Deprotonative metallation of ferrocenes using mixed lithium-zinc and lithium-cadmium combinations.

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**A mixed lithium-cadmium amide and a combination of lithium
and zinc amides were reacted with a range of ferrocenes;**
10 **deprotonative mono- or di-metallation in general occurred
chemoselectively at room temperature, as evidenced by
subsequent quenching with iodine.**

Metallocenes have met an important development. Ferrocene
has notably been extensively used to synthesize a variety of
15 derivatives with applications ranging from catalysis[1] to
materials science[2] and bioorganometallic chemistry.[3]

Among the methods used to functionalize ferrocene
compounds, deprotonative metallation plays an important
role.[4] The presence of a substituent containing heteroatoms on
20 ferrocene usually directs deprotonation to the adjacent
position, giving after subsequent quenching 1,2-
unsymmetrical ferrocenes. The reagents classically used for
this purpose are lithium bases, which are highly polar
reagents, hardly tolerating the presence of reactive functional
25 groups. For these reasons, restricted conditions such as low
temperatures or solvents of low polarity have to be used in
order to ensure good results, when attained.

In recent studies, ferrocene was mono- or poly-metallated
using mixed alkali metal-magnesium, -zinc, and -manganese
30 bases, and the species isolated were studied by X-ray
diffraction.[5] Another mixed lithium-magnesium base,
TMPMgCl·LiCl (TMP = 2,2,6,6-tetramethylpiperidino),
allowed chemoselective deprotonation reactions of ferrocenes
bearing an ester, a nitrile and a carboxylic acid function, when
35 used in a polar solvent at temperatures around 0 °C.[6]

Among recently documented non cryogenic alternatives for
the deprotonative metallation of aromatics,[5] *in situ* prepared
mixtures of $ZnCl_2 \cdot TMEDA$[7] (TMEDA = *N,N,N',N'*-
tetramethylethylenediamine), or $CdCl_2 \cdot TMEDA$,[8] and 3
40 equivalents of LiTMP proved efficient for the
functionalization of a large range of ferrocene substrates
including aromatics bearing reactive functions and sensitive
heterocycles. Hence we decided to attempt their use in the
ferrocene series.

45 It is known[9] that ferrocene can be lithiated using 2 equiv of
tert-butyllithium in the presence of 0.1 equiv of potassium
tert-butoxide in THF (tetrahydrofuran) at –75 °C. The
lithium-cadmium base, which can be considered as
$(TMP)_3CdLi$,[8] was first chosen to attempt the metallation of
50 ferrocene (**1**). When treated with 0.5 or 1 equiv (with respect
to Cd) of $(TMP)_3CdLi$ in THF at room temperature for 2 h,
ferrocene (**1**) remained unchanged, as demonstrated by

subsequent quenching with iodine. In contrast, when the
deprotonation step was carried out using 1 equiv of base at the
55 reflux temperature of pentane for 3 h, the iodide **2a** was
isolated in 86% yield (Scheme 1).
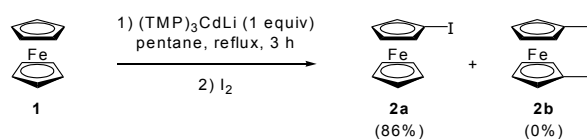
Scheme 1 Deprotonative cadmiation of ferrocene

In the presence of a chelating group, the same reaction is
60 favoured. Thus, the similar functionalization of the acetal **3**
can be performed either at the reflux temperature of pentane
to afford the acetal-protected iodide **4a** in 76% yield, or at
room temperature in THF to give, after subsequent
deprotection of the aldehyde, the derivative **5a** in 51% overall
65 yield. When THF was the solvent, the 2,5-diodo derivative **4b**
was also formed in 10% yield (Scheme 2). It is pertinent to
mention that lithium bases were previously used to
deprotonate the acetal **3**, albeit at lower temperatures in order
to prevent substantial cleavage of the dioxane ring.[10]
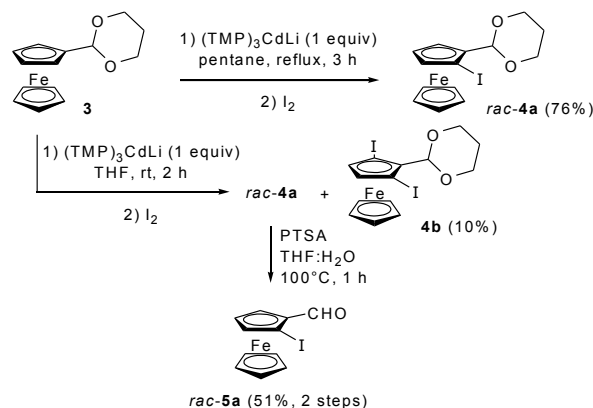
Scheme 2 Deprotonative cadmiation of 2-ferrocenyl-1,3-dioxane

In order to check the chemoselectivity of reactions using
$(TMP)_3CdLi$, the metallation of ferrocene ketones was
attempted. Starting from acetylferrocene (**6**) logically resulted
75 in THF or pentane in a complex mixture presumably due to
the presence of acidic α-protons. From benzoylferrocene (**7**),
it proved possible using 0.5 equiv of base in THF at room
temperature for 2 h to isolate the mono- and diiodide **8a,b** in
36 and 2% yield, respectively (Scheme 3).

80 We then turned to methyl ferrocenecarboxylate (**9**), which

should be less sensitive than ketones **6,7**. Indeed, employing only 0.5 equiv of base resulted in the formation of the mono- and diiodide **10a,b** in 73 and 10% yield, respectively. Reaction times of 0.5 and 4 h did not modify significantly the yields. The dimetallation could be favoured using 1 equiv of base, to furnish the diiodide **10b** in 82% yield (Scheme 4).
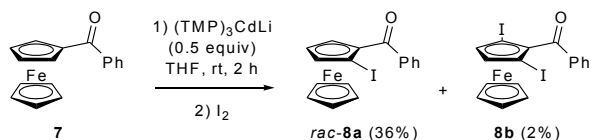
Scheme 3 Deprotonative cadmiation of benzoylferrocene
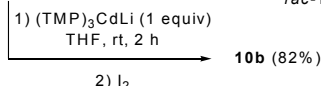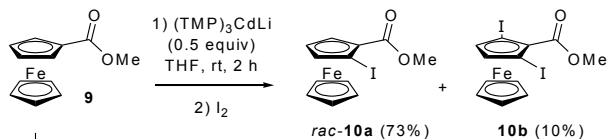
Scheme 4 Deprotonative mono- and dicadmiation of methyl ferrocenecarboxylate

The structure of the latter was determined unequivocally by X-ray diffraction analysis of crystals obtained by slow evaporation of a dichloromethane solution (Figure 1).†
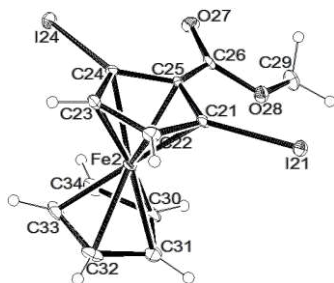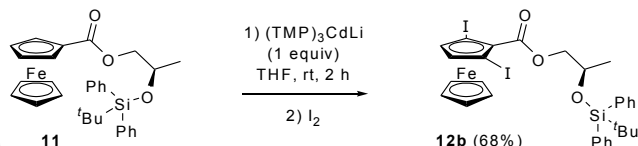

Figure 1 ORTEP diagram (30% probability) of the diiodide **10b**.

This possibility was successfully extended to the ferrocenecarboxylate **11**, for which the corresponding diiodides **12b** was isolated in a satisfying yield (Scheme 5).


Scheme 5 Deprotonative dicadmiation of ferrocenecarboxylates **11-13**

The base *in situ* prepared from ZnCl$_2$·TMEDA and 3 equivalents of LiTMP, which can be considered as a 1:1 mixture of (TMP)$_2$Zn and LiTMP,[7] was then chosen to attempt the metallation of some ferrocene compounds. Bare ferrocene (**1**) remained unchanged when treated at room temperature in THF with the lithium-zinc base. Exchanging THF for pentane and carrying out the reaction at reflux resulted in the formation of a mixture of monoiodide **2a**, 1,1'-diiodide **2b** and unreacted ferrocene (**1**). This contrasts with what has been obtained using (TMP)$_3$CdLi, and showed that the lithium-cadmium base is more efficient for the functionalization of bare ferrocene.

In the case of the acetal **3**, as previously observed using (TMP)$_3$CdLi, a mixture of the mono- and the diiodide **4a,b** (80:20 ratio) was obtained using 1 equiv of ZnCl$_2$·TMEDA and 3 equiv of LiTMP in THF at room temperature. Dividing by two the amount of base allowed to discard the diiodide **4b**, but to the detriment of the conversion (Scheme 6).
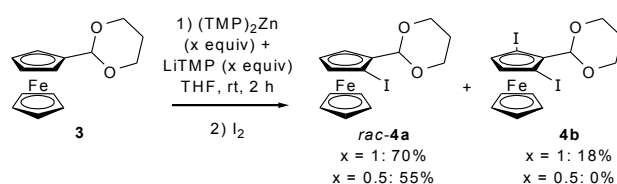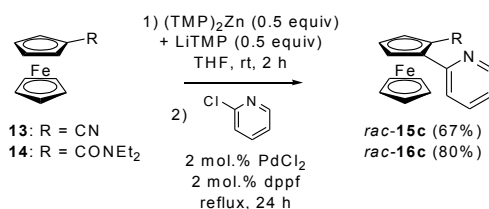

Scheme 6 Deprotonative zincation of 2-ferrocenyl-1,3-dioxane

In the presence of electron-withdrawing substituents, the ferrocene ring can be efficiently deprotonated using the *in situ* generated mixture of (TMP)$_2$Zn (0.5 equiv) and LiTMP (0.5 equiv). From the ferrocene ester **9**, the monoiodide **10a** was selectively obtained, and isolated in 83% yield (the ^{1}H NMR spectra showed that remaining starting material was the only impurity present in the crude). The dideprotonation was similarly not observed when cyanoferrocene (**13**) and *N,N*-diethylferrocenecarboxamide (**14**) were involved in the reaction, and the expected iodides **15a** and **16a** were isolated in 87 and 91% yield, respectively (Scheme 7).

9: R = CO$_2$Me   *rac*-**10a** (83%)
13: R = CN   *rac*-**15a** (87%)
14: R = CONEt$_2$ *rac*-**16a** (91%)
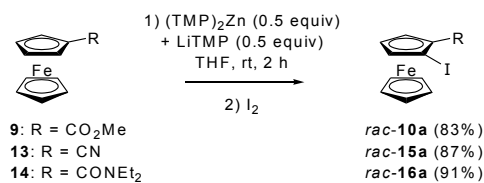
Scheme 7 Deprotonative zincation of methyl ferrocenecarboxylate, cyanoferrocene and *N,N*-diethyl ferrocenecarboxamide

Deprotonative zincation of aromatic compounds followed by *in situ* palladium-catalyzed cross-coupling of the lithium zincate such generated constitutes a straightforward access to biaryl compounds.[7] Using catalytic amounts of PdCl$_2$ as palladium source and 1,1'-diphenylphosphinoferrocene (dppf) as ligand with 2-chloropyridine allowed the synthesis of the pyridine derivatives **15c** and **16c** in satisfying yields (Scheme 8). The structure of the compound **15c** was determined unequivocally by X-ray diffraction analysis (Figure 2).†

13: R = CN   *rac*-**15c** (67%)
14: R = CONEt$_2$ *rac*-**16c** (80%)

Scheme 8 Deprotonative zincation of cyanoferrocene and *N,N*-diethylferrocenecarboxamide followed by cross-coupling

Monometallation mediated by the lithium-zinc base also proved possible for methyl ferrocene-1,1'-dicarboxylate (**17**). Under the same reaction conditions, the iodide **18a** was obtained in 72% yield. Unfortunately, using 1 equiv of (TMP)$_3$CdLi with this substrate failed in only giving one

diiodide. Indeed, two diiodides (compounds **18b**) and even a triiodide (**18c**) were isolated from the complex mixture obtained (Scheme 9).
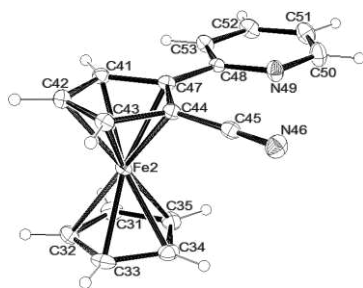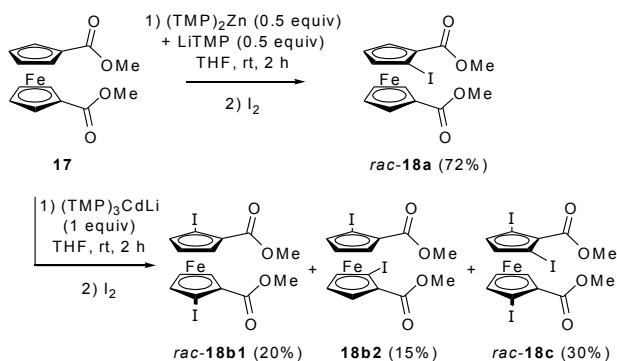

Figure 2 ORTEP diagram (30% probability) of the compound **15c**.

Scheme 9 Deprotonative metallation of methyl ferrocene-1,1'-dicarboxylate

Finally, the behaviour of bromoferrocene (**19**) towards the lithium-zinc base was considered. Under the conditions described above, 1-bromo-2-iodoferrocene (**20a**) was obtained as the main product (64% yield). 1-Bromo-3-iodoferrocene (**20b**) concomitantly formed, and was isolated in 7% yield (Scheme 10). Such a migration of a heavy halogen has previously been observed using lithium amides as metallating agents,[11] and could be explained herein by the presence of LiTMP in the basic mixture.
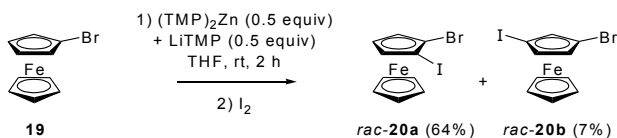
Scheme 10 Deprotonative zincation of bromoferrocene

The structure of the iodide **20a** was established on the basis of its NMR spectra, by comparison with previously reported data.[12] By slow evaporation of a dichloromethane solution of the iodide **20a**, it also proved possible to collect suitable crystals for X-ray diffraction analysis. The presence of bromo and iodo groups at adjacent positions was confirmed by this way. However, the analysis of the data was complicated by a phenomenon which could be interpreted by a partial enrichment in favour of one enantiomer during the crystallization (Figure 3).†

In summary, (TMP)$_3$CdLi is an efficient reagent, allowing the monodeprotonation of weakly activated ferrocenes and the dideprotonation of ferrocenes activated by an ester function. The corresponding Li-Zn base is more suitable for the room

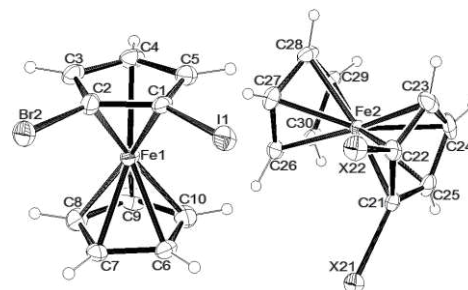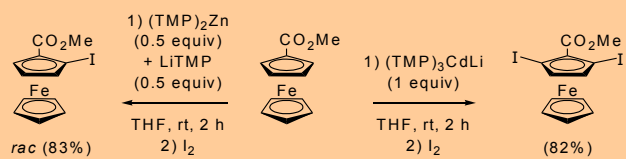temperature monofunctionalization of activated ferrocenes.

Figure 3 ORTEP diagram (30% probability) of the iodide **20a**: main enantiomer (left) and racemic mixture (right, X21 = Br, X22 = I and X22 = Br, X21 = I)

References

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† Electronic Supplementary Information (ESI) available: Experimental procedures and characterization of compounds, CIF files of **10b** (CCDC 755178), **15c** (CCDC 755179) and **20a** (CCDC 755180). See DOI: 10.1039/b000000x/

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Graphical and textual abstract for the contents pages.

(TMP)$_3$CdLi is an efficient reagent for the monodeprotonation of weakly activated ferrocenes and the dideprotonation of ferrocenes activated by an ester function. The corresponding Li-Zn base is more suitable for the monofunctionalization of ferrocenes activated by different functions.