Highly Efficient Generation of Radicals from Ester Enolates by the Ferrocenium Ion. Application to Selective α-Oxygenation and Dimerization Reactions of Esters†

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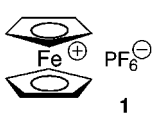
The challenge of synthetic efficiency calls for the design of transformations that allow the flexible combination of different intermediates in reaction sequences. In contrast to well documented "homointermediate reaction sequences"[1] that involve a single type of intermediate (eq 1), much less is known about "heterointermediate reaction sequences",[2] where different intermediates are selectively generated and reacted along a carbon chain (eq 2).

$$M \rightarrow R^{*} \rightarrow R^{1*} \rightarrow R^{2*} \rightarrow R^{3*} \rightarrow \rightarrow R^{n*} \rightarrow P \qquad * = {}^{+} \text{ or } {}^{\bullet} \text{ or } {}^{-} \qquad \text{(eq 1)}$$

$$M \rightarrow R^{-} \rightarrow R^{1-} \rightarrow R^{2\bullet} \rightarrow R^{3\bullet} \rightarrow R^{4+} \rightarrow R^{5+} \rightarrow P \qquad \text{(eq 2)}$$

This strategy requires efficient electron transfer steps between reaction steps and selective SET reagents. Traditionally, SET oxidations of alkali enolates[3] are mediated by Cu(II)[4] or Fe(III)[5] salts, I_2,[4cf,6] or anodic oxidation,[7] as studied mainly in oxidative dimerizations. For reaction sequences (eq 2), however, problems may arise with these reagents, since varying yields depending on the ester structure[4g,6b] and ligand transfer[4d,f,g] were observed.

Recently, we introduced ferrocenium hexafluorophosphate **1** as a mild, stable and *recyclable* SET oxidant for malonate enolates and certain nucleophilic radicals in "heterointermediate tandem reactions" (eq 2).[8] The predictable general



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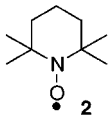

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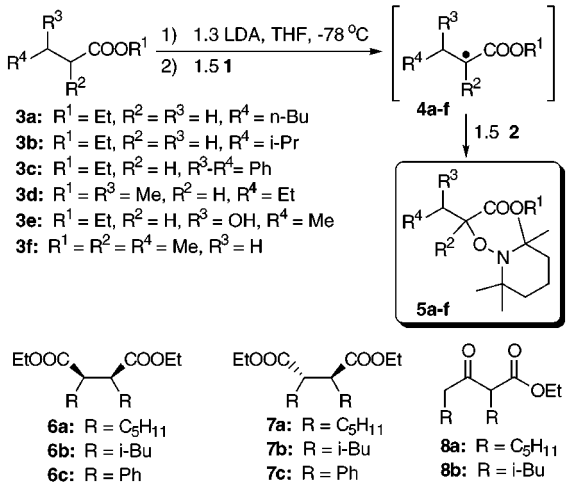
applicability of **1** in enolate oxidations is a crucial requirement for the design of oxidative heterointermediate reaction sequences. As a prelude, we report about the efficient SET oxidation of simple ester enolates **3** with **1** and the application of the so generated α-carbonyl radicals in efficient oxygenation by TEMPO[9] **2** according to Scheme 1, and dimerization reactions.

Scheme 1



Deprotonation of **3a**, oxidation to radical **4a**, and trapping by **2** at −78 °C at a [75 mM] enolate concentration provided TEMPO adduct **5a** in 42 % yield (Table 1, entry 1). Other products isolated were the *meso*- and *d*/*l*-dimers[10] **6** and **7** in a 1:1 ratio, small amounts of the β-keto ester **8**,[11] and a mixture of trimers **9** (not shown) (entry 1). Increasing either the concentration of **3a** to 0.2 M or of TEMPO to 2.5 equiv to facilitate trapping provided compounds **5**−**9** in comparable amounts, indicating a negligible influence of the reactant concentrations (entries 2, 3). Remarkably, however, upon addition of 6 equiv (relative to LDA) of HMPA prior to enolate formation, the yields of **5a** and *d*/*l*-dimer **7a** increased to 67% and 25%, respectively, with concomittant decrease in the yields of *meso*-dimer **6a**, **8**, and **9** (entry 4).

The structure of esters **3b**−**f** significantly influenced the results of the α-oxygenation by LDA/**1**/**2**/(HMPA). γ-Branched ethyl isocaproate **3b** gave a similar result as the straight chain ester **3a** (entry 5). Again, the addition of HMPA facilitated the formation of **5b** at the expense of dimerization products **6**−**8** (entry 6). If branching occurs closer to the reaction center, selectivity improved considerably. Ester enolates **3c**−**f** gave uniformly high yields of oxygenated products **5c**−**f** (entries 7−14). Dimer and oligomer formation played essentially no role, except for **3c**, where small amounts of dimers **6c/7c** were detected (entry 7). The reaction can be scaled up without influence on the yield, as exemplified for the oxygenation of **3c** (entry 8). The applied solvent system has only a minor influence on yield and stereoselectivity, so that THF is the solvent of choice with α- or β-branched esters (entries 7, 8, 9, 11, 13). Methyl 3-methylvalerate **3d** provided adduct **5d** in ca. 90% yield as a diastereomeric mixture in a 2:1 ratio (entries 9, 10). The configuration of the adducts could not be assigned at this

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(9) While this work was in progress, an example of Cu(II)-promoted oxygenation appeared.[4b]

(10) For configuration assignment see ref 4d.

(11) **8** was probably formed during enolate generation.

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Table 1. Oxygenation of Lithium Enolates of Esters 3 by the Ferrocenium Ion 1/TEMPO 2[a]

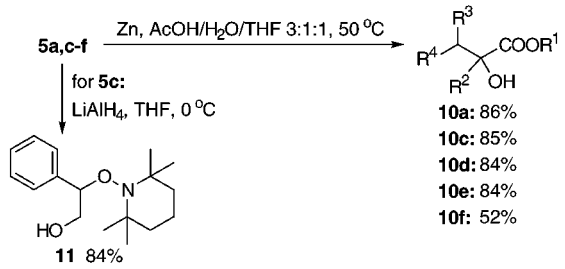
entry	3	concentration (M)/additive[b]	yield (%)[c] 5	6[d]	7[d]	8	9[e]
1	**a**	0.075/none	42	22	20	3	11
2	**a**	0.2/none	45	15	16	4	9
3	**a**	0.075/none[f]	44	25	20	–	6
4	**a**	0.075/HMPA	67	–[g]	25	–[g]	–[g]
5	**b**	0.075/none	42	16	7	10	14
6	**b**	0.075/HMPA	72	6	14	3	–[g]
7	**c**	0.075/none	94	6[h]		–	–
8	**c**	0.1/none[i]	93	7[h]		–	–
9	**d**	0.075/none	91[j]	–	–	–	–
10	**d**	0.075/HMPA	89[k]	–[g]	–[g]	–	–
11	**e**[l]	0.075/none	90[m]	–	–	–	–
12	**e**[l]	0.075/HMPA	73[n]	–	–	–	–
13	**f**	0.075/none	95	–	–	–	–
14	**f**	0.075/HMPA	92	–	–	–	–

[a] 1.3 equiv of LDA, THF, 1.5 equiv of **2**, 1.5 equiv of **1**, −78 °C. [b] 6 equiv relative to LDA. [c] Isolated, unless noted. [d] Yield based on starting material, configuration assigned according to ref 4d. [e] Yield determined by NMR. [f] 2.5 equiv of TEMPO used. [g] Trace amounts by NMR. [h] *meso*-/*d*/*l*-mixture, configuration not assigned. [i] Scale 50 mmol. [j] 2:1 *syn*/*anti*-mixture. [k] 1.75:1 *syn*/*anti*-mixture. [l] 2.5 equiv of LDA used. [m] 1:2.85 *syn*/*anti*. [n] 1:3.3 *syn*/*anti*.

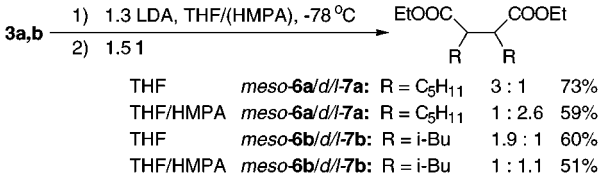
stage (vide infra). The oxidation of double deprotonated β-hydroxybutyrate **3e** gave a separable mixture of *syn*/*anti*-diastereomers **5e** in a ratio of ca. 1:3 (entries 11, 12). The configuration was assigned on the basis of the 2,3-dihydroxybutyrates (vide infra).[12] The stereoselectivity may be rationalized on the same basis as the Frater alkylation.[13] Products, derived from alkoxyl radicals, were not detected, and the amount of **1** needed to complete the reaction indicated that the enolate is chemoselectively oxidized in the presence of the alkoxide. Thus, ester enolates of **3** can be oxidized efficiently under mild conditions to α-carbonyl radicals **4**. Trapping of **4** by TEMPO to α-(2,2,6,6-tetramethylpiperidinoxy) esters **5** occurred in good to excellent yields. Straight chain esters, however, provided acceptable yields of **5** only, if conditions favoring *Z*-enolates (THF/HMPA) were applied. The enolate oxidation occurred chemoselectively in the presence of an alkoxide. From all reaction mixtures, ferrocene was recovered in 75−97% yield. The presented method compares well with the widely used electrophilic oxygenation reagents as MoOPH, Davis's oxaziridines or peroxy dicarbonates, which are only in part commercially available.[14] In contrast, our method applies to only commercial, reasonably priced, stable reagents and requires only the usual precautions of enolate chemistry.

A later deprotection has to be secured, to liberate the masked hydroxy functionality. By modification of Boger's method,[15] deprotection of the α-(piperidinoxy) esters **5** to α-hydroxy esters **10** was achieved with Zn/AcOH at 50 °C (Scheme 2). Esters **5a**,**c**−**e** gave the free α-hydroxy esters

Scheme 2



Scheme 3



10a,**c**−**e** in good yields. The reduced yield of **10f** was due to its high volatility. Compound **5d** provided a 1.3:1 mixture of *syn*/*anti*-diastereomers in 84% yield.[16] *anti*-Ester **5e** afforded *anti*-2,3-dihydroxybutyrate **10e** without epimerization.[12] The reduction of **5c** with LAH afforded the 2-monoprotected 1,2-diol **11** in 84% yield, which has gained considerable importance as starter unit in the "living" radical polymerization of styrene.[17] Thus, reductive N−O bond cleavage is possible by Zn/AcOH while hydride reduction selectively provides 2-(2,2,6,6-tetramethylpiperidin-1-yl)-protected 1,2-diols.

The surprising condition-dependent formation of dimers **6** and **7** during the oxygenation of **3a**,**b** (vide supra) necessitated a closer inspection (Scheme 3). The oxidation of **3a** with **1** and omission of TEMPO **2** gave *meso*-**6a** and *d*/*l*-**7a** in a ratio of 3:1 in THF (*E*-enolate conditions[18]) together with trimers **9a** (12% based on **3a**, not shown). In THF/HMPA (*Z*-enolate), the ratio of *meso*-**6a** and *d*/*l*-**7a** was reversed to 1:2.6 (11% trimers **9a**, not shown, 16% recovered **3a**). A less pronounced trend was observed with **3b**. While the dimerization in THF showed a 1.9:1 *meso*:*d*/*l*-selectivity (12% trimers **9b**), the reaction in THF/HMPA afforded the dimers **6b**/**7b** in a 1:1 ratio (22% trimers **9b**). Besides this, small amounts of α,β-unsaturated esters resulting from disproportionation were detected. Further investigations are clearly necessary to elucidate the mechanism of this dimerization, since the results are not consistent with a radical−radical coupling mechanism, where the product ratio should be independent of the enolate geometry.[19] It seems more likely that radical addition of a α-carbonyl radical to the enolate occurs before a second oxidation of the adduct radical provides the dimer.

In conclusion, we have shown that α-ester radicals are generated efficiently on SET oxidation of the corresponding enolates by the ferrocenium ion **1**. This method can be applied conveniently to the oxygenation by TEMPO and provides O-protected α-hydroxy esters **5**. They may serve as valuable building blocks for selective synthesis as well as starting materials for the development of new "living" polymerization strategies. Investigations along these lines are actively pursued in these laboratories.

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Supporting Information Available: Experimental procedures and characterization for compounds **5**−**7**, **9**−**11** (17 pages).

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