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Allylic oxidation: easy synthesis of alkenones from activated alkenes with TEMPO

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Abstract—Activated alkenes and dienes are converted into the corresponding alkenone in excellent yields (>90%). In aqueous acetonitrile, the transformations are catalyzed by 2,2,6,6-tetramethyl-1-oxopiperidinium ($TEMPO^+$) in the presence of water and 2,6-lutidine. $TEMPO^+$ cations were regenerated electrochemically from the radical parent ($TEMPO^{\cdot}$) at a vitreous carbon anode.
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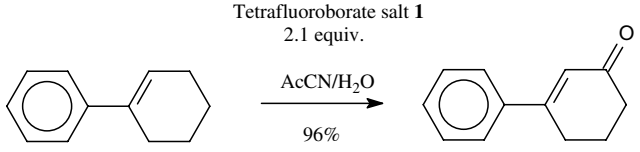
Oxoammonium ions **1**, obtained by oxidation of persistent nitroxyl radicals **2**, are successfully used principally for the regioselective alcohol oxidation.[1,2] The focus of our work has been the evaluation of synthetic utility of **1** in the functionalization of unsaturated compounds. To our knowledge the oxidation of alkenes with **1** has never been described moreover it is admitted that **1** does not react with non-activated alkenes. Conversely, conjugated alkenes or 1,4-dienes were found to undergo relatively easily allylic oxidation in the presence of water leading to the corresponding alkenones.[3]

To assess the reactivity of **1** in the allylic oxidation of activated alkenes, a sample experiment between 1-phenylcyclohexene **3** and 2.1 equiv of tetrafluoroborate salt **1**[4] in acetonitrile/water (95/5) was performed as outlined in Scheme 1. The reaction has led exclusively to the 1-phenylcyclohexene-3-one **4** in 96% yield.

In the absence of water, no conversion was observed.



Scheme 1.

An important aspect of our synthetic approach will be the use of the commercially available 2,2,6,6-tetramethylpiperidinyl-1-oxy (TEMPO) **2** in catalytic amount. The regeneration of **1** is achieved electrochemically[5] at controlled potential in the presence of lutidine (Scheme 2). All electrolyses were carried out at 0.55 V (Ag/$AgNO_3$) in aqueous acetonitrile AcCN/H_2O (95:5), the substrate (2 mmol) and the TEMPO (0.15 equiv) were dissolved in the presence of 2 equiv of 2,6-lutidine (4 mmol). At the end of electrolysis, acetonitrile was evaporated and 20 mL of aqueous HCl (5%) was added. Then, the products were extracted with diethylether, dried and chromatographied.

In alkaline medium (2,6-lutidine) a rapid *syn*-proportionation between **1** and the corresponding hydroxylamine **5** yields two molecules of **2**, which undergo electrochemical oxidation at the anode into **1**. Such regeneration process is carried out under controlled potential at 0.55 V (Ag/$AgNO_3$), which corresponds to the diffusion limited current observable under stirred conditions (Fig. 1).

We were able to oxidize various activated alkenes into the corresponding α-carbonyl compounds under standard conditions using 0.05 equiv of **2** as catalyst (Table 1). The electrochemical regeneration of **1** allowed to oxidize **3** into **4** with the same yields as obtained during the preliminary essay under stoichiometric conditions. We therefore decided to carry out the allylic oxidation of cycloheptatriene **5**. It arose from the results an improved route to tropone **6** with the consumption of 4 F mol^{-1} corresponding to 2 equiv of **1**.[8] The reaction rate

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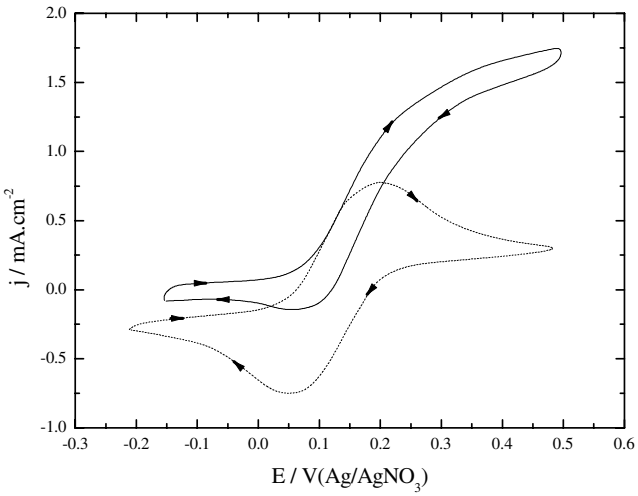


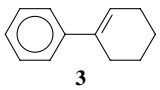
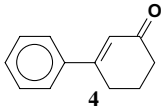
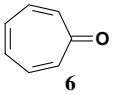
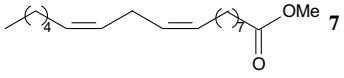
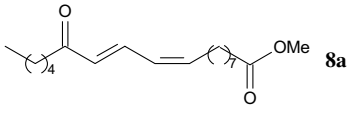
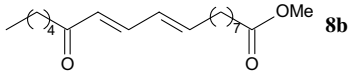
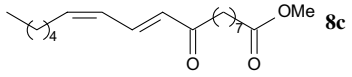
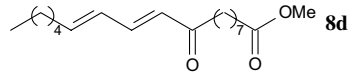
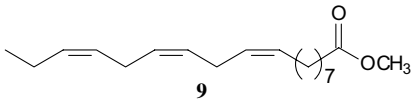
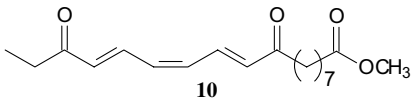
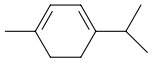
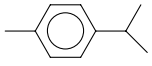
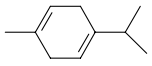
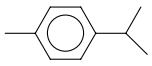
Figure 1. Electrocatalytic oxido-reduction of **1** on a vitreous carbon anode. Voltammograms recorded at 50 mV s^{-1} in 50 mL of 0.2 mol L^{-1} $NaClO_4$ AcCN/water (95:5) solution: (···) unstirred, (—) stirred.

(0.5 mmol L^{-1} min^{-1}) and the chemical yield (96%) were excellent and no traces of alkenol were detected indicating that the alkenol intermediates are more reactive than the corresponding alkene.

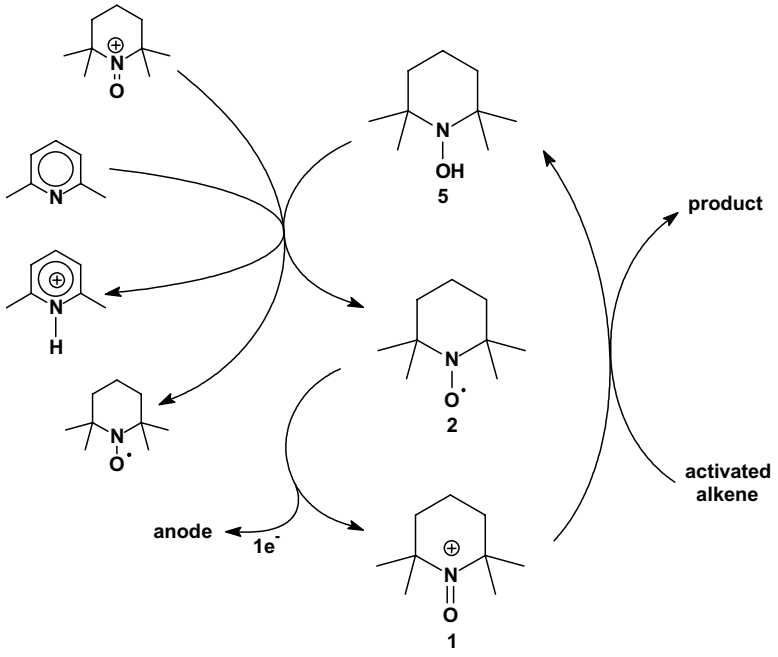
In our research programme concerned with the allylic oxidation we have also investigated the functionalization of fatty esters. Linoleic acid methyl ester **7** was converted into the corresponding conjugated dienone isomers **8a** (47%), **b** (6%), **c** (43%) and **d** (4%) with a good Faradaic yield and reaction rate (0.2 mmol L^{-1} min^{-1}). As far as oxidation of the 9- and 13-positions is concerned, it is clear that the allylic functionalization proceeds via a conjugation step leading to an inversion of configuration (Scheme 3). The compounds **8a–d** were characterized by ^{1}H and ^{13}C NMR.[9]

More explicitly, in the case of non-conjugated diene, the hydride abstraction (step A) leads to a delocalized carbocation. The nucleophilic attack of the hydroxyl displayed

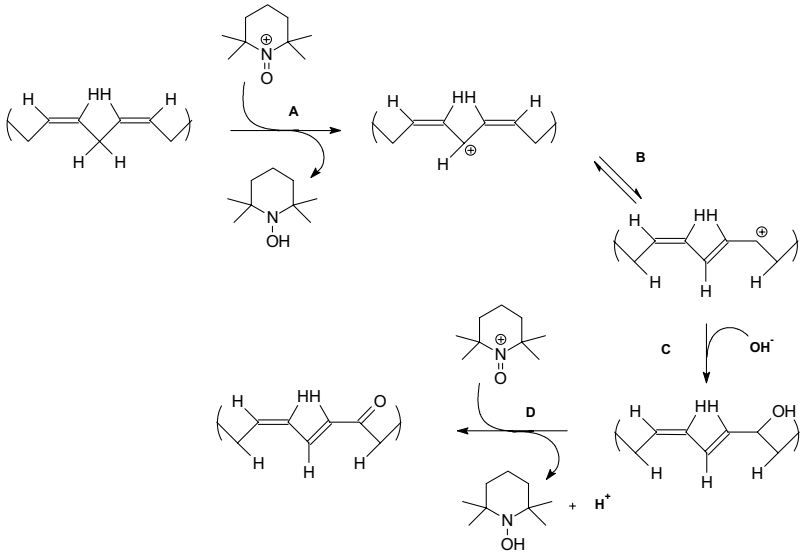
Table 1. Electromediated oxidation of activated olefin by TEMPO at controlled potential

Substrate	Product	Yield[a]/%	Q/F mol^{-1}
 **3**	 **4**	95	4.2
 **5**	 **6**	96[b]	4.1
 **7**	 **8a**  **8b**  **8c**  **8d**	93[c]	3.8
 **9**	 **10**	35	5.8
 **11**	 **13**	96[d], 63[a]	2.1
 **12**	 **13**	94[d], 60[a]	2.1

[a] Isolated.
[b] At 5 °C in order to avoid the formation of benzaldehyde (Refs. 6 and 7).
[c] Mixture of **8a–d**.
[d] By GC.



Scheme 2. Electrochemical regeneration of **1** via the *syn*-proportionation route in the presence of 2,6-lutidine.



Scheme 3.

a penchant for the conjugated diene carbocation (step C). The resulting alkenol is finally oxidized by a second molecule of **1** (step D). This mechanism requires the transfer of four electrons.

The proposed mechanism holds true for the oxidation of linolenic acid methylester **9** under aqueous acetonitrile conditions: unfortunately the reaction was not found to be selective and a complex mixture of different isomers containing carbonyl or hydroxyl groups was obtained. However, 9,16-dioxo-(10-*trans*,12-*cis*,14-*trans*)-octadecatrienoic acid methylester **10** was isolated in 35% yield.[10]

We were intrigued by the effect of the double bond position and this prompted an investigation of the oxidation of 1,3 and 1,4-dienes: α-**11** and γ-terpinene **12**, respectively. Noteworthy results are the aromatization of both terpinenes giving *p*-cymène **13** with excellent chemical yields (96%). Only 2 Faradays per mole were consumed before the current reached its lower value (capacitive current). As the experiments were carried out in aqueous acetonitrile the reaction was expected to proceed via a rapid intramolecular dehydration reaction of the hydroxyl substituted **11** and **12**. However, in dry acetonitrile the reaction exhibited the same selectivity towards **13**. Analysis of these results suggests that the hypothesis

of the hydroxyl substituted intermediates is rejected in favour of a direct aromatization of the carbocation derivatives.

In conclusion this study has outlined the synthetic potential of **1** in allylic oxidation reactions of activated dienes and the extension of the methodology to the aromatization of cyclohexadienes.

References and notes

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8. Compound **6** was previously obtained via a multistep synthesis using direct anodic oxidation of cycloheptatriene in methanol in 35% yield: Shono, T.; Nozoe, T.; Maekawa, H.; Kashimura, S. *Tetrahedron Lett.* **1988**, *29*, 555.
9. Compound **8a**: ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.44 (dd, 1H, *J* 15.8, *J* 11.6, H_{11}); 6.12 (d, 1H, *J* 15.30, H_{12}); 6.07 (dd, 1H, *J* 10.67, H_{10}); 5.90–5.80 (m, 1H, H_9); 3.63 (s, 3H, OMe); 2.52 (t, 2H, *J* 7.31, H_{14}); 2.29 (t, 2H, *J* 6.43, H_2); 2.29 (q, 2H, H_8); 1.59 (m, 4H, H_3, H_{15}); 1.39 (m, 2H, H_{16}); 1.29 (m, 10H, H_{17}, H_7, H_6, H_5, H_4); 0.86 (t, 3H, *J* 6.19, H_{18}). ^{13}C NMR (300 MHz, $CDCl_3$), δ: 201.0 (C_{13}), 174.3 (C_1); 142.7 (C_{11}) 137.0 (C_9); 129.3 (C_{12}); 126.9 (C_{10}); 51.4 (OMe); 41.1 (C_{14}); 34.0 (C_2); 31.5 (C_{16}); 29.4 (C_7); 29.2 (C_5); 29.1 (C_6); 29.0 (C_8); 28.2 (C_4); 24.8 (C_3); 24.0 (C_{15}); 22.5 (C_{17}); 13.9 (C_{18}). Compound **8b**: ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.13 (dd, 1H, *J* 15.6, H_{11}); 6.17 (m, 2H, H_9, H_{10}); 6.07 (d, 1H, *J* 15.52, H_{12}); 3.63 (s, 3H, OMe); 2.53 (t, 2H, *J* 7.35, H_{14}); 2.30 (t, 2H, *J* 7.37, H_2); 2.17 (q, 2H, H_8); 1.61 (m, 4H, H_3, H_{15}); 1.43 (m, 2H, H_{16}); 1.31 (m, 10H, H_{17}, H_7, H_6, H_5, H_4); 0.89 (t, 3H, *J* 6.21, H_{18}). ^{13}C NMR (300 MHz, $CDCl_3$), δ: 201.1 (C_{13}); 174.2 (C_1); 145.4 (C_{11}) 142.8 (C_9); 128.9 (C_{12}); 127.9 (C_{10}); 51.4 (OMe); 40.4 (C_{14}); 34.0 (C_2); 33.0 (C_{16}); 31.5 (C_7); 29.1 (C_5); 29.0 (C_6); 28.9 (C_8); 28.8 (C_4); 28.4 (C_3); 24.8 (C_{15}); 22.4 (C_{17}); 13.9 (C_{18}). Compound **8c**: ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.44 (dd, 1H, *J* 15.8, *J* 11.6, H_{11}); 6.12 (d, 1H, *J* 15.30, H_{10}); 6.07 (dd, 1H, *J* 10.67, H_{12}); 5.90–5.80 (m, 1H, H_{13}); 3.63 (s, 3H, OMe); 2.52 (t, 2H, *J* 7.31, H_8); 2.29 (t, 2H, *J* 6.43, H_2); 2.29 (q, 2H, H_{14}); 1.59 (m, 4H, H_3, H_7); 1.39 (m, 2H, H_6); 1.29 (m, 10H, H_5, H_{15}, H_{16}, H_{17}, H_4); 0.86 (t, 3H, *J* 6.19, H_{18}). ^{13}C NMR (300 MHz, $CDCl_3$), δ: 201.0 (C_9); 174.3 (C_1); 142.7 (C_{11}); 137.0 (C_{13}); 129.3 (C_{10}); 126.9 (C_{12}); 51.4 (OMe); 41.0 (C_8); 34.0 (C_{16}); 31.4 (C_2); 29.3 (C_{15}); 29.2 (C_6); 29.1 (C_4); 29.0 (C_{14}); 28.2 (C_5); 24.8 (C_3); 24.2 (C_7); 22.5 (C_{17}); 13.9 (C_{18}). Compound **8d**: ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.13 (dd, 1H, *J* 15.6, H_{11}); 6.17 (m, 2H, H_{12}, H_{13}); 6.07 (d, 1H, *J* 15.52, H_{10}); 3.63 (s, 3H, OMe); 2.53 (t, 2H, *J* 7.35, H_8); 2.30 (t, 2H, *J* 7.37, H_2); 2.17 (q, 2H, H_{14}); 1.61 (m, 4H, H_3, H_7); 1.43 (m, 2H, H_6); 1.31 (m, 10H, H_5, H_{15}, H_{16}, H_{17}, H_4); 0.89 (t, 3H, *J* 6.21, H_{18}). ^{13}C NMR (300 MHz, $CDCl_3$), δ: 201.1 (C_9); 174.2 (C_1); 145.4 (C_{11}) 142.8 (C_{13}); 128.9 (C_{10}); 127.9 (C_{12}); 51.4 (OMe); 40.4 (C_8); 34.0 (C_{16}); 33.0 (C_2); 31.5 (C_{15}); 29.1 (C_6); 29.0 (C_4); 28.9 (C_8); 28.8 (C_{14}); 28.4 (C_3). 28.2 (C_5); 24.8 (C_7); 22.4 (C_{17}); 13.9 (C_{18}).
10. Compound **10**: ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.22 (m, 2H, *J* 15, H_{11}, H_{14}); 6.68 (dd, 2H, *J* 7, H_{12}, H_{13}); 6.32 (dd, 2H, *J* 15.1, H_{10}, H_{15}); 3.66 (s, 3H, OMe); 2.62 (q, 2H, *J* 7.3, H_{17}); 2.57 (t, 2H, *J* 6.5, H_8); 2.30 (t, 2H, *J* 6.6, H_2); 1.61 (m, 2H, H_5); 1.32 (m, 8H, H_3, H_4, H_6, H_7); 1.01 (t, 3H, *J* 7.3, H_{18}). ^{13}C NMR (300 MHz, $CDCl_3$), δ: 200.9 (C_9), 200.6 (C_{16}); 174.4 (C_1); 140.4 (C_{11}); 140.3 (C_{14}); 138.3 (C_{12}); 138.2 (C_{11}); 132.2 (C_{10}); 132.0 (C_{15}); 51.5 (OMe); 41.1 (C_8); 34.3 (C_{17}); 34.0 (C_2); 29.0 (C_7); 29.0 (C_5); 28.9 (C_6); 24.4 (C_4); 14.1 (C_3); 8.1 (C_{18}).