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Mild and chemoselective catalytic deprotection of ketals and acetals using cerium(IV) ammonium nitrate

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Abstract—Cerium(IV) ammonium nitrate (CAN) is a powerful, though mild, reagent for the efficient and selective removal of a range of ketals and acetals. This novel deprotection method requires only catalytic amounts of CAN and tolerates a variety of functional and protecting groups. Mechanistic insights suggest that the Ce(IV) salts act as unique Lewis acids and not as redox active species.

The protection–deprotection sequence is probably the most recurrent functional group interconversion in organic synthesis.[1] Amongst the numerous groups employed to protect aldehydes and ketones, ketals and acetals occupy a cardinal position.[2] The plethora of ingenious methods developed to append and subsequently remove them is a clear testimony to their paramount importance.[3]

Unfortunately, most of these procedures require rather harsh acidic conditions, often incompatible with other sensitive functions present in the substrate. Over the past few years, milder protocols have emerged based upon the use of catalytic amounts of Lewis acids or of non acidic reagents.[4] In this context, we have recently described two original procedures for the unveiling of ketals and acetals using stoichiometric[5] and catalytic[6] amount of cerium(IV) ammonium nitrate (CAN). In this Article, we wish to describe our results in full and discuss in some details the intimate mechanism of this reaction (Fig. 1).

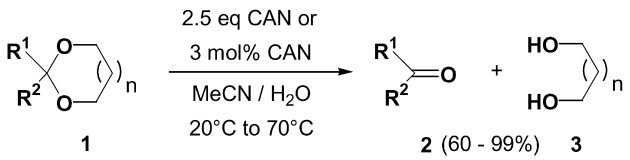

Figure 1.

During the course of some synthetic studies directed towards the preparation of natural products embodying a medium ring system,[7] we had the opportunity to examine the radical-mediated fragmentation of the β-hydroxy-ketal **4**. A large variety of reagents, able to generate an alkoxy radical from a hydroxyl function, have been reported in the literature.[8] Unfortunately, most of them proved unsuitable to our purpose, affording poor yields of the desired ketone **5**. Attention was then focused on the use of cerium(IV) ammonium nitrate, a reagent introduced by Trahanovski for these kind of fragmentations[9] and championed by Ho for numerous other applications.[10]

Upon addition of 2.5 equiv. of CAN to a H_2O/MeCN solution of ketal **4**, maintained at 70°C, a deep red tinge developed instantaneously.[11] Within 2 min, it vanished affording a colourless solution. At this stage, TLC analysis indicated that the starting material **4** had been completely consumed and that a single new product was

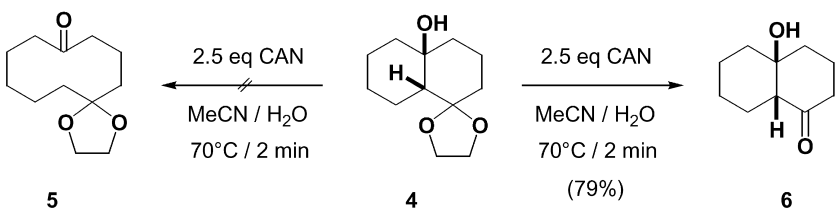

Figure 2.

Keywords: acetals; ketals; cerium and compounds; catalysis; deprotection.
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formed. Unexpectedly, this compound proved to be the β-hydroxy-ketone **6** rather than the anticipated fragmentation product **5** (Fig. 2).

Whilst CAN is well-reputed as a powerful oxidising agent that can be used for the deprotection of S,S and O,S acetals and ketals,[12] for the cleavage of *tert*-butyldimethyl silylethers[13] and for the unravelling of *t*BOC groups,[14] it had not been employed, to the best of knowledge, to unmask acetals and ketals. The surprisingly rapid and efficient conversion of ketal **4** into the highly sensitive aldol product **6** spurred our interest and encouraged us to investigate in greater detail the scope and limitations of this novel deprotection protocol.

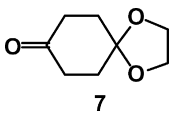
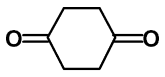
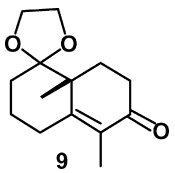
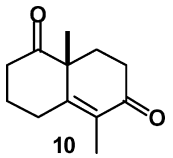
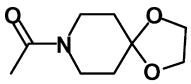
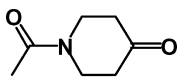
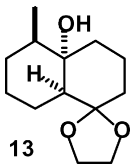
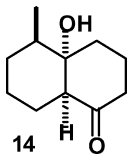
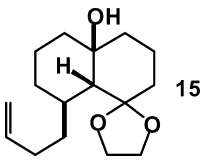
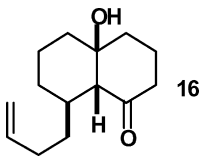
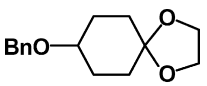
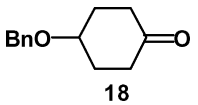
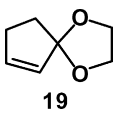
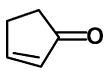
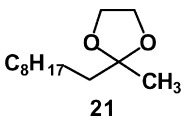
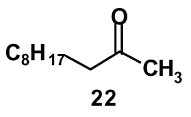
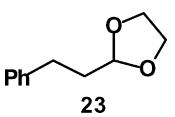
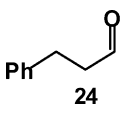
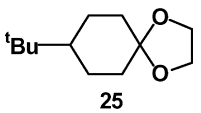
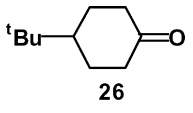
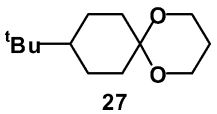
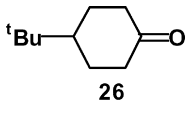
Thus, a range of substrates bearing representative functional groups were prepared according to literature procedures and reacted with CAN under the above-mentioned conditions. Some pertinent results are collected in Table 1.

As can be seen from Table 1, a wide range of acetals and ketals can be smoothly deprotected to the corresponding aldehydes and ketones in good to excellent yields.[15] Furthermore, the procedure tolerates a variety of functional and protecting groups. For example, the presence of a ketone or enone function in the same substrate is perfectly compatible with the reaction conditions (Table 1, entries 1 and 2). The removal of the dioxolane moiety can also be performed in the presence of an amide, a free alcohol, an alkene and a benzyl ether (Table 1, entries 3–6). Interestingly, the treatment of enone-derived ketals with CAN leads in high yields to the regeneration of the desired enones (Table 1, entry 7). Moreover, this reaction proceeds equally efficiently with acyclic ketals and acetals (Table 1, entries 8 and 9). It is noteworthy that over-oxidation of the aldehyde product to the corresponding carboxylic acid was not observed under these conditions. Finally, six-membered ring ketals can be unravelled with equal ease and competence as the corresponding five-membered analogues (Table 1, entries 10 and 11). It is interesting to note that in all cases, the removal of the dioxolane moiety occurs within minutes, in stark contrast to the more classical acid-catalysed protocols that usually require lengthy periods of time. For example, whilst the treatment of ketal **15** (Table 1, entry 5) with PTSA (20 mol%) in acetone necessitated 5 days to reach completion, quantitative conversion of **15** to **16** was accomplished in 3 min using the cerium(IV)-based protocol. Although this novel, CAN-mediated, deprotection technique appears to be broadly applicable, dimethylacetals and TBS protecting groups are incompatible with this procedure.[16]

Despite the use of an excess of CAN and the requirement for moderately high temperatures, the reaction conditions appear to be sufficiently mild to tolerate some rather acid-sensitive products (Fig. 3).

For example, attempted transformation of bicyclic ketal **28** into the corresponding ketone **29**, using a variety of acid-catalysed conditions, uniformly led to enone **30** in high yields. In stark contrast, CAN-mediated removal of the dioxolane protecting group afforded quantitatively the desired β-hydroxy ketone **29**. It is worthy to note that **29**

Table 1. CAN-mediated deprotection of ketals and acetals

Entry	Substrate	Product	Yield[a] (%)	Time (min)
1			71	3
2			98	2
3			60	4
4			79	2
5			77	3
6			97	2
7			84	5
8			83	4
9			70[b]	5
10			71	4
11			65	5

[a] All yields refer to pure, homogeneous products. In all cases, the crude yield of essentially pure product (>95%) is quantitative. The discrepancy in yields is due to mechanical losses/volatily during the purification step.
[b] Performed using a borate buffer (Merck, buffer pH=8).

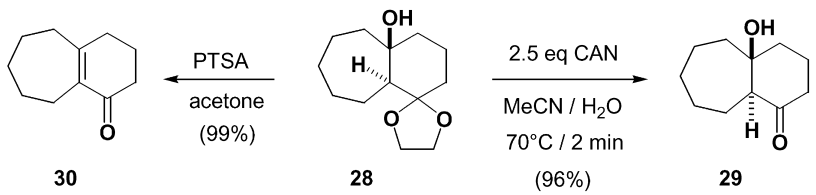


Figure 3.

is exquisitely sensitive to acidic conditions and eliminates water at the slightest incitement, generating enone **30**.[17]

Despite its synthetic interest, this protocol suffers from the significant shortcoming that substantial quantities of CAN (2.5 equiv. of a heavy and rather expensive complex) are required, which precludes its transposition to large-scale experiments. In order to remove this stringent limitation, alternative procedures, employing catalytic quantities of CAN in conjunction with stoichiometric amounts of an inexpensive oxidant, were investigated. Examination of the literature revealed that a variety of functional groups can be oxidised using sub-stoichiometric quantities of CAN in the presence of a range of co-oxidants.[14] Among these methods, the use of $NaBrO_3$ attracted our attention[18] and the deprotection of the hydrindane derivative **31** was attempted using 3 mol% of CAN and 1.5 equiv. of $NaBrO_3$ (Table 2).

Gratifyingly, the reaction proceeded smoothly and afforded ketone **32** in 99% yield (Table 2, entry 1). Since the medium proved to be acidic (vide infra), a borate buffer solution (Merck, pH 8) was added in order to minimise eventual side-reactions. Again, the desired product **32** was obtained in high yield (Table 2, entry 2). The serendipitous omission of the co-oxidant led to an unexpected observation. Remarkably, even in the absence of $NaBrO_3$, efficient regeneration of ketone **32** from ketal **31** occurred, suggesting that CAN was not acting as an oxidant but rather as a specific Lewis acid (Table 2, entry 3). Some pertinent examples, demonstrating the usefulness of this novel protocol and the mildness of the reaction conditions are collected in Table 3.

As can be seen from Table 3, a variety of ketals and acetals can be smoothly deprotected using only catalytic quantities of CAN (3 mol%) in the presence of a slightly basic buffer and in the absence of a co-oxidant. This procedure tolerates a wide range of functional groups, including unprotected secondary and tertiary alcohols (Table 3, entries 2 and 3), ketones and enones (Table 3, entries 4 and 5) and even triisopropylsilyl (TIPS) ethers (Table 3, entry 6). It is noteworthy that alcohols are not oxidised and that aldehydes, stable under these conditions, do not form the corresponding carboxylic acids (Table 3, entry 7). In sharp contrast to the earlier protocol, employing stoichiometric amounts of CAN, the epimerisation of acid-sensitive substrates is suppressed with this catalytic variant (Table 3, entry 8).[19]

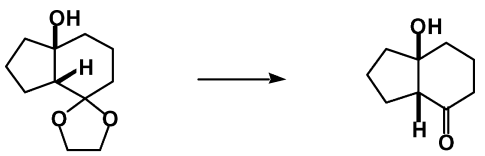
The surprising observation that CAN was not acting as an oxidant in this process is further reinforced by the isolation, in essentially quantitative yields, of the diol by-product **47**, generated during the unmasking of ketone **46** (Fig. 4).

This diol was not observed when the deprotection of ketal **45** was performed using stoichiometric amounts of CAN, owing probably to its subsequent cleavage by the cerium (IV) salts. The conditions of the catalytic CAN protocol are sufficiently lenient to allow the selective unravelling of a single dioxolane moiety in bis-protected ketals (Table 4).

Under more forcing conditions, double deprotection can also be achieved in excellent yield without interference with the alcohol functions or the *exo*-cyclic double bond. Not only dioxolanes but also a variety of other cyclic ketals can be smoothly unveiled using this catalytic system (Fig. 5).

The complete inertness of the pinacol-derived substrate **57** suggests that the cerium catalyst is highly sentient to steric hindrance in the ketal protecting group and/or in its immediate vicinity. This sensitivity is further illustrated by the prolonged reaction time required for the unmasking of the decalone derivative **9** (Table 3, entry 5). It is noteworthy that acidic treatment of **57** readily affords *tert*butyl-cyclohexanone **26** in high yields, highlighting again the paramount role of the cerium salt in this process and strongly suggesting the non-involvement of an acid-catalysed manifold.

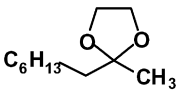
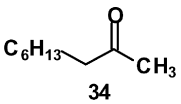
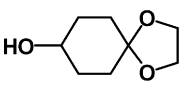
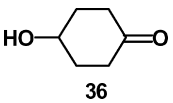
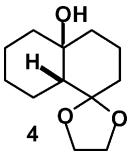
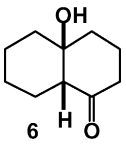
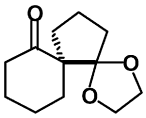
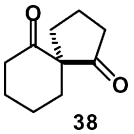
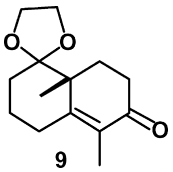
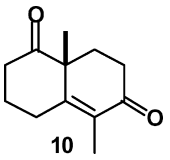
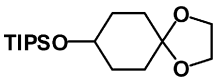
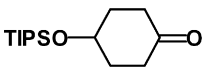
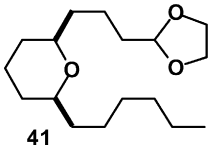
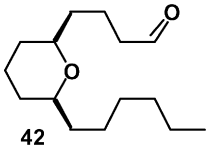
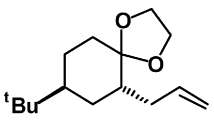
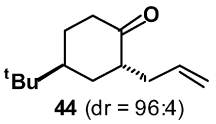
Table 2. Catalytic deprotection of ketal **31** with CAN



Entry	Conditions	Yield[a] (%)
1	3 mol% CAN/1.5 equiv. $NaBrO_3$ MeCN/H_2O (1/1), 70°C	99
2	3 mol% CAN/1.5 equiv. $NaBrO_3$ MeCN/borate buffer (pH 8), 70°C	90
3	3 mol% CAN/borate buffer (pH 8) MeCN/H_2O (1/1), 70°C	93

[a] All yields are for pure, isolated products.

Table 3. CAN-catalysed deprotection of acetals and ketals

Entry	Substrate	Product	Yield[a] (%)	Time
1	 **33**	 **34**	95	30 min
2	 **35**	 **36**	92	25 min
3	 **4**	 **6**	99	1.5 h
4	 **37**	 **38**	86[b]	1.5 h
5	 **9**	 **10**	95	48 h
6	 **39**	 **40**	91[c]	45 min
7	 **41**	 **42**	95	2.5 h
8	 **43** (dr = 96:4)	 **44** (dr = 96:4)	96[c]	20 min

[a] All yields are for pure, isolated products.
[b] Performed using 4 mol% CAN.
[c] The reaction was carried out in the presence of 1.5 equiv. of $NaBrO_3$.

To gain some insights into the mechanism of this novel catalytic reaction, the deprotection of **25** was monitored using cyclic voltamperometry (Fig. 6).

At the onset, an acetonitrile–borate buffer solution was prepared as a blank and the spectrum was recorded (Fig. 6, curve a). Then, cerium(IV) ammonium nitrate was added and the spectrum, displaying the reduction and oxidation potentials, was registered again. Under these conditions, and using a sweep rate of 100 mV/s, CAN is reduced to the

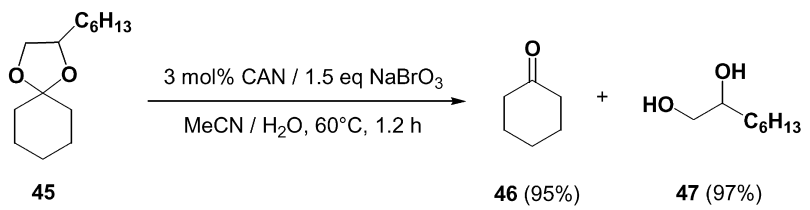
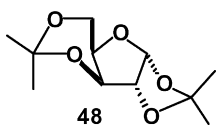
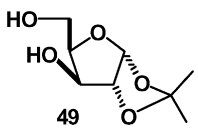
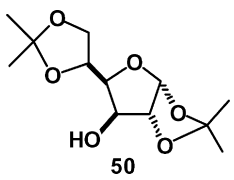
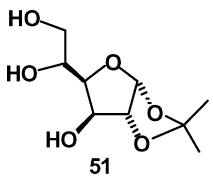
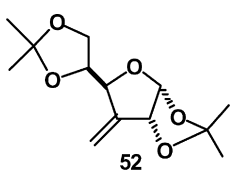
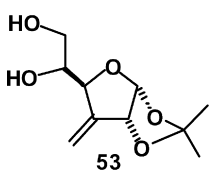


Figure 4.

Table 4. Chemoselective CAN-catalysed deprotections of sugars

Entry	Substrate	Product	Yield[a] (%)
1	 **48**	 **49**	98
2	 **50**	 **51**	81
3	 **52**	 **53**	97

[a] All yields are pure, isolated products.

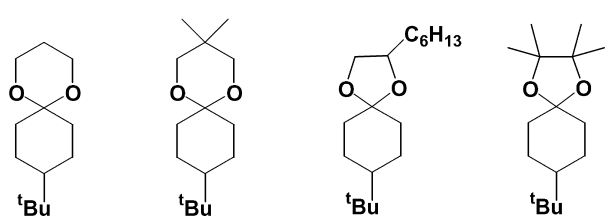


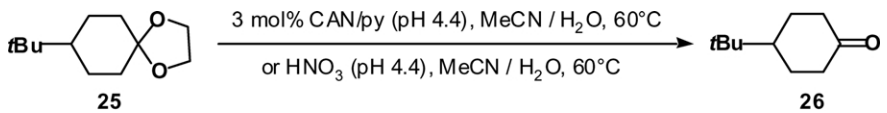
Figure 5.

Ce(III) state at a potential of −485.7 mV and is reoxidised to Ce(IV) at −357.2 mV vs SCE (Fig. 6, curve b). The shape of the curve and the positions of the oxidation and reduction peaks remained unaltered after the addition of ketal **25**, during the course of the reaction and at the end of the deprotection (Figure 6, curve c). The only species detected throughout the course of this reaction was Ce(IV), clearly indicating that CAN does not behave as a redox catalyst.

In order to discriminate between Brønstedt and Lewis acid catalysis, a series of experiments were performed under various pH conditions. Whilst it is difficult to ascertain with precision the exact pH of an organic/water mixture, it appears that a solution of CAN (3 mol%) in MeCN/H_2O (1/1) is rather acidic (pH∼1.8). However, several experiments have already hinted at the dearth of Brønstedt acid participation, including the inertness of the pinacol-derived ketal **57** (Fig. 5), the absence of epimerisation in the unravelling of substrate **43**, particularly rapid under acid-catalysed conditions (Table 3, entry 8), and the lack of fragmentation during the generation of diketone **38**, a process that occurs readily in the presence of various acids (Table 3, entry 4).[20]

Nonetheless, some buffered solutions of nitric acid and CAN were prepared (pH=1.8–4.4) and the deprotection of ketal **21** was performed at different pH and monitored by GC (Fig. 7).

At low pH, the rate of disappearance of **21** and the velocity of formation of **22** proved to be virtually identical using either CAN or HNO_3, thus thwarting our efforts to distinguish between the two possible competing manifolds. However, whilst reaction of **21** with 3 mol% CAN (buffered at pH 4.4 with pyridine) led to almost complete formation of **22** after 1 h (Fig. 7, Chromatogram 1) and quantitative unveiling of **21** after 3 h (Fig. 7, Chromatogram 2), less than 20% of ketone **22** was produced when a pyridine/HNO_3 solution (pH=4.4) was employed (Fig. 7, Chromatogram 3). This result clearly establishes that the cerium(IV) salts are the active catalytic species in this unique, mild deprotection



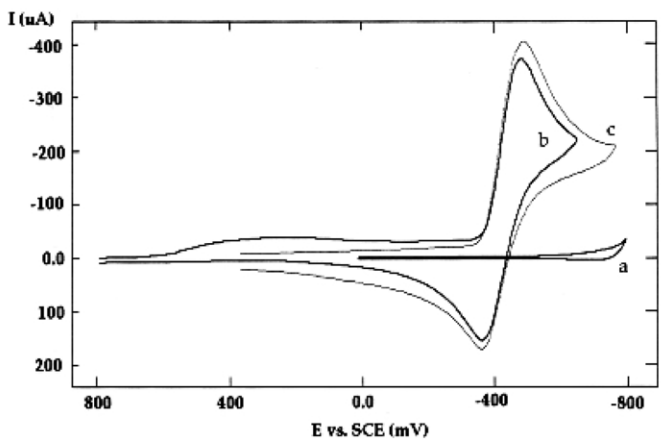


Figure 6.

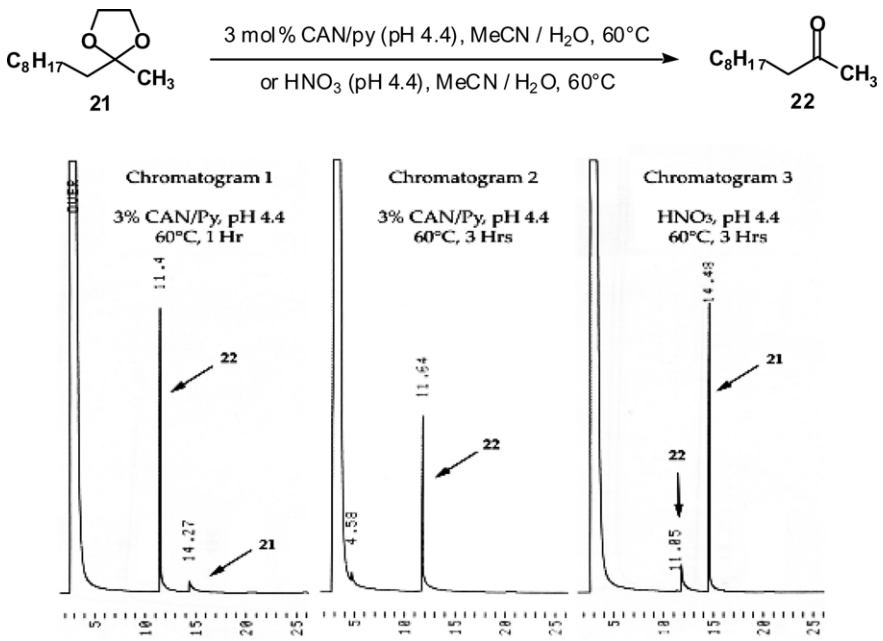


Figure 7.

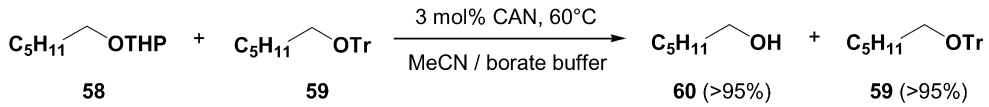


Figure 8.

methodology.[21] Finally, the tolerance of this system towards acid-sensitive functions is further illustrated by the competition experiment displayed in Figure 8.

Thus, treatment of an equimolar mixture of THP ether **58** and trityl protected alcohol **59** with 3 mol% CAN in MeCN/borate buffer, at 60°C, smoothly afforded **60** and recovered **59** in essentially quantitative yields. The inertness of the trityl protecting group, usually highly labile towards acids, under the CAN-catalysed conditions stands as a clear testimony to the lack of involvement of Brønstedt acids in this protocol. The steric bulk of the trityl group efficiently shields the ether oxygen from the cerium reagent and inhibits its deprotection.

In summary, we have shown that cerium(IV) ammonium nitrate is a powerful reagent for the efficient and selective unravelling of a variety of ketal and acetal protecting groups. The conditions are mild, employ a catalytic amount of the cerium reagent and tolerate a wide range of functionalities, including unprotected alcohols, ketones, aldehydes, enones and even trityl ethers.[22] The mechanism of the stoichiometric CAN-mediated deprotection seems to proceed via a sequence of single electron-transfer—as suggested by the appearance of a transient deep-red colour[11]—whilst the catalytic CAN protocol appears to involve the participation of Ce(IV) salts which act as highly selective Lewis acids and not as redox active species (no deep-red colour was observed in these cases). Finally, we have demonstrated that Brønstedt acid catalysis did not play a significant role in the mechanism of this unique procedure and that the use of CAN/pyridine (pH=4.4) was the preferred choice when acid-labile functions had to be preserved.

1. Experimental

Most of the commercially available reagents were used without further purification. Methylene chloride and acetonitrile were distilled over calcium hydride. Diethylether and THF were distilled over sodium and benzophenone. Whenever required, the glassware was flame dried prior to use and the reactions were carried out under an argon atmosphere. NMR spectra were recorded on Varian Gemini 200 and 300 MHz FT-NMR spectrometers. IR spectra were recorded on a Bio-Rad FTS FT-IR spectrometer. Mass analyses were performed in the mass spectroscopy laboratory of the Université catholique de Louvain on VARIAN Matt 44S or Finnigan-Matt TSQ-70 spectrometers. Elemental analyses were performed at the Institut für Organishe Chemie, Universität Stuttgart, Germany. High resolution mass spectra were obtained from the laboratory of mass spectrometry of the Université de Mons-Hainaut, Belgium. Thin-layer chromatography was carried out on aluminium-supported plates and stained by potassium permanganate or UV light. Purifications by column chromatography were performed on Merck 60 silica gel (0,040–0,063 mm). Fused silica capillary column, Chrompack, CP-Sil 8 CB, 30 m×0.25 mm, 0.25 m. Program used: initial temperature (50°C), rate (10°/min), final temperature (290°C). Voltammetry performed using a potentiostat/galvanostat from Princeton Applied Research (software M270) with a scanning rate of 100 mV/s.

1.1. Stoichiometric CAN mediated deprotections (typical procedure)

To a stirred solution (60–70°C) of the substrate (1 mmol), dissolved in acetonitrile (3 ml), was added in one portion, a solution of CAN (1.36 g, 2.5 mmol) in water (3 ml). The resulting mixture became instantaneously red-brown and the colour discharged after the required amount of time (Table 1) to give a slightly yellow solution. After extraction with ether or dichloromethane (3×10 ml), the combined organic layers were dried over $MgSO_4$, filtered and the solvents were removed in vacuo. The crude product was purified, if required, by silica-gel column chromatography.

Crude compound **8** was >95% pure (colourless oil, 71%), data identical to an authentic commercial sample, (RN [106-51-4], Aldrich). Crude compound **18**[23] was >95% pure (97%), data identical to an authentic sample, (RN [2987-06-6]). Crude compound **20** was purified by bulb-to-bulb distillation (60°C, 20 mm Hg; colourless oil, 84%), data identical to an authentic commercial sample, (RN [930-30-3], Fluka). Crude compound **22** was >95% pure (83%), data identical to an authentic commercial sample, (RN [112-12-9], Fluka). Crude compound **24** was purified by silica-gel column chromatography (dichloromethane/petroleum ether 1/1; colourless oil, 70%), data identical to an authentic commercial sample, (RN [104-53-0], Fluka). Crude compound **26** was >95% pure (71% starting from compound **25** and 65% starting from compound **27**), data identical to an authentic commercial sample, (RN [98-53-3], Aldrich).

1.1.1. 4a-Hydroxy-octahydro-naphthalen-1-one (6). The crude mixture was purified by column chromatography over silica-gel (petroleum ether/ethyl acetate 2/1) to give **6** as a colourless oil (78%). IR (neat) 3437, 2934, 2864, 1707, 1450, 1353, 1141 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.14–1.92 (9H, m), 1.93–2.52 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.5, 22.6, 23.7, 25.6, 33.7, 38.2, 38.3, 59.1, 74.6, 212.7; MS (EI, 70 eV) *m/z* ($M^{+\cdot}$) 168.1 (100%), 150 (50%), 140 (10%), 139.2 (20%), 125.1 (26%), 113 (30%), 55 (12%); Anal. calcd for $C_{10}H_{16}O_2$: C, 71.39%; H, 9.59%. Found: C, 70.93%; H, 9.70%.

1.1.2. 5,8a-Dimethyl-3,4,8,8a-tetrahydro-2*H*,7*H*-naphthalen-1,6-dione (10). Crude compound **10** was >95% pure (colourless oil, 98%); ^1H NMR (300 MHz, $CDCl_3$) δ 1.43 (3H, s), 1.66–1.87 (4H, m), 2.01–2.24 (3H, m), 2.37–2.60 (4H, m), 2.69 (1H, ddd, *J*=15.9, 10.5, 6.0 Hz), 2.9 (1H, dtd, *J*=15.9, 5.0, 1.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.1, 21.3, 23.2, 27.2, 29.6, 33.2, 37.2, 50.6, 130.7, 158.3, 197.6, 211.9; RN [41019-71-0].

1.1.3. 1-Acetyl-piperidin-4-one (12). Crude compound **12** was >95% pure (60%). IR (neat) 2967, 2883, 1717, 1649, 1429.3, 1237 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.20 (3H, s), 2.48 (2H, t, *J*=6.1 Hz), 2.51 (2H, t, *J*=6.1 Hz), 3.73 (2H, t, *J*=6.6 Hz), 3.89 (2H, t, *J*=6.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.6, 169.3, 44.7, 40.9, 40.5, 40.4, 21.2; MS (70 eV) *m/z* ($M^{+\cdot}$) 141 (100), 113 (45), 98 (23); RN [32161-06-1].

1.1.4. (4aS^*,5R^*,8aS^*)-4a-Hydroxy-5-methyloctahydro-1(2H)-naphthone (14). Crude compound **14** was >95% pure (79%). IR (neat) 3401, 2932, 2668, 1696, 1459, 1443, 1244, 1144, 971 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.95 (3H, d, *J*=7.1 Hz), 1.24 (1H, dddd, *J*=12.5, 12.5, 12.0, 3.5 Hz), 1.32 (1H, ddddd, *J*=12.5, 12.5, 12.5, 3.6, 3.6 Hz), 1.46 (1H, dqd, *J*=12.0, 7.1, 3.5 Hz), 1.56–167 (3H, m), 1.68–1.93 (5H, m), 2.02 (1H, ddddd, *J*=13.4, 13.4, 13.4, 4.4, 4.4 Hz), 2.12–2.17 (1H, m), 2.18–2.25 (1H, m), 2.43 (1H, ddd, *J*=14.5, 13.4, 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.4, 20.3, 23.2, 25.2, 29.3, 31.7, 37.0, 43.1, 61.7, 77.3, 215.6; MS (70 eV) *m/z* ($M^{+\cdot}$) 182 (80%), 167 (6%), 164 (28%), 154 (20%), 139 (78%), 126 (100%), 55 (60%), 43 (42%), 41 (38%); Anal. calcd for $C_{11}H_{18}O_2$: C, 72.72%; H, 10.07%. Found: C, 72.49%; H, 9.95%.

1.1.5. (4aR^*,8S^*,8aS^*)-8-(3-Butenyl)-4a-hydroxyoctahydro-1(2H)-naphthone (16). Crude compound **16** was >95% pure (77%). IR (neat) 3419, 3075, 2930, 2867, 1702, 1641, 1450, 1353, 1315, 1262 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.88 (1H, dddd, *J*=13.5, 13.5, 13.5, 4.1 Hz), 1.15 (1H, dddd, *J*=14.5, 9.4, 9.4, 5.1 Hz), 1.28 (1H, dddd, *J*=14.5, 9.6, 7.2, 3.3 Hz), 1.37 (1H, ddd, *J*=13.5, 13.5, 4.1 Hz), 1.42–1.47 (1H, m), 1.49 (1H, ddddd, *J*=13.5, 13.5, 13.5, 3.5, 3.5 Hz), 1.63 (1H, s), 1.71–1.81 (2H, m), 1.84 (1H, dddd, *J*=13.5, 3.5, 3.15, 1.1 Hz), 1.87–1.98 (4H, m), 2.10 (1H, ddddd, *J*=13.5, 13.5, 13.5, 4.2, 4.2 Hz), 2.13 (1H, m), 2.19 (1H, ddd, *J*=13.5, 13.5, 4.1 Hz), 2.22 (1H, m), 2.35 (1H, ddd, *J*=13.5, 13.5, 4.1 Hz), 4.90–5.05 (2H, m), 5.70 (1H, dddd, *J*=17, 10, 7.3, 6.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5, 22.7, 30.2, 30.3, 32.6, 37.6, 37.7, 40.5, 66.7, 76.2, 114.8, 138.2, 215.0; MS (70 eV) *m/z* ($M^{+\cdot}$) 222 (31%), 205 (25%), 204 (30%), 194 (12%), 162 (38%), 149 (80%), 113 (95%), 55 (100%), 41 (77%); Anal. calcd for $C_{14}H_{22}O_2$: C, 75.65%; H, 9.94%. Found: C, 75.63%; H, 9.97%.

1.1.6. (4aR^*,9aR^*)-4a-Hydroxydécahydro-1H-benzo[*a*]cycloheptan-1-one (29). The crude product was purified by column chromatography over silica-gel (petroleum ether/ethyl acetate 3/1) to give **29** as a white solid (96%). Mp 77–78°C. IR (neat) 3460, 2918, 2853, 1696, 1450, 1390, 1296, 1177, 1003, 945, 827 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.18–1.28 (1H, m), 1.35–1.53 (3H, m), 1.64–1.79 (4H, m), 1.84–1.97 (4H, m), 2.05–2.16 (2H, m), 2.27 (1H, ddd, *J*=13.2, 13.2, 6.6 Hz), 2.34–2.40 (1H, m), 2.42 (1H, d, *J*=10.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.1, 21.4, 21.7, 26.9, 28.5, 39.1, 40.4, 43.7, 60.5, 78.6, 211.5; MS (70 eV) *m/z* ($M^{+\cdot}$) 182 (100%), 164 (22%), 154 (45%), 139 (66%), 126 (43%), 122 (41%), 111 (37%); Anal. calcd for $C_{11}H_{18}O_2$: C, 72.49%; H, 9.95%. Found: C, 71.97%; H, 9.83%.

1.1.7. 2,3,4,5,6,7,8,9,-Octahydro-1H-benzo[*a*]cyclohepten-1-one (30).[24] To a stirred solution of substrate **28** (100 mg, 0.44 mmol) dissolved in acetone (5 ml) was added in one portion, solid PTSA (10 mg, 5% wt). The resulting mixture was refluxed 15 h and then cooled to room temperature. Solid $NaHCO_3$ (35 mg) was added and the solvent was removed in vacuo. Water (15 ml) was then added and the aqueous phase was extracted with dichloromethane (3×20 ml). The organic extracts were dried over $MgSO_4$, filtered and the solvent was removed in vacuo to afford **30** as a colourless oil (71.6 mg, 99%). IR (neat) 2921, 2850, 1662, 1629, 1450, 1378, 1323, 1292, 1187, 1103 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.40 (2H,

quint J=5.1 Hz), 1.55 (2H, quint J=4.8 Hz), 1.77 (2H, quint, J=5.5 Hz), 1.93 (2H, quint, J=6.0 Hz), 2.30–2.58 (8H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.3, 23.7, 25.2, 26.1, 32.0, 33.2, 36.6, 37.0, 138.0, 162.9, 198.2; MS (70 eV) m/z ($M^{+\cdot}$) 164 (100%), 149 (81%), 136 (65%), 121 (16%), 108 (38%), 93 (55%).

1.2. Catalytic CAN mediated deprotections (typical procedure)

To a stirred solution of substrate (1 mmol) dissolved in acetonitrile (3 ml) was added a borate buffer (Merck, pH 8, 3 ml). The mixture was heated at 60–70°C and solid CAN (16 mg, 3 mol%) was added. The resulting slightly yellow solution was stirred for the required amount of time (Table 2) at this temperature. After cooling to room temperature, the reaction mixture was extracted with ether (3×10 ml). The combined organic layers were dried over $MgSO_4$ filtered and the solvents were removed in vacuo. The crude product was purified, if required, by silica-gel column chromatography.

Crude compound **36** was purified by column chromatography over silica-gel (ethyl acetate/ether 4/1; colourless oil, 92%), data identical to an authentic sample, (RN [13482-22-9]). Crude compound **6** was >95% pure (99%), see above for analysis. Crude compound **10** was >95% pure (99%), see above for analysis. Crude compound **60** was >95% pure (95%), data identical to an authentic commercial sample, (RN [100-51-6], Acros).

1.2.1. (3aS^*,7aR^*)-7a-Hydroxyoctahydro-4H-inden-4-one (32).[25] To a stirred solution of **31** (200 mg, 1.01 mmol) dissolved in acetonitrile (4 ml) was added water (4 ml) and sodium bromate (228 mg, 1.51 mmol). The mixture was heated at 70°C and solid CAN (16 mg, 3 mol%) was added. The resulting, slightly yellow solution was stirred 20 min at this temperature. After cooling to room temperature, the reaction mixture was extracted with dichloromethane (3×10 ml). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed in vacuo to afford **32** as a colourless oil (155 mg, 99%). Using the same procedure, but adding a borate buffer (pH 8) instead of water, compound **32** was isolated in 90% yield. Using the same procedure, but adding a borate buffer (pH 8) instead of water and omitting sodium bromate, compound **32** was isolated in 93% yield. Colourless oil. IR (neat) 3423, 2959, 2875, 1699, 1458, 1345, 1311, 1157, 1079, 987 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.52–2.28 (10H, m), 2.29–2.49 (2H, m), 2.51–2.74 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.0, 21.3, 24.5, 34.7, 38.0, 39.3, 60.8, 84.3, 211.6; MS (70 eV) m/z ($M^{+\cdot}$) 154 (100%), 139 (78%), 137 (81%), 136 (93%), 126 (82%), 125 (61%), 113 (63%), 111 (90%), 108 (95%), 97 (64%), 94 (70%), 84 (82%), 70 (63%), 55 (96%), 42 (83%). This compound could not be purified by silica-gel column chromatography due to its rapid transformation into the corresponding enone.

1.2.2. Spiro[5,4]decan-2,7-dione (38).[26] Solid cerium ammonium nitrate (CAN, 18 mg, 4 mol%) was added at room temperature to a stirred solution of 2-oxo-7-dioxolano-bicyclo [5,4,1] octane (237 mg, 1.13 mmol) dissolved in MeCN (3.5 ml)/Borate buffer (3.5 ml, Merck, pH=8). The faint yellow solution was heated at 60°C during 1.5 h. After cooling to room temperature, H_2O (10 ml) was added. The organic layer was separated and the aqueous phase was extracted with dichloromethane (2×15 ml). The combined organic extracts were dried over $MgSO_4$, filtered and the solvents were removed in vacuo. The crude mixture was purified by column chromatography over silica gel (ethyl acetate/hexane 3/7) to give Spiro[5,4]-decane-2,7-dione **38** as a colourless liquid (144 mg, 86%). IR (neat) 1734, 1700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.7 (2H, m), 2.42 (1H, dt, J=14.1, 5.1 Hz), 2.31 (2H, dt, J=8, 1.7 Hz), 2.2–1.6 (9H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.9, 21.0, 26.6, 33.7, 35.9, 38.4, 39.7, 64.3, 207.9, 215.5; MS (70 eV) m/z ($M^{+\cdot}$) 166 (92), 167 (100).

1.2.3. 3-(6-Hexyl-tetrahydro-pyran-2-yl)-propionaldehyde (42). The crude mixture was purified by column chromatography over silica-gel (dichloromethane) to give **42** as a colourless oil (95%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.72 (1H, t, J=1.7 Hz), 3.10–3.26 (2H, m), 2.38–2.60 (2H, m), 1.64–1.83 (3H, m), 0.98–1.55 (15H, m), 0.83 (3H, t, J=6.51 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.7, 77.9, 76.6, 40.4, 36.5, 31.8, 31.7, 31.6, 29.3, 29.0, 25.5, 23.6, 22.6, 14.0.

1.2.4. 2-Allyl-4-*tert*-butyl-cyclohexanone (44) (*trans*/*cis* 96/4). To a stirred solution of **43** (238 mg, 1 mmol) dissolved in acetonitrile (3 ml) was added water (3 ml) and sodium bromate (226 mg, 1.5 mmol). The mixture was then heated at 70°C and solid CAN (16.5 mg, 3 mol%) was added. The resulting slightly yellow solution was stirred 20 min at this temperature. After cooling to room temperature, the reaction mixture was extracted with dichloromethane (3×10 ml) and the combined organic layers were dried over $MgSO_4$, filtered and the solvents were removed in vacuo to afford **44** as a colourless oil. Crude compound **44** was >95% pure (186 mg, 96%). (*trans*) RN [15781-18-7]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.78–5.62 1H, m), 5.10–5.02 (2H, m), 2.52–1.01 (10H, m), 0.89 (9H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.9, 135.5, 116.9, 48.5, 41.1, 38.6, 35.5, 32.4, 30.3, 27.4, 26.6; *cis*) RN [15781-11-0]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.88–5.71 (1H, m), 5.02–4.98 (2H, m), 2.59–1.02 (10H, m), 0.91 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.1, 136.6, 116.1, 49.1, 47.0, 41.6, 33.7, 32.5, 28.7, 27.7, 27.6.

1.2.5. Cyclohexanone (46) and 1,2-octanediol (47). To a stirred solution of **19** (200 mg, 0.88 mmol) dissolved in acetonitrile (4 ml) was added water (4 ml) and sodium bromate (290 mg, 1.33 mmol). The mixture was then heated at 80°C and solid CAN (14 mg, 3 mol%) was added. The resulting slightly yellow solution was stirred 20 min at this temperature. After cooling to room temperature, the reaction mixture was extracted with ether (3×10 ml). The organic layers were dried over $MgSO_4$, filtered and the solvents removed in vacuo to afford 225 mg of a crude oil. The crude product was further purified by column chromatography over silica-gel (ethyl acetate/petroleum ether 1/2) to give **46** as a colourless oil (81 mg, 95%) and **47** as a white solid (124 mg, 97%). Data identical to the authentic commercial samples (**46**, RN [108-94-1]; **47**, RN [1117-86-8], Acros).

1.2.6. 1,2-*O*-Isopropylidene-α-D-xylofuranose (49).[27] To a stirred solution of 1,2-3,4 diisopropylidene xylose **48** (66 g, 0.287 mol) dissolved in water (265 ml) and acetonitrile (250 ml) was added solid CAN (4.7 g, 8.6 mmol, 3 mol%). The resulting solution was stirred 18 h at room temperature. After that, NH_4OH (28%, 20 ml) was added and the resulting yellow-orange suspension was filtered over Celigel (celite/silica-gel: 9/1 w/w) and washed with MeOH (150 ml). The solvents were removed in vacuo and the residue dried overnight at room temperature to afford **49** as a pale yellow oil (53.4 g, 98%); ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.91 (1H, d, J=3.7 Hz), 4.46 (1H, d, J=3.7 Hz), 4.24 (1H, d, J=3.0 Hz), 4.11 (1H, q, J=3.0 Hz), 3.96 (2H, t, J=4.0 Hz), 1.42 (3H, s), 1.25 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 111.4, 104.5, 85.1, 79.8, 75.2, 60.1, 26.4, 25.9. Data identical to an authentic, commercial sample, (**49**, RN [20031-21-4], Aldrich).

1.2.7. 1,2-*O*-Isopropylidene-α-D-glucofuranose (51). To a stirred solution of diacetone-D-glucose **50** (1 g, 3.8 mmol) dissolved in water (2 ml) and acetonitrile (10 ml) was added solid CAN (21 mg, 0.038 mmol, 1.5 mol%). The resulting solution was stirred 2 days at room temperature. After that, NH_4OH (28%, 1 ml) was added and the resulting suspension was filtered over Celigel (celite/silica-gel: 9/1 w/w) and washed with MeOH (10 ml). The solvents were removed in vacuo and the residue dried using an azeotropic-toluene distillation to afford **51** as a white powder (812 mg, 81%); ^{1}H NMR (200 MHz, CD_3OD) δ 5.75 (1H, d, J=3.6 Hz), 4.36 (1H, d, J=3.6 Hz), 4.09 (1H, d, J=2.6 Hz), 3.90 (1H, dd, J=2.6, 8.4 Hz), 3.65 (2H, m), 3.45 (1H, dd, J=5.9, 11.7 Hz), 1.33 (3H, s), 1.18 (3H, s); ^{13}C NMR (50 MHz, CD_3OD) δ 114.3, 107.9, 88.0, 82.8, 77.0, 71.9, 66.7, 28.6, 28.0. Data identical to an authentic, commercial sample, (**51**, RN [18549-40-1], Aldrich).

1.2.8. α-D-*Ribo*-hexofuranose, 3-deoxy-3-methylene-1,2-*O*-isopropylidene (53).[28] To a stirred solution of α-D-*ribo*-hexofuranose, 3-deoxy-3-methylene-1,2-4,5-*O*-diisopropylidene **52** (3 g, 11.7 mmol) dissolved in water (30 ml) and acetonitrile (30 ml) was added solid CAN (192 mg, 0.35 mmol, 3 mol%). The resulting solution was stirred 24 h at room temperature. After that, NH_4OH (28%, 5 ml) was added and the resulting suspension was filtered over Celigel (celite/silica-gel: 9/1 w/w) and washed with MeOH (50 ml). The solvents were removed in vacuo and the residue dried overnight at room temperature to afford **53** as a colourless oil (2.05 g, 97%). Data identical to the reported spectroscopic values.

1.3. Preparation of CAN and nitric acid solutions for catalytic experiments

CAN in water (pH 1.6), to a stirred water solution (19 ml) was added CAN (105 mg, 0.19 mmol). CAN in borate buffer (pH 1.8), to a stirred borate buffer solution (Merck, pH 8, 19 ml) was added CAN (105 mg, 0.19 mmol). CAN in water/pyridine (pH 4.4), to a stirred water solution (19 ml) was added CAN (105 mg, 0.19 mmol) and pyridine (60 μl, 0.76 mmol). Nitric acid in water (pH 4.4), to a stirred water solution (19 ml) was added dropwise a concentrated nitric acid solution (14 M) until a pH value of 4.4 was reached.

1.4. 4-*tert*-Butyl-cyclohexanone (26) (voltammetry experiment)

To a stirred solution of acetonitrile (30 ml) and borate buffer (Merck, pH 8, 30 ml) was added CAN (164 mg, 3 mol%) followed by potassium nitrate (6.1 g, 60 mmol) as the electrolyte. A cyclic voltammetry of this solution was recorded. After that, substrate **27** was added (2 g, 10 mmol). The resulting mixture was then stirred 20 min at room temperature. Complete deprotection of compound **27** had occurred during that time (GC analysis) and a cyclic voltammogram was recorded under the same conditions as described above. The two curves were shown to be identical; only cerium(IV) species were detected.

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16. In the case of dimethylacetals, the competitive formation of the corresponding methyl esters has been observed. For sometime, we have not been able to define suitable reaction conditions under which unmasking of a dioxolane function could be accomplished chemoselectively in the presence of a TBS protecting group. Recently, we and others have shown that in some cases, such selective deprotections could be accomplished using CAN/Py (pH 4.4). (a) Ates, A.; Markó, I. E. Unpublished results. (b) Barone, G.; Bedini, E.; Iadonisi, A.; Manzo, E.; Parrilli, M. *Synlett* **2002**, 1645. For the removal of ketals using $CeCl_3$, see: (c) Marcantoni, E.; Nobili, F.; Bartoli, G.; Bosco, M.; Sambri, L. *J. Org. Chem.* **1997**, *62*, 4183. For the selective CAN-mediated deprotection of TBS ethers in the presence of ketals, in MeOH/water, see Ref. 13.
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20. Under acidic conditions, a competitive fragmentation of the spiro bicyclic system has been observed, leading to the corresponding cyclohexanone derivative bearing at the α-position a 2′-hydroxyethyl-4-butanoic ester side chain.
21. The CAN/py (pH 4.4) system has been discovered in this laboratory by Dr Ali Ates during the mechanistic study of the CAN-catalysed deprotection of **21**. These results have been communicated in all good faith to Dr Manzo, E. (visiting scientist) and Professor Parrilli, M. who subsequently published them Manzo, E.; Barone, G.; Bedini, E.; Iadonisi, A.; Mangoni, L.; Parrilli, M. *Tetrahedron* **2002**, *58*, 129. and Ref. 16b.
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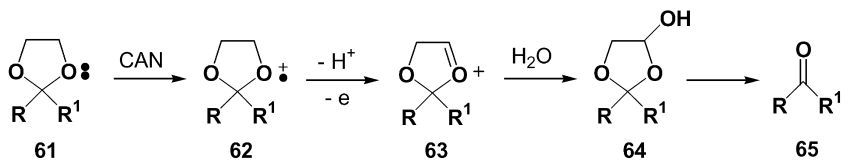

Figure 9.

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