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About diastereoselective oxidations of ferrocenyl amino alcohols

Olivier Delacroix,[a] Bakolinirina Andriamihaja,[b] Sophie Picart-Goetgheluck[a,*] and Jacques Brocard[a,*]

[a]*Laboratoire de Catalyse de Lille, Equipe de Catalyse Homogène, UMR CNRS 8010, ENSCL, Cité Scientifique, BP 108, F-59652 Villeneuve d'Ascq Cedex, France*
[b]*Laboratoire de Chimie Organométallique, Faculté des Sciences, Université d'Antananarivo BP 906, 101 Antananarivo, Madagascar*

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Abstract—Oxidation of some 2-(*N*,*N*-dimethylaminomethyl)ferrocenylalkylcarbinols by MnO_2 is totally diastereoselective: only one diastereomer is oxidized. A study was performed to highlight the influential factors of this phenomenon. Several ferrocenyl alcohols have been studied. First, two diastereomers of the ferrocenyl amino alcohol bearing a deuterium as an R group have been synthesized and oxidized. The good reactivity of both diastereomers displayed the importance of the size of the alkyl group, which needs to be bulkier than a deuterium. The synthesis and the oxidation of *endo*- and *exo*-α-hydroxy [4](1,2)ferrocenophane enabled the elimination of the hypothesis involving the spatial position of the hydroxy group, while the two diastereomers were oxidized. The replacement of the dimethylamino group by a methoxy or a methyl, the oxidation of these compounds, and the study of the preferential conformation of each diastereomer showed clearly the influence of an intramolecular hydrogen bond. So,the diastereoselectivity was shown to depend on the steric bulk of the alkyl group and on the presence of a strong intramolecular hydrogen bond between the hydroxy group and the nitrogen.

1. Introduction

Chiral ferrocenyl ligands have been used with success in a large number of asymmetric catalytic reactions.[1–3] These compounds can be synthesized by various methods. However, pathways using a totally diastereoselective oxidation have not been frequently used to produce diastereopure alcohols.[4,5] In the most representative examples of stereoselective oxidation, a chiral agent[6] or a biocatalyst[7–9] have been employed. In our laboratory, we synthesized chiral ferrocenyl amino alcohols with the purpose of using them as chiral ligands in asymmetric catalysis.[10,11] Interestingly, during the synthesis of one of these ligands, a rare totally diastereoselective oxidation has been observed. Indeed, only one isomer of a diastereomeric mixture of 2-(*N*,*N*-dimethylaminomethyl)ferrocenylethanol **1** was converted by MnO_2 into the corresponding ketone without any external chiral inducing agent (Fig. 1).[11,12] In this paper, we report on the study of this particular phenomenon by considering the different factors possibly responsible for this total diastereoselectivity.

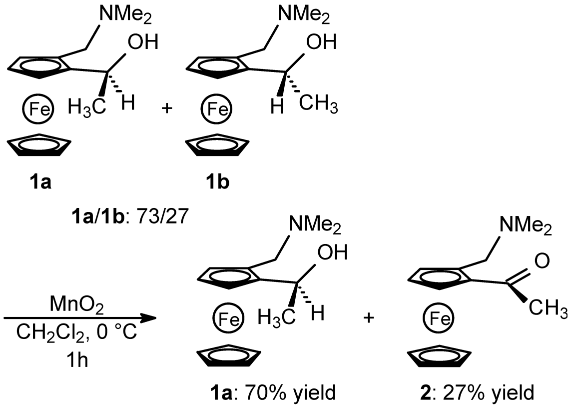

Figure 1. Diastereospecific oxidation of **1**.

2. Results

During our research on chiral ferrocenyl amino alcohols, the oxidation of a **1a**/**1b**[13] mixture had to be performed (Fig. 1).[11,12] Very surprisingly, the reaction was totally diastereoselective since diastereomer **1b** was completely oxidized whereas **1a** stayed unchanged.[14]

Different factors could be considered responsible for the observed stereospecificity: substitution on the carbon bearing the OH function to be oxidized, interaction of the OH moiety with iron, participation of a hydrogen bond between OH moiety and the nitrogen atom. We sought to perform experiments that might help to determine which factor controls the diastereospecificity of the process.

Keywords: Ferrocene; Alcohol; Diastereoselectivity; Oxidation.

* Corresponding authors. Tel.: +33-320434893; fax: +33-320436585 (S.P.-G.); tel.: +33-320436501; fax: +33-320436585 (J.B.); e-mail addresses: sophie.goetgheluck@ensc-lille.fr; jacques.brocard@univ-lille1.fr

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2.1. Influence of the substitution

The synthesis of a new ferrocenyl amino alcohol and of two previously described[11] ones has been carried out.

In these three selected derivatives, the methyl group of **1** has been replaced, respectively, by deuterium (**4**, Fig. 2), *n*-butyl, and phenyl (**5** and **6**, Fig. 3).

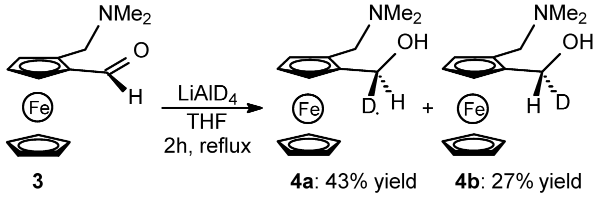

Figure 2. Synthesis of **4**.

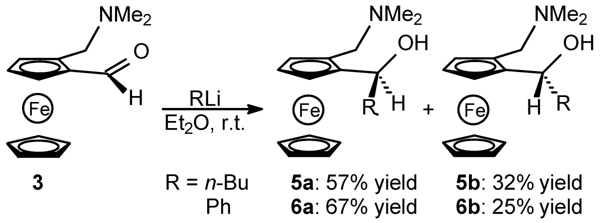

Figure 3. Synthesis of **5** and **6**.

The required diastereomeric mixture of derivatives **4** has been obtained by reduction of aldehyde **3**[15] by $LiAlD_4$. The resulting diastereomeric ratio **4a/4b** could be determined by comparison of the ^1H NMR spectrum recorded on the mixture of **4a/4b** with the ^1H NMR data obtained from non-deuterated **4**. As a matter of fact, the $CH_2{-}O$ protons of **4** are diastereotopic. They are observed as two doublets located at 4.12 and 4.75 ppm (J_{H-H}=12.2 Hz). In the case of the deuterated mixture **4a/4b**, the spectrum presents two singlets at 4.11 ppm (**4a**) and 4.74 ppm (**4b**) in the ratio **4a/4b**: 62:38.

The mixtures of diastereomers **5a/5b** and **6a/6b** were prepared as depicted in Figure 3 following earlier reported procedures.[11]

Then, in separate experiments, the three mixtures of diastereomers were stirred in the presence of MnO_2 in dichloromethane at 0 °C. The structures of the products obtained are presented in Figure 4.

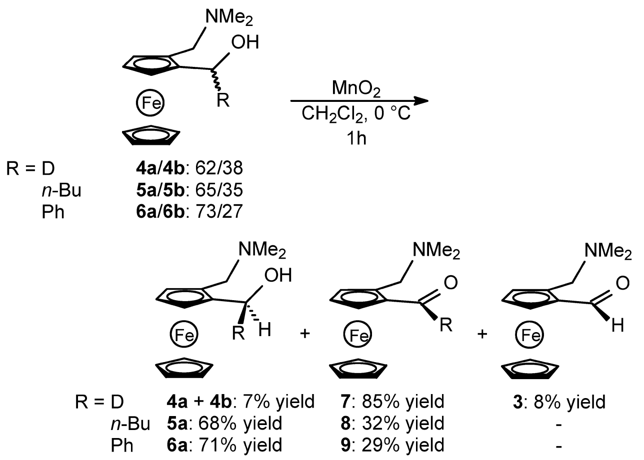

Figure 4. Oxidation of **4**, **5** and **6**.

The oxidation of **5a/5b** and **6a/6b** led to results identical to those obtained during oxidation of **1** via diastereoselective transformation. As such, **5b** and **6b** were converted quantitatively into ketones **8** and **9**, whereas **5a** and **6a** remained unchanged and could be completely recovered.[11]

Interestingly, the oxidation of the mixture **4a/4b** provided four products: deuterated aldehyde **7** (85%), non-deuterated aldehyde **3** (8%), and recovered **4a/4b** (7%). For the latter, the diastereomeric ratio is identical to that of the starting mixture. In this particular case, the reaction was not stereoselective. The increased amount of **7** as compared to **8** and **9** can be attributed to the isotopic effect rather than to a selective oxidation. In fact, it is well known that hydrogen reacts more readily than deuterium in such reactions.[16]

2.2. Influence of the relative position of the OH group versus iron

In order to get information about the influence of the location of the OH moiety onto the selectivity of the oxidation, two substrates have been synthesized (Fig. 5).

Thus, ferrocene **10** and succinic anhydride were reacted providing the Friedel–Craft's ketoacide **11**.[17] A Clemmensen's reduction furnished acid **12**, which was further cyclized in the presence of trifluoroacetic anhydride providing a racemic mixture of **13**.[18,19] Finally, the targeted mixture of the two diastereomeric alcohols **14a/14b** was obtained by reduction of the ketone by $LiAlH_4$.[20] The two diastereomers were produced in a 86:14 ratio in favour of the *endo* isomer **14a**. **14a** and **14b** could be easily separated through column chromatography.

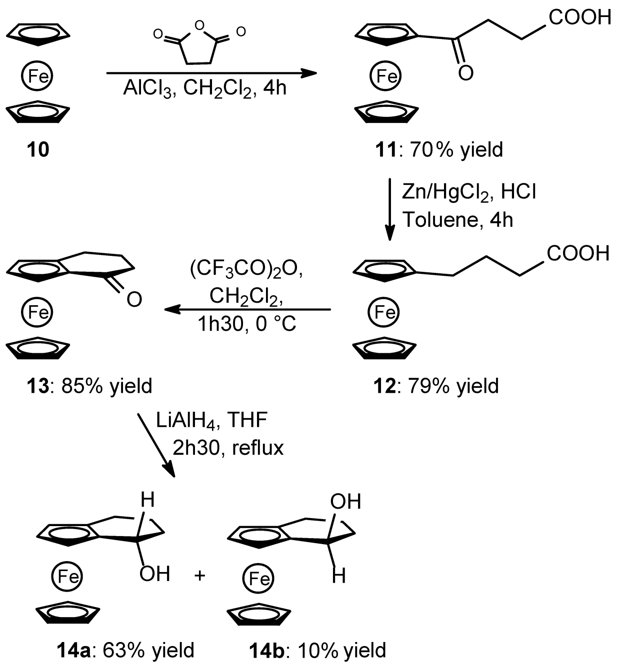

Figure 5. Synthesis of **14**.

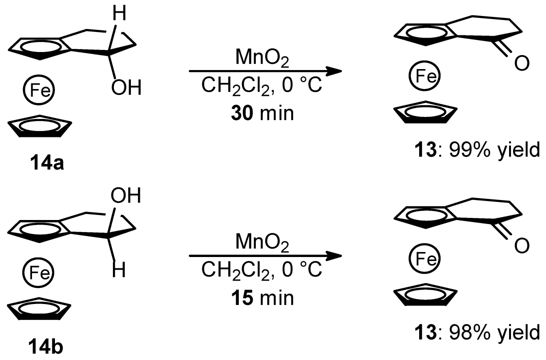

Figure 6. Oxidation of **14**.

In separated experiments, **14a** and **14b** were oxidized in a way similar to the one used above (Fig. 6).[21]

Both derivatives were converted into ketone **13**. Nevertheless, the oxidation of **14b** was twice as fast as that of **14a**. It has to be noticed that a hydrogen bond may exist between the OH moiety and iron[19] which can slow the oxidation process. In order to assess the influence of such a hydrogen bond, additional compounds were synthesized.

2.3. Influence of hydrogen bonds

Next, two new compounds bearing a chain possessing different 'electronic properties' were thought, this chain being *ortho* to the hydroxyethyl residue. Thus, the two derivatives **18** and **23** were prepared. In these compounds, the initial amine residue was replaced by respectively a methoxymethyl moiety and an ethyl group.

The syntheses of these compounds are depicted in Figures 7 and 8.

First, the ferrocenylcarbinol **15** was methylated by methanol in the presence of acetic acid providing ether **16**. The latter was converted into the corresponding aldehyde by a deprotonation (n-BuLi)/addition (DMF) sequence. The *ortho* selectivity of the process is attributed to the oxygen assistance via coordination to the intermediate metalated Fc–Li species.[22–24] The addition of CH_3Li onto the aldehyde **17** produced the diastereomeric mixture of alcohols **18a/18b**. The relative ratio (**18a/18b**: 64:36) was determined by ^1H NMR. Indeed, **18a** exhibited a quadruplet at 4.91 ppm attributed to Fc–C*H*(OH), whereas the corresponding quadruplet is located at 4.60 ppm for **18b**.

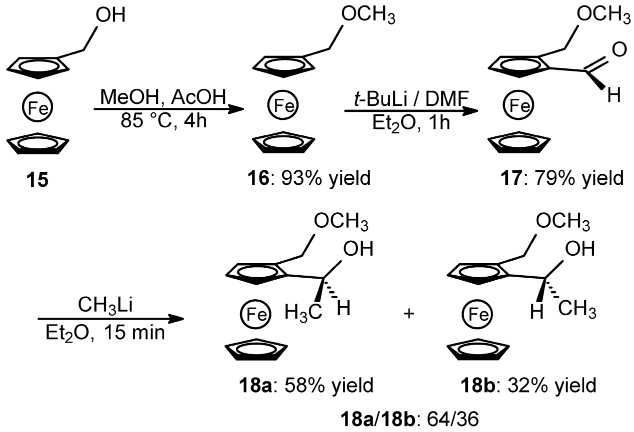

Figure 7. Synthesis of **18**.

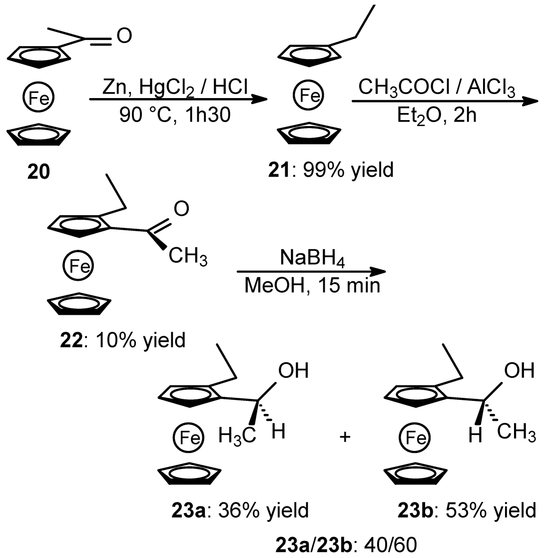

Figure 8. Synthesis of **23**.

Secondly, acetyl ferrocene **20** was reduced according to Clemmensen's method. Ethyl ferrocene **21** was obtained in 99% yield and was then acylated by a Friedel–Craft's reaction in the presence of CH_3COCl and $AlCl_3$. However, only 10% of the 1,2-disubstituted product **22** were formed due to the competitive formation of two other isomers (1,3- and 1,1′-disubstituted ferrocenes).[25] Nevertheless, the reduction of **22** by $NaBH_4$ was carried out and afforded a mixture of **23a** and **23b**. The relative ratio was again determined by ^1H NMR: diastereomer **23a** exhibits a deshielded doublet located at 1.56 ppm (vs. 1.33 ppm for **23b**) corresponding to the methyl group near the alcohol function and a deshielded quadruplet located at 4.78 ppm (vs. 4.61 ppm for **23b**) corresponding to the Fc–C*H*(OH). The proximity of the methyl residue and iron can explain the deshielding observed (see below). A 40:60 ratio of **23a/23b** could be determined by integration.

Then, in separate experiments, the oxidation was performed on both mixtures (Figs. 9 and 10). Thus, the **18a/18b**

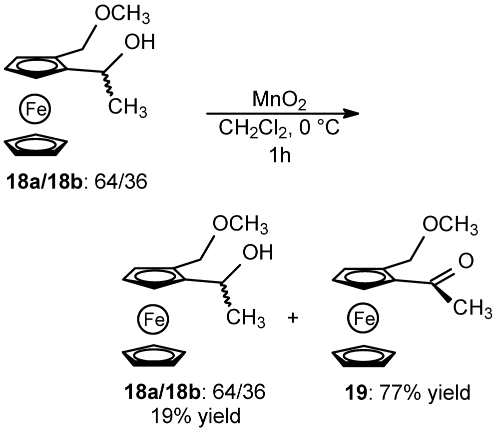

Figure 9. Oxidation of **18**.

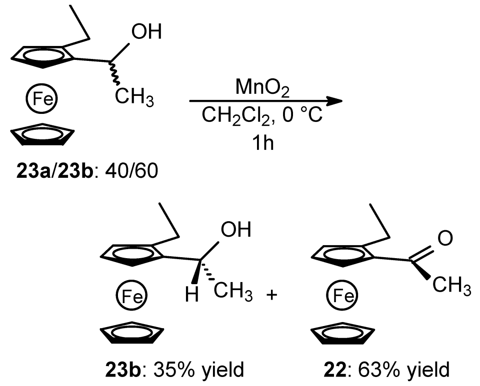

Figure 10. Oxidation of **23**.

mixture was oxidized in the presence of MnO_2 and the reaction was followed by ^1H NMR. It could be observed that both isomers were transformed with approximately the same rate.

The oxidation of the mixture constituted by **23a** and **23b** behaved differently. Indeed, **23a** was completely oxidized whereas **23b** reacted slower during the same time.

3. Discussion

The first factor examined was the effect of the substitution on the carbon atom bearing the OH moiety to be oxidized (Fig. 4). When R is a deuterium, the only effect, as expected, is an isotopic effect, as the deutero aldehyde was mainly produced. When R was an alkyl group (CH_3, *n*-Bu, Ph) a total diastereoselectivity was clearly observed, regardless of the size of the alkyl group (Figs. 1 and 4). Indeed, one diastereomer was totally oxidized while the other remained unchanged. In our compounds (**1**, **4**, **5** and **6**), two types of hydrogen bonds can exist: one between the OH moiety and NMe_2, the other one between the OH moiety and iron (via d orbitals).[26] On the basis of molecular models and literature, we can propose the most stable conformation for each derivative. The structure of four conformers are given in Figure 11.[27,28]

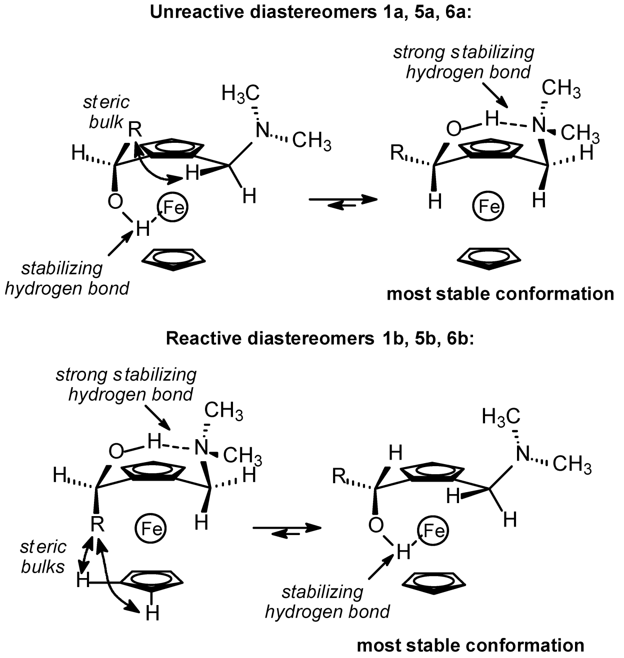

Figure 11. Different conformations of diastereomers of **1**, **5** and **6** (R=CH_3, *n*-Bu, Ph).

When considering the most stable structures possessing the less hindered and most accessible (reactive) OH moiety, that is, presenting the weakest hydrogen bond (OH–Fe),[27,28] only diastereomer **b** can be sorted out. The latter is selectively oxidized providing the results observed experimentally.

For carbon skeleton rigidity reasons, such an hydrogen bond can exist but in a lesser extent in compound **14b** (Fig. 12).[19]

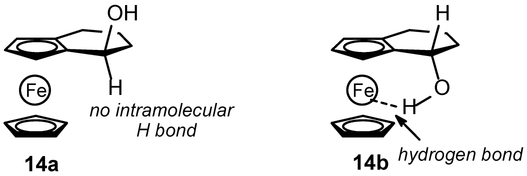

Figure 12. Possibility of an H bond in diastereomers **14a** and **14b**.

Accordingly both isomers **14a** and **14b** are oxidized but with lower rate for the species presenting the hydrogen bond OH–Fe (**14b**, Fig. 6).

For diastereomers **18a** and **18b**, in which the NMe_2 residue has been replaced by an ether function (OCH_3), two hydrogen bonds can still exist (with iron and with OCH_3). Nevertheless, the interaction between OH and OCH_3 is certainly weaker as compared to OH–NMe_2 inducing an identical reactivity for the two most stable diastereomers (Fig. 13).

For the two diastereomers of **23a** and **23b** where only a weak hydrogen bond can exist with the iron atom (Fig. 14),[19] both isomers are oxidized with nevertheless a greater rate

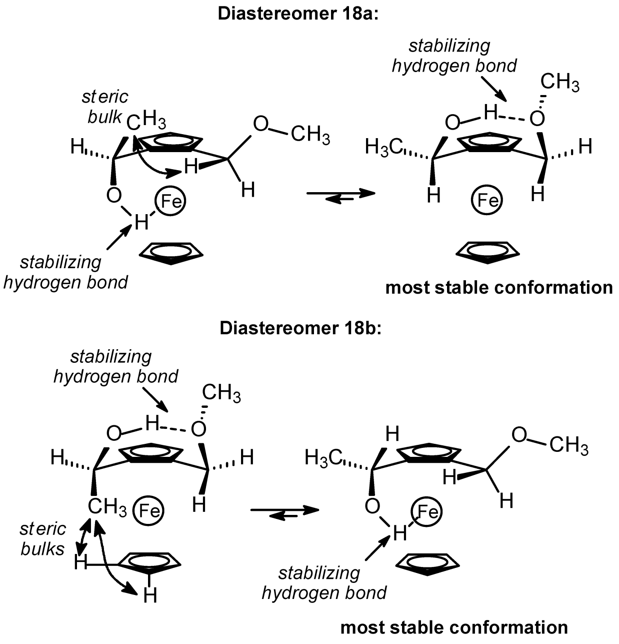

Figure 13. Different conformations of diastereomers **18a** and **18b**.

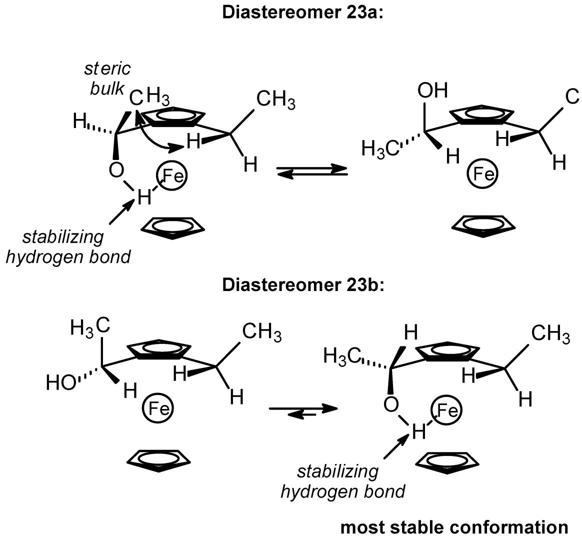

Figure 14. Different conformations of diastereomers **23a** and **23b**.

difference if compared to the closely related situation encountered during the oxidation of **14a/14b**.

Finally, an infrared study has been carried out in order to correlate the strength of the hydrogen bonds and the reactivity of several isomers. Table 1 presents the vibration frequencies of the OH groups in compounds **1**, **18** and **23** along with the oxidation results.

When comparing isomers **1a** with **18a** and **23a**, their relative reactivity increased in the order **1a**<**18a**<**23a** as compared to the order **1b**>**18b**>**23b**. Indeed, diastereomer **1a** is less reactive than **1b** (less than 1% of **1a** reacted while oxidation of **1b** was complete, entries 1 and 2). Compounds **18a** and **18b** presented the same reactivity (respectively, 80 and 81% reacted during the same period of time, entries 4 and 5). Finally, alcohol **23a** is more reactive than **23b** (100% of **23a** reacted while **23b** was oxidized only in 44% yield, entries 7 and 8).

The only isomer that was totally inert towards oxidation is **1a**. As a matter of fact, in **1a** a strong hydrogen bond exists between OH and NMe_2 (ν_{OH}: 3220 cm^{-1}, entry 1). That bond is weaker in the other compounds (ν_{OH}>3220 cm^{-1}).[29] That could be oxidized even with different rates.

Even if the mechanism of the oxidation of alcohols with MnO_2 is unknown, we have clear evidence that the main factor governing the selectivity of the oxidation process is the strength of the hydrogen bonds that might exist for the OH moiety to be oxidized.

4. Conclusion

The total diastereoselectivity of the oxidation process observed for compounds **1**, **5** and **6** has been related to the hydrogen bonds that might involve the OH group to be oxidized. The important role of a strong intramolecular H bond has been highlighted. Indeed, the strength of the hydrogen bond plays a significant role in the selectivity of the oxidation process. When several similar types of hydrogen bonds can coexist (OH–OR, OH–Fe), the selectivity is less important. The variable bond strengths will provide essentially different rates of oxidation.

5. Experimental

5.1. General

The reactions were performed in glassware under an atmosphere of nitrogen. Diethyl ether was freshly distilled from sodium. Manganese dioxide was obtained from Acros and alkyllithium reagents from Aldrich. Column chromatography were performed on SiO_2 (Merck, 70–230 mesh, Kieselgel 60). ^1H NMR, and ^{13}C NMR spectra were measured at room temperature with a Bruker AC 300 spectrometer for samples in $CDCl_3$ with tetramethylsilane as an internal reference. Mass spectra were obtained with a RIBER 10-10 (EI) or Kratos Concept II H–H (FAB) mass spectrometers. The infrared spectra were performed with a PERKIN–ELMER 1420 and a Nicolet Impact 400D. Elemental analyses were performed at the Laboratoire de Chimie Marine in Lille.

Table 1. Comparison reactivity/nature of the hydrogen bond of both diastereomers of **1**, **18** and **23**

Entry	Compound	Percentage of compound before oxidation	Percentage of compound after oxidation	Percentage of disappeared compound	Reactivity[a]	Nature of the intramol. H bond[b]	Frequencies of O–H (cm^{-1})[c]
1	**1a**	73	72	<1	0	OH–N	3220
2	**1b**	27	<1	100	+++	OH–Fe	3392
3	**2**	—	28	—	—	—	—
4	**18a**	64	13	80	++	OH–O	3431
5	**18b**	36	7	81	++	OH–Fe	3432
6	**19**	—	80	—	—	—	—
7	**23a**	40	<1	100	+++	OH–Fe	3356
8	**23b**	60	36	44	+	OH–Fe	3384
9	**22**	—	64	—	—	—	—

[a] Depending on the conversion in ketone and on the reaction time.

[b] In the most stable comformation.

[c] The IR analyses were performed without any solvent.

5.2. General procedure for oxidation

Manganese dioxide (18.4 mmol, 1.6 g) was added to a solution containing the mixture of alcohols (1.9 mmol) in dichloromethane (30 ml) at 0 °C. The reaction was then allowed to warm to room temperature. After 1 h, the mixture was filtered on celite and the solvent evaporated under reduced pressure. The remaining alcohols and the ketone were separated through silica gel chromatography.

5.3. Preparation of new compounds

5.3.1. [2-(*N*,*N*-Dimethylaminomethyl)ferrocenyl]deuteriomethanol (4a and 4b). A solution of 2-(*N*,*N*-dimethylaminomethyl)ferrocenecarboxaldehyde (900 mg, 3.3 mmol) in dry THF (10 ml) was added drop wise to $LiAlD_4$ (694 mg, 18.3 mmol) in dry THF (10 ml) at room temperature. The solution turned from grey to green. The mixture was refluxed for 2.5 h. To the cooled solution 40 ml of water saturated diethyl ether was slowly added followed by 20 ml of water. The organic compounds were extracted with several portions of diethyl ether, the extracts were combined, washed twice with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure. A purification through column chromatography (70% diethyl ether, 20% petroleum ether and 10% triethylamine) yielded 70% (630 mg) of a 62:38 mixture of alcohols **4a** and **4b** as a yellow oil: ^{1}H NMR δ 4.74 (0.62H, m, CHD **4a**), 4.18 (1H, m, C_5H_3), 4.11 (0.38H, m, CHD **4b**), 4.08 (1H, m, C_5H_3), 4.06 (5H, m, C_5H_5), 4.00 (1H, m, C_5H_3), 3.88 (1H, d, J=4.2 Hz, CH_2N), 2.75 (1H, d, J=4.2 Hz, CH_2N), 2.15 (6H, s, $N(CH_3)_2$).

5.3.2. Deuterio[2-(*N*,*N*-dimethylaminomethyl)ferrocenyl]carboxaldehyde (7). The general procedure described above was applied to the mixture of diastereomers **4a** and **4b** (430 mg, 1.6 mmol) using 1.369 g (15.7 mmol) of MnO_2. A purification through column chromatography (70% diethyl ether, 20% petroleum ether and 10% triethylamine) afforded 30 mg (7% yield) of a mixture of alcohols **4a** and **4b** and 383 mg (88% yield) of a 91:9 mixture of aldehydes **7** and **3** as a red oil: ^{1}H NMR δ 10.10 (0.09H, s, CHO **3**), 4.81 (1H, m, C_5H_3), 4.61 (1H, m, C_5H_3), 4.56 (1H, m, C_5H_3), 4.21 (5H, m, C_5H_5), 3.85 (1H, d, J=13.1 Hz, CH_2N), 3.35 (1H, d, J=13.1 Hz, CH_2N), 2.23 (6H, s, $N(CH_3)_2$).

5.3.3. Oxidation of *endo*-α-hydroxy [4](1,2)ferro-cenophane (14a). The general procedure described above was applied to **14a** (130 mg, 0.5 mmol) using 421 mg (4.8 mmol) of MnO_2. The reaction lasted 30 min. A purification through column chromatography (50% diethyl ether and 50% petroleum ether) afforded 128 mg (99% yield) of α-oxo [4](1,2)ferrocenophane **13**.

5.3.4. Oxidation of *exo*-α-hydroxy [4](1,2)ferro-cenophane (14b). The general procedure described above was applied to **14b** (130 mg, 0.5 mmol) using 421 mg (4.8 mmol) of MnO_2. The reaction lasted 15 min. A purification through column chromatography (50% diethyl ether and 50% petroleum ether) afforded 127 mg (98% yield) of α-oxo [4](1,2)ferrocenophane **13**.

5.3.5. 2-(Methoxymethyl)ferrocenecarboxaldehyde (17). Methoxymethylferrocene **16** (1.7 g, 7.4 mmol) was placed at room temperature under an inert atmosphere in a round-bottomed flask and then dissolved in dry diethyl ether (30 ml). After 5 min stirring, *t*-BuLi (7.4 ml, 11.1 mmol, 1.5 M in pentane) was added slowly and the solution was stirred for another 1 h. Then, 1.15 ml of DMF (14.8 mmol) was added. The solution was stirred for 15 min, quenched with water saturated diethyl ether (20 ml) and with brine (20 ml). The organic compounds were extracted with diethyl ether (2×20 ml), the extracts were combined, washed with brine (2×60 ml) and dried over Na_2SO_4. The solvent was removed under reduced pressure and purification through column chromatography (50% diethyl ether and 50% petroleum ether) yielded 79% (1.5 g) of **17** as a red oil: ^{1}H NMR δ 10.08 (1H, s, CHO), 4.78 (1H, m, C_5H_3), 4.68 (1H, m, C_5H_3), 4.64 (1H, d, J=11.6 Hz, CH_2O), 4.56 (1H, m, C_5H_3), 4.41 (1H, d, J=11.6 Hz, CH_2O), 4.25 (5H, m, C_5H_5), 3.39 (3H, s, OCH_3); ^{13}C NMR δ 193.6 (CHO), 86.3 (CIV C_5H_3), 77.4 (CIV C_5H_3), 74.8 (CIII C_5H_3), 72.0 (CIII C_5H_3), 71.1 (CIII C_5H_3), 70.4 (C_5H_5), 68.7 (CH_2), 58.3 (CH_3); MS *m*/*e* 258 [M^+] (100), 152 (26), 122 (491), 56, (42). Anal. Calcd for $C_{13}H_{14}FeO_2$: C, 60.50; H, 5.47. Found: C, 60.35; H, 5.37.

5.3.6. [2-(Methoxymethyl)ferrocenyl]ethanol (18a and 18b). A solution of **17** (1 g, 3.9 mmol) in dry diethyl ether (40 ml) was stirred at room temperature under nitrogen. After 5 min 3.6 ml (5.8 mmol) of methyllithium (1.6 M) were slowly added. After 15 min, the solution was hydrolysed with 20 ml of water saturated diethyl ether and then with 20 ml of water. Products were extracted with several portions of diethyl ether, the extracts were combined, washed twice with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure and purification through column chromatography (50% diethyl ether and 50% petroleum ether) yielded 90% (959 mg) of the 64:36 mixture **18a/18b** as an orange oil: **18a**: ^{1}H NMR δ 4.91 (0.64H, q, J=6.5 Hz, CH–O), 4.69 (0.64H, d, J=11.0 Hz, CH_2O), 4.3–4.0 (4H, m, C_5H_3 and CH_2O), 3.34 (1.92H, s, CH_3O), 1.53 (1.92H, d, J=6.5 Hz, CH_3); ^{13}C NMR δ 92.2 (CIV C_5H_3), 81.6 (CIV C_5H_3), 70.6 (CIII C_5H_3), 70.0 (CH_2), 68.9 (C_5H_5), 66.7 (CIII C_5H_3), 66.4 (CIII C_5H_3), 58.5 (OCH_3), 20.1 (CH_3); **18b**: ^{1}H NMR δ 4.60 (0.36H, q, J=6.5 Hz, CH–O), 4.41 (0.36H, d, J=11.0 Hz, CH_2O), 4.3–4.0 (4H, m, C_5H_3 and CH_2O), 4.21 (5H, s, C_5H_5), 3.33 (1.08H, s, CH_3O), 1.53 (1.08H, d, J=6.5 Hz, CH_3); ^{13}C NMR δ 95.1 (CIV C_5H_3), 81.3 (CIV C_5H_3), 69.5 (CH_2), 68.7 (C_5H_5), 66.5 (CIII C_5H_3), 66.1 (CIII C_5H_3), 64.6 (C–OH), 64.2 (C–OH), 57.8 (OCH_3), 24.3 (CH_3); MS *m*/*e* (MALDI-TOF, matrix: thap) 313 [$(M+K)^+$], 297 [$(M+Na)^+$], 275 [MH^+], 274 [M^+].

5.3.7. 1-Acetyl-2-(methoxymethyl)ferrocene (19). The general procedure described above was applied to the mixture of the two diastereomers **18a** and **18b** (130 mg, 0.47 mmol) using 400 mg (4.6 mmol) of MnO_2. A purification through column chromatography (50% diethyl ether and 50% petroleum ether) afforded 25 mg (19% yield) of a 64:36 mixture of alcohols **18a** and **18b** and 99 mg (77% yield) of aldehyde **19** as a red oil: ^{1}H NMR δ 4.74 (1H, d, J=12.0 Hz, CH_2), 4.65 (2H, m, C_5H_3), 4.45 (1H, d,

J=12.0 Hz, CH_2), 4.42 (1H, m, C_5H_3), 4.17 (5H, s, C_5H_5), 3.43 (3H, s, CH_3O), 2.41 (3H, t, J=7.5 Hz, CH_3); ^{13}C NMR δ 203.2 (CO), 86.4 (CIV C_5H_3), 76.7 (CIV C_5H_3), 73.9 (CIII C_5H_3), 73.2 (CIII C_5H_3), 72.1 (CIII C_5H_3), 70.4 (C_5H_5), 69.8 (CH_2), 58.5 (OCH_3), 28.3 (CH_3); MS *m*/*e* (MALDI TOF, matrix: thap) 311 $[M+K]^+$, 295 $[M+Na]^+$, 273 $[MH^+]$, 272 $[M^+]$. Anal. Calcd for $C_{14}H_{16}FeO_2$: C, 61.79; H, 5.93. Found: C, 61.62; H, 5.88.

5.3.8. (2-Ethylferrocenyl)methylketone (22). To ferrocenylethane **21** (2.85 g, 13.3 mmol) diluted in dry dichloromethane (30 ml), a solution of acetyl chloride (1.3 ml, 18.8 mmol) and aluminium chloride (2.4 g, 17.7 mmol) in dichloromethane (30 ml) was added drop wise over 1 h. The mixture was then stirred for 1 h. Hydrolysis was performed by adding water saturated dichloromethane drop wise followed by water. The organic compounds were extracted with dichloromethane (2×20 ml), the extracts were combined, washed with water (2×100 ml) and dried over Na_2SO_4. The solvent was removed under reduced pressure and purification through column chromatography (30% diethyl ether and 70% petroleum ether) yielded 10% (341 mg) of **22** as a red oil: ^1H NMR δ 4.61 (1H, m, C_5H_3), 4.45 (1H, m, C_5H_3), 4.33 (1H, m, C_5H_3), 4.15 (5H, s, C_5H_5), 2.80 (1H, m, CH_2), 2.66 (1H, m, CH_2), 2.41 (3H, s, CH_3CO), 1.17 (3H, t, J=7.5 Hz, CH_3); ^{13}C NMR δ 203.5 (CO), 93.5 (CIV C_5H_3), 76.1 (CIV C_5H_3), 72.5 (CIII C_5H_3), 71.5 (CIII C_5H_3), 70.2 (C_5H_5), 69.6 (CIII C_5H_3), 28.6 ($COCH_3$), 21.3 (CH_2), 14.9 (CH_3); MS *m*/*e* 256 $[M^+]$ (84), 213 (84), 121 (147). Anal. Calcd for $C_{14}H_{16}FeO$: C, 65.65; H, 6.30. Found: C, 65.52; H, 6.21.

5.3.9. (2-Ethylferrocenyl)ethanol (23a and 23b). To a solution of (2-ethylferrocenyl)methylketone **22** (154 mg, 0.6 mmol) in methanol (20 ml) was added $NaBH_4$ (228 mg, 6 mmol). The solution was stirred until discolouration. A hydrolysis was performed by adding water saturated dichloromethane and water. The organic compounds were extracted with dichloromethane (2×20 ml), the extracts were combined, washed with water (2×60 ml) and dried over Na_2SO_4. The solvent was removed under reduced pressure and purification through column chromatography (50% diethyl ether and 50% petroleum ether) yielded 89% (138 mg) of a 40:60 mixture of alcohols **23a** and **23b** as a yellow oil: **23a**: ^1H NMR 4.78 (1H, q, J=6.5 Hz, CH–O), 4.16 (1H, m, C_5H_3), 4.12 (1H, m, C_5H_3), 4.07 (5H, s, C_5H_5), 4.05 (1H, m, C_5H_3), 2.55–2.40 (2H, m, CH_2), 1.56 (3H, d, J=6.5 Hz, CH_3), 1.19 (3H, t, J=7.5 Hz, CH_3); **23b**: ^1H NMR 4.61 (1H, q, J=6.4 Hz, CH–O), 4.21 (1H, m, C_5H_3), 4.14 (5H, s, C_5H_5), 4.13 (1H, m, C_5H_3), 4.04 (1H, m, C_5H_3), 2.45–2.25 (2H, m, CH_2), 1.33 (3H, d, J=6.4 Hz, CH_3), 1.14 (3H, t, J=7.5 Hz, CH_3); ^{13}C NMR δ 94.0 (CIV C_5H_3), 89.2 (CIV C_5H_3), 68.9 (C_5H_5), 67.8 (CIII C_5H_3), 65.6 (CIII C_5H_3), 64.1 (CIII C_5H_3), 64.0 (CH–O), 24.3 (CH_3), 20.7 (CH_2), 14.9 (CH_3); MS *m*/*e* (MALDI-TOF, matrix: thap) 297 $[M+K]^+$, 281 $[M+Na]^+$, 259 $[MH^+]$, 258 $[M^+]$, 241 $[M-OH]^+$.

5.3.10. Oxidation of (2-ethylferrocenyl)ethanol (23a and 23b). The general procedure described above was applied to the mixture of diastereomers **23a** and **23b** (100 mg, 0.4 mmol) using 339 mg (3.9 mmol) of MnO_2. A purification through column chromatography (40% diethyl ether and 60% petroleum ether) afforded 36 mg (35% yield) of alcohol **23b** and 65 mg (63% yield) of ketone **22**.

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References and notes

1. Togni, A.; Hayashi, T. Ferrocenes. VCH: Weinheim, 1995.
2. See for example: Shu-Li, Y.; Xue-Long, X.; Li-Xin, D.; Yi-Hua, Y.; Wei, X. *J. Org. Chem.* **2002**, *67*, 4684–4695.
3. Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757–824.
4. Mijs, W. J.; De Jonge, C. R. H. I. Organic syntheses by oxidation with metal compounds. Plenum: New York, 1986; pp 132–134.
5. Parish, E. J.; Schroepfer, G. J., Jr. *Chem. Phys. Lipids* **1980**, *27*, 281–288.
6. Mueller, J. A.; Jensen, D. R.; Sigman, M. S. *J. Am. Chem. Soc.* **2002**, *124*, 8202–8203.
7. See for example: Boyd, R. B.; Sharma, N. D.; Ljubez, V.; Byrne, B. E.; Shepherd, A. D.; Allen, C. C. R.; Kulakov, L. A.; Larkin, J. M.; Dalton, H. *Chem. Commun.* **2002**, 1914–1915.
8. Simpson, H. D.; Alphand, V.; Furstoss, R. *J. Mol. Catal. B: Enzym.* **2001**, *16*, 101–108.
9. Molinari, F.; Villa, R.; Aragozzini, F.; Leon, R.; Prazeres, D. M. F. *Tetrahedron: Asymmetry* **1999**, *10*, 3003–3009.
10. Brunin, T.; Cabou, J.; Bastin, S.; Pelinski, L. *Tetrahedron: Asymmetry* **2002**, *13*, 1241–1243.
11. Delacroix, O.; Picart-Goetgheluck, S.; Maciejewski, L.; Brocard, J. *Tetrahedron: Asymmetry* **1999**, *10*, 4417–4425.
12. Delacroix, O.; Picart-Goetgheluck, S.; Maciejewski, L.; Brocard, J. *Tetrahedron: Asymmetry* **1999**, *10*, 1835–1837.
13. All diastereomers named **a** in this article are those which have a 1*RS*,*SR*$_p$ configuration and all diastereomers named **b** a 1*RS*,*RS*$_p$ configuration. The denomination 1*RS* refers to the central chirality and the denominations *RS*$_p$ and *SR*$_p$ refer to the planar chirality. All the metallocene chiralities were determined according to the nomenclature of Cahn, Ingold and Prelog extended to planar chiralities by Schlögl: Schlögl, K. *Top. Stereochem.* **1967**, *1*, 39–91.
14. Oxidation of the compound was not achieved on increasing reaction time to 6 h or adding 21 equiv. of MnO_2. We could not heat the solution or the amine chain would be oxidized into a carboxaldehyde group: Malfait, S.; Pelinski, L.; Maciejewski, L.; Brocard, J. *Synlett* **1997**, *7*, 830–832.
15. For the synthesis of **3**, see: Picart-Goetgheluck, S.; Delacroix, O.; Maciejewski, L.; Brocard, J. *Synthesis* **2000**, *10*, 1421–1426.
16. March, J. *Advanced organic chemistry, reactions, mechanisms, and structure*; 4th ed. Wiley-Interscience: New York, 1992; p 1170.

17. Rinehart, K. L.; Curby, R. J. *J. Am. Chem. Soc.* **1957**, *79*, 3420–3423.
18. Rinehart, K. L.; Curby, R. J. *J. Am. Chem. Soc.* **1957**, *79*, 3290–3291.
19. Hill, E. A.; Richards, J. H. *J. Am. Chem. Soc.* **1961**, *83*, 4211–4216.
20. Trifan, D. S.; Bacskai, R. *Tetrahedron Lett.* **1960**, *13*, 1–8.
21. The ^{1}H NMR spectrum of the mixture of these alcohols was complex, so it did not allow us to determine the proportion of each diastereomer. For this reason the oxidation needed to be performed separately on each compound.
22. Valkovich, P. B.; Gokel, G. W.; Ugi, I. K. *Tetrahedron Lett.* **1973**, *31*, 2947–2950.
23. Slocum, D. W.; Koonsvitsky, B. P.; Ernst, C. R. *J. Organomet. Chem.* **1972**, *38*, 125–132.
24. Slocum, D. W.; Engelmann, T. R.; Ernst, C.; Jennings, C. A.; Jones, W.; Koonsvitsky, B.; Lewis, J.; Shenkin, P. *J. Chem. Educ.* **1969**, *46*, 144–150.
25. Rinehart, K. L.; Motz, K. L.; Moon, S. *J. Am. Chem. Soc.* **1957**, *79*, 2749–2753.
26. Trifan, D. S.; Hoglen, J. J. *J. Am. Chem. Soc.* **1960**, *82*, 5010–5011.
27. A study on a similar ferrocenic amino alcohol was made and highlighted the preferential conformation of each diastereomer and the nature of the intramolecular hydrogen bond: Battelle, L. F.; Bau, R.; Gokel, G. W.; Oyakawa, R. T.; Ugi, I. K. *J. Am. Chem. Soc.* **1973**, *95*, 482–486.
28. Battelle, L. F.; Bau, R.; Gokel, G. W.; Oyakawa, R. T.; Ugi, I. K. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 138–140.
29. Hesse, M.; Meier, H.; Zeeh, B. Méthodes spectroscopiques pour la chimie organique. Masson: Paris, 1997.