto-metallation of **3c** using the lithium-zinc combination (Scheme 4). It is interesting to note that the structure obtained by X-ray diffraction of suitable crystals of **3c** corresponds to the most stable conformer (Figure 2, right).


25 **Figure 2** Calculated most stable conformer (M06/LanL2DZ(Fe)&6-31G(d)) and ORTEP diagram (30% probability) of **3c**.

Scheme 4 Observed diastereoselectivity in the deproto-metallation of **3c**.

Conclusions

30 Sugar-based ferrocene esters were deproto-metallated by using mixed lithium-zinc amido-based bases, with diastereoselectivities up to 91% under the '*double asymmetric induction*' protocol.

40 ## Notes and references

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† Electronic Supplementary Information (ESI) available: procedures, X-ray diffraction analysis and CIF files of **1** (CCDC 872139) and **3c** (CCDC 798863), NMR spectra of **1**, geometrical optimization of **3c** and computational details. See DOI: 10.1039/b000000x/

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16 The calculations using the SCRF method (PCM, solvent = THF) gave similar results. For details, see ESI.†

Graphical and textual abstract for the contents pages.

(R_P)- and (S_P)-ferrocene[1,2-c]1H-quinolin-2-one were synthesized from sugar-derived ferrocene esters using diastereoselective deproto-metallation by lithium-zinc combinations followed by iodination and cyclizing coupling.