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Mild and Neutral Deprotections Catalyzed by Cerium(IV) Ammonium Nitrate

NUNO MAULIDE,[†]
JEAN-CHRISTOPHE VANHERCK,[†]
ARNAUD GAUTIER,[‡] AND ISTVÁN E. MARKÓ*,[†]

Laboratoire SEESIB, CNRS-UMR 6504, Département de Chimie, Université Blaise Pascal, Clermont-Ferrand II, 24 avenue des Landais, 63177 Aubière cedex, France, and Université catholique de Louvain, Département de Chimie, Bâtiment Lavoisier, Place Louis Pasteur 1, 1348 Louvain-la-Neuve, Belgium

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ABSTRACT

The development of a novel, chemoselective, and catalytic deprotection methodology that proceeds under mild and neutral conditions is described, and its mechanism of action is analyzed in some detail. The scope, limitations, and advantages of this protocol are discussed. Selected applications in synthesis are also highlighted.

Introduction

In the art of multistep total synthesis of natural products, protection and deprotection sequences are often unavoidable.[1] Examples abound in the chemical literature, where interesting synthetic targets could not be attained, either because the protective groups that were employed stubbornly resisted cleavage or because the deprotection conditions that were required were too harsh for advanced, sensitive synthetic intermediates. As a response to these unfortunate predicaments, a number of new methods for the cleavage of commonly employed protective groups appear regularly.[2] This Account describes the genesis and development of a general and selective deprotection methodology mediated by cerium(IV) ammonium nitrate (CAN). In addition, selected applications of this procedure in diverse synthetic contexts, by us and by others, are also discussed.

Initial Observations and Discovery of the Stoichiometric Procedure

Within the frame of a research program aimed at the efficient preparation of functionalized, medium-sized carbocycles,[3] we became interested in the fragmentation reactions of bicycle **1**. In particular, we were intrigued by

* To whom correspondence should be addressed.
† Université catholique de Louvain.
‡ Université Blaise Pascal.

Nuno Maulide was born in Lisbon, Portugal, in 1979. After receiving his B.Sc. from the Instituto Superior Técnico (Lisbon, Portugal), in 2003, he moved to the Université catholique de Louvain to pursue a Ph.D. under the supervision of Professor István E. Markó. He received a FRIA scolarship in 2003 and since 2005 became an "Aspirant FNRS" at the same university. His research focuses on novel applications of functionalized ortho esters in synthesis.

Jean-Christophe Vanherck was born in Brussels, Belgium, in 1973. He studied chemistry at the Faculty of Sciences of the Université catholique de Louvain from which he graduated in 1997. He obtained his Ph.D. in 2004, for which he worked on a novel methodology for the construction of spirocyclic compounds, under the guidance of Professor István E. Markó. After that, he moved to the Institut Européen de Chimie et Biologie as a postdoctoral fellow working with Professor Léon Ghosez on the design and the syntheses of PACE4 inhibitors. In 2006, after a second postdoctoral stay for Janssen Pharmaceutica in the group of Professor István E. Markó, he joined Elbion Bioscience as a medicinal chemist. His research focuses on the design and the syntheses of bioactive molecules.

Arnaud Gautier was born in Chamalières, France. He obtained his Ph.D. from the Université d'Auvergne in 1995 and undertook postdoctoral training at Stanford University under the supervision of Professors B. M. Trost and W. S. Johnson (1995–1997). In 1997, he moved to the group of Professor István E. Markó at the Université catholique de Louvain before joining the CNRS at the Institut de Recherche en Chimie Organique Fine (Rouen, France) (1999). In 2005, he moved to his current location at the Université Blaise Pascal (UBP). He is currently one of the coordinators in the Bioactive Molecules group at UBP. His current interests include the development of click chemistry in the synthesis of ligands for transition metals and their interactions with nucleic acids and applications as anticancer agents.

István E. Markó was born in Pápa, Hungary, in 1956. He received his B.Sc. (1978) and Ph.D. (1983) degrees at the Université catholique de Louvain, under the supervision of Professor Léon Ghosez. After a two-year stay as a postdoctoral associate at the same university, he pursued Postdoctoral studies at the University of Vermont (Martin Kuehne, 1985–1987) and the Massachussets Institute of Technology (K. Barry Sharpless, 1987–1988). He then joined the University of Sheffield as a Lecturer (1988–1993) before taking up his present position as Professor in Chemistry at the Université catholique de Louvain (from 1993 to the present). His main research interests are in the field of short, efficient, and stereocontrolled total synthesis of natural products, the development of new organometallic reagents, electroorganic synthesis, and ecological processes.

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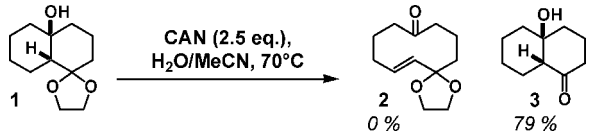
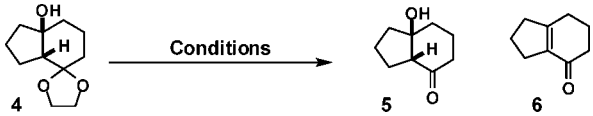


FIGURE 1

Table 1. Deprotection of Ketal 4



entry	conditions	product (yield)
1	PTSA (0.1 equiv), acetone, room temperature	**6** (95%)
2	$PdCl_2(MeCN)_2$ (0.04 equiv), acetone, reflux	**6** (95%)
3	CAN (2.5 equiv), $MeCN/H_2O$ (1:2), 70 °C	**5** (53%)

an oxidative cleavage reaction previously reported by Trahanovski that employed cerium(IV) ammonium nitrate (CAN).[4]

In the event, upon addition of 2.5 equiv of CAN to a water/acetonitrile solution of the β-hydroxy ketal **1**, at 70 °C, a dark red color immediately appeared and then vanished within 2 min. At this point, TLC analysis indicated complete conversion of the starting material (**1**) to a single new compound. Astonishingly, this product proved to be the keto alcohol **3** and not the expected medium ring system **2** (Figure 1).

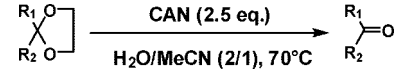
While CAN was already a well-known reagent for the oxidative deprotection of S,S- and O,S-acetals and ketals,[5] the oxidative cleavage of *tert*-butyldimethylsilyl ethers[6] and the removal of *tert*-Boc groups,[7] to the best of our knowledge, it had not been used to unmask acetals and ketals. The surprisingly rapid and efficient deprotection of ketal **1** prompted us to investigate in greater detail the scope and limitations of this novel reaction.

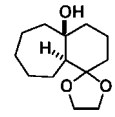
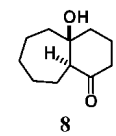
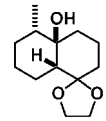
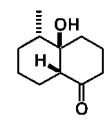
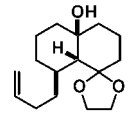
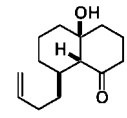
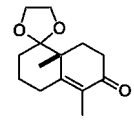
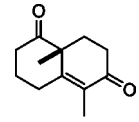
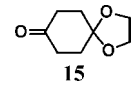
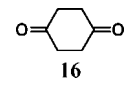
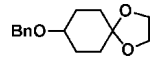
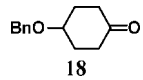
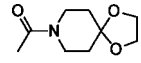
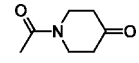
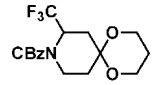
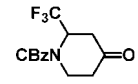
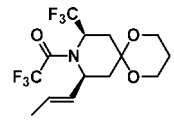
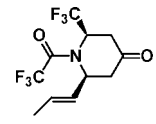
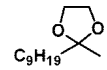
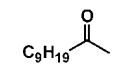
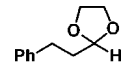
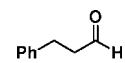
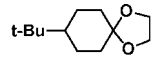
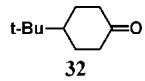
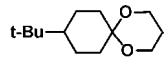
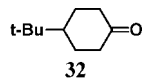
The potential of this hitherto unknown procedure became apparent when deprotection of hydrindane **4** was attempted (Table 1). Indeed, upon exposure to acidic conditions, rapid and quantitative formation of enone **6** could be ascertained (Table 1, entry 1). Similar results were obtained when catalytic amounts of a Pd(II) complex were used (Table 1, entry 2).[8] In stark contrast, the sensitive β-keto alcohol **5** was smoothly formed, albeit in modest yield, under the conditions described above. Furthermore, it is noteworthy that no epimerization of *cis*-**4** or *cis*-**5** took place under these conditions to afford the *trans* isomer.

These results further stimulated us to examine the efficiency of this protocol on a range of substrates bearing different functional groups. Selected results, obtained in deprotection reactions mediated by 2.5 equiv of CAN, are listed in Table 2.[9]

Several interesting trends emerge from these experiments. On one hand, the previous observations on hydrindane **4** can be extended to analogous substrates. Once more, no dehydration or epimerization is detected (Table 2, entries 1–3). Furthermore, the procedure tolerates the presence of a terminal alkene, a ketone, or an enone in the same molecule (Table 2, entries 3–5), as well as benzyl ethers or protected amide functionalities (Table 2, entries

Table 2. CAN-Mediated Deprotection of Ketals and Acetals[a]



entry	substrate	product	yield (%)	time (min)
1	 **7**	 **8**	96	2
2	 **9**	 **10**	79	>2
3	 **11**	 **12**	77	3
4	 **13**	 **14**	98	>2
5	 **15**	 **16**	71	>3
6	 **17**	 **18**	>97	>2
7	 **19**	 **20**	60	4
8	 **21**	 **22**	>84	5
9	 **23**	 **24**	80[10]	>ND[b]
10	 **25**	 **26**	75[10]	30
11	 **27**	 **28**	83	4
12	 **29**	 **30**	70	5
13	 **31**	 **32**	71	5
14	 **31a**	 **32**	65	5

[a] All yields refer to pure, isolated products. [b] Not determined.

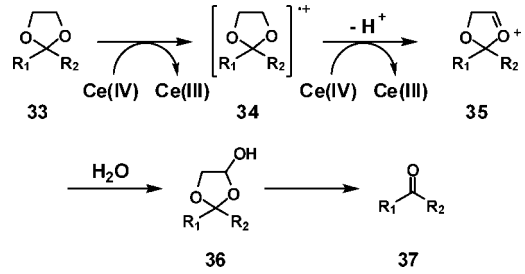


FIGURE 2. Initial mechanistic rationale for the deprotection of **33** with 2.5 equiv of CAN.

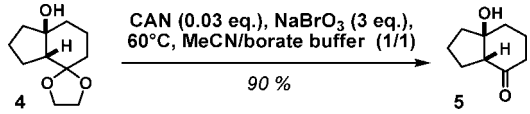


FIGURE 3

7, 9, and 10).[10] Moreover, ketals and acetals derived from acyclic carbonyl compounds are also unraveled smoothly.

Finally, the ketal tether length does not appear to be an important factor for the efficiency of this deprotection procedure, since both 1,2-dioxolanes and 1,3-dioxanes are cleanly excised (Table 2, entries 11–14). It should be emphasized that, in each case, the reactions reached completion within a few minutes, in stark contrast to the classical acid-catalyzed protocols that often require lengthy periods of time.

At this stage, the sequence of events depicted in Figure 2 became our working mechanistic hypothesis for the conversion of ketal **33** to ketone **37** upon treament with 2.5 equiv of CAN. On the basis of the well-known ability of CAN to function as a single-electron oxidant,[11] it appeared reasonable to consider radical cation **34** and oxocarbenium ion **35** as key intermediates. If this was indeed the case, then a catalytic version of our procedure, hinging upon the well-documented use of co-oxidants in conjunction with CAN, could be within reach.

Toward a Catalytic Procedure

From the wealth of co-oxidants known to efficiently promote the use of catalytic amounts of Ce(IV) complexes, $NaBrO_3$ retained our attention. In preliminary studies, 3 mol % CAN and 3 equiv of $NaBrO_3$ were added to an acetonitrile solution of ketal **4** (Figure 3). To prevent dehydration of the tertiary alcohol **5**, the reaction mixture was buffered using a borate buffer[12] at pH 8 ($pH_{solution} \approx$ 2.5). Gratifyingly, the reaction proceeded smoothly to afford ketone **5** in 90% yield.

Particularly striking was the yield increase (ca. 40%) compared to our previous experiments using stoichiometric amounts of CAN (cf. Table 1), suggesting that this catalytic version was somewhat milder in nature. Selected crucial experiments that eventually confirmed this assumption are summarized in Table 3. A diastereomerically enriched mixture of ketals **38** (98:2 *trans*:*cis* ratio) was subjected to both the stoichiometric and the catalytic protocols. Though in each case the isolated yields of the unmasked ketones **39** were very high, the diastereomeric purity of the products clearly depended upon the conditions that were employed. Thus, no erosion of stereochemical information was observed when the aforementioned catalytic procedure was used, as opposed to its stoichiometric counterpart.

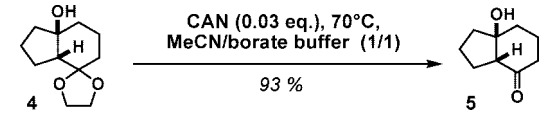
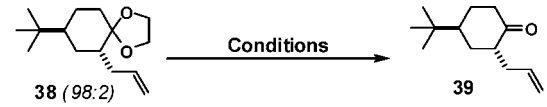


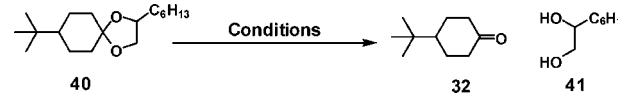
FIGURE 4

Table 3. Deprotection of Epimerizable Ketal 38



entry	conditions	yield (%)	diastereomeric ratio (%)
1	CAN (2.5 equiv), MeCN/H_2O (1:2)	99	80:20
2	CAN (0.03 equiv), $NaBrO_3$ (1.5 equiv), MeCN/borate buffer (pH 8) (1:1)	96	98:2

Table 4. Production of Glycol from the CAN-Mediated Deprotection of Dioxolane 40



entry	conditions	**32**	**41**
1	CAN (2.5 equiv), MeCN/H_2O (1:2), 70 °C	100%	ND[a]
2	CAN (0.03 equiv), $NaBrO_3$ (1.5 equiv), 60 °C, MeCN/borate buffer (pH 8) (1:1)	95%	97%

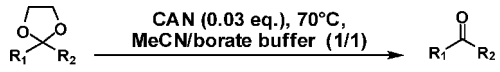
[a] Not detected.

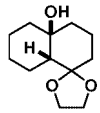
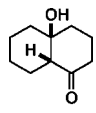
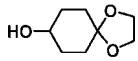
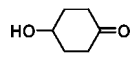
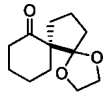
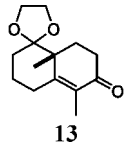
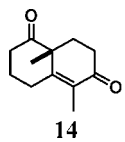
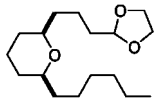
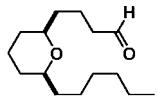
Subsequent studies aimed at fully grasping the scope and limitations of the deprotection mediated by the CAN/$NaBrO_3$ couple unveiled what would become a key element in the development of this methodology: the presence of significant amounts of glycols that could be observed in the reaction mixture (Table 4). With the intention of verifying these observations, the deprotection of ketal **40** was performed in the presence of a catalytic amount of CAN. The isolation of the diol **41** in quantitative yields implied that CAN was not acting as an oxidant but rather as a Lewis acid (Table 4, entry 2). Furthermore, when the same reaction was carried out with 2.5 equiv of the cerium complex, 1,2-octanediol **41** was never observed (Table 4, entry 1). These experiments clearly suggest that the mechanism for dioxolane cleavage with catalytic amounts of CAN, in buffered acetonitrile, does not involve oxidative cleavage.

Consequently, the adjunction of a stoichiometric co-oxidant should not be necessary to effect full deprotection!

These surprising but coherent observations prompted us to revisit the deprotection of **4** in the absence of $NaBrO_3$ (Figure 4). Remarkably, 0.03 equiv of CAN in the presence of a borate buffer and without co-oxidant smoothly excised the dioxolane moiety of the hydrindane **4**. A truly catalytic deprotection protocol had been uncovered.[13]

Table 5. CAN-Catalyzed Deprotection of Ketals and Acetals



entry	substrate	product	yield (%)
1	 **42**	 **43**	99
2	 **44**	 **45**	92
3	 **46**	 **47**	86
4	 **27**	 **28**	95
5	 **13**	 **14**	95
6	 **48**	 **49**	95

After some optimization, conditions that proved to be quite efficient were found, and a large variety of ketals and acetals could be easily deprotected using only a catalytic amount of CAN, in buffered acetonitrile (Table 5). Due to the mild conditions involved, this method is compatible with a wide range of functionalities, including free secondary or tertiary alcohols (Table 5, entries 1 and 2). It is interesting to note that unprotected alcohols are neither oxidized nor eliminated. It is also noteworthy that aldehydes can be easily unveiled from the corresponding acetals, without overoxidation to the carboxylic acid by the cerium(IV) catalyst (Table 5, entry 6). The contrast with "classical" acidic conditions is apparent from the deprotection of **46**, a compound which is otherwise prone to retro aldol fragmentation. Finally, a distinctive feature of this operationally simple protocol is its high chemoselectivity, as most reactions deliver analytically pure products after a mere aqueous workup.

Mechanistic Studies

Although the mechanistic hypothesis put forward in Figure 2 had seemed plausible at that time, the development of the catalytic version of this deprotection procedure casts serious doubts on the true role of Ce(IV) throughout the reaction. We thus sought additional insights into the oxidation states experienced by the metal center during the reaction. The deprotection of model substrate **31** was thus monitored using cyclic voltamperometry (Figure 5). At the onset, an acetonitrile/borate buffer solution was prepared as a blank and the spectrum was recorded (Figure 5, curve a). Then, CAN was added, and the spectrum, displaying the cerium(IV) reduction and oxidation potentials, was recorded again. Under these conditions, and using a sweep rate of 100 mV/s, reduction to the Ce(III) state occurs at a potential of −485.7 mV and reoxidation takes place at −357.2 mV versus SCE (Figure

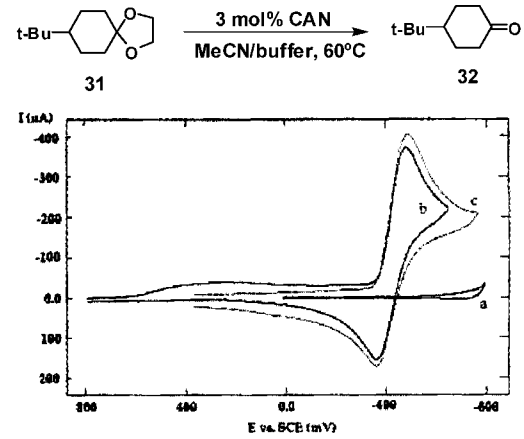
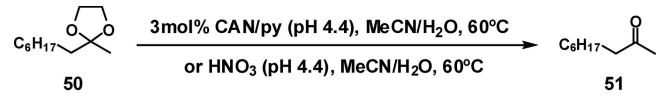


FIGURE 5



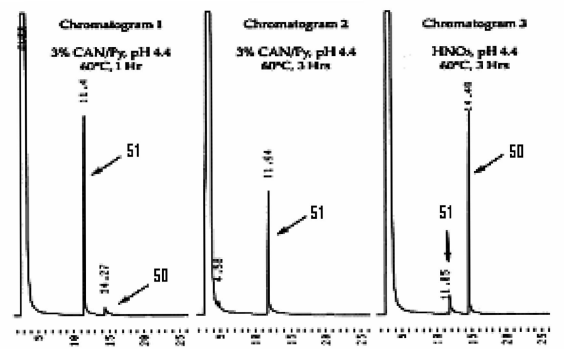


FIGURE 6

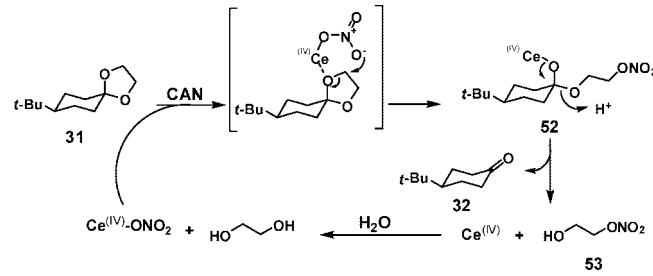


FIGURE 7. Ce^{IV}-mediated hydrolysis of **53**?

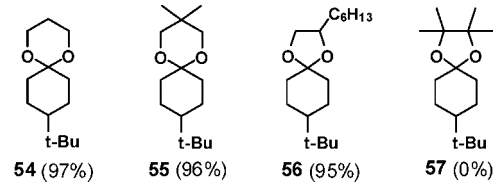


FIGURE 8

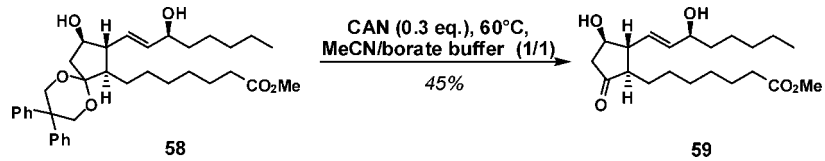


FIGURE 9

5, curve b). Importantly, the shape of the curve as well as the position of the oxidation and reduction peaks remained unaltered after the addition of ketal **31** during the course of the reaction and at the end of the deprotection (Figure 5, curve c). The only species detected throughout the reaction was Ce(IV), clearly demonstrating that CAN does not act as a redox catalyst.

To discriminate between possible Brönsted and Lewis acid catalysis, we performed a series of experiments under various pH conditions. While it is difficult to determine precisely the pH of an organic/water mixture, it appears that a solution of CAN (3 mol %) in MeCN and H_2O (1:1) is rather acidic (pH ~1.8). Nevertheless, several experiments have already hinted at the absence of Brönsted acid participation, including the absence of epimerization in the deprotection of substrate **38** (Table 3), which is particularly rapid under acid-catalyzed conditions, and the lack of fragmentation during the generation of spirodiketone **47**, a process that occurs readily in the presence of various acids.

Notwithstanding these observations, buffered solutions of nitric acid and CAN were prepared (pH 1.8–4.4), and the deprotection of model ketal **50** was performed at different pH values and monitored by gas chromatography (Figure 6).

While at low pH, the rates of deprotection proved to be nearly identical between HNO_3 and CAN, interesting results were obtained with pyridine-buffered solutions. Reaction of **50** with CAN (buffered at pH 4.4 with pyridine) led to almost complete formation of ketone **51** within 1 h and quantitative unveiling after 3 h. In contrast, less than 20% of **51** was produced when a pyridine/HNO_3 solution (pH 4.4) was employed.

Importantly, a literature survey revealed that lanthanide cations are particularly efficient in the hydrolysis of phosphodiesters,[14] and among them, cerium(IV) is the most active species, as documented by Moss and co-workers.[15] This cation-mediated hydrolysis has been investigated in detail, and it has been concluded that cerium(IV) acts as a dimeric Lewis acid in solution. Our own investigations, coupled with this literature precedent, strongly suggest that the cerium(IV) salts present in solution are the active catalytic species in this unique, mild deprotection methodology.

Taking into account the importance of the nitrate counteranion,[16] we propose the mechanistic scenario depicted in Figure 7. Coordination of the Lewis acidic Ce(IV) to one of the oxygen atoms of the ketal **31** presumably triggers intramolecular delivery of nitrate with concomitant ring opening to hemiacetal **52**. Elimination to form a carbonyl group then releases Ce(IV) in solution as well as nitrate monoester **53**. It has been shown that hydrolysis of such alkyl nitrates is fast in aqueous basic media,[17] and this presumably regenerates a cerium(IV) nitrate, which re-enters the cycle. This mechanism nicely accommodates the absence of epimerization that is observed in the case of substituted ketones (Table 3), since no oxonium intermediates are involved. It also provides a rationale for the drop in the deprotection rate as the steric hindrance around the ketal oxygens increases, since both Ce(IV) coordination and nitrate delivery are likely to be slower.

Selectivity in Dioxolane/Dioxane Deprotection

Given the efficiency observed in the deprotections mentioned above, it is important to outline the range of cyclic ketals that are amenable to unraveling by CAN. Relevant results are compiled in Figure 8.[9] Both simple and 3,3-disubstituted dioxanes can be smoothly deprotected under this protocol. Monosubstituted dioxolanes behave likewise. However, pinacol-derived substrate **57** remained completely inert to the reaction conditions. This observation bears some interesting consequences. On the one hand, it suggests that the cerium catalyst is highly sensitive to steric hindrance in the ketal protecting group and/or in its vicinity (vide infra). On the other hand, the fact that acidic treatment of **57** readily affords *tert*-butylcyclohexanone in high yields lends further credence to the noninvolvement of an acid-catalyzed manifold in the CAN-catalyzed procedure.

The mild conditions of the CAN-catalyzed protocol have already proved useful in some synthetic ventures. In a catalytic enantioselective synthesis of (–)-prostaglandin E_1 methyl ester **59**, Feringa and co-workers prepared enantiopure ketal **58** via a five-step sequence involving a stereoselective conjugate addition–electrophilic capture reaction (Figure 9).[18] The final step in their synthetic pathway, the chemoselective deprotection of the ketone functionality, revealed a particularly labile β-hydroxyketone. In the event, the CAN-catalyzed procedure proved to be up to the task, delivering **59** in 45% yield. Despite the moderate yield, this is still a remarkable result in that no elimination or epimerization of the rather sensitive product occurs.

The CAN-catalyzed deprotection of ketals also proved its effectiveness in a supramolecular context (Figure 10). Fréchet and co-workers were interested in the preparation of self-assembled dendritic "bow ties".[19] In one of the pivotal steps of this sequence, tetraisopropylidene ketal **60** was fully deprotected using 0.16 equiv of CAN, affording polyol **61** in 85% isolated yield. This spectacular deprotection set the stage for a key esterification which led to the coveted dendrimer.

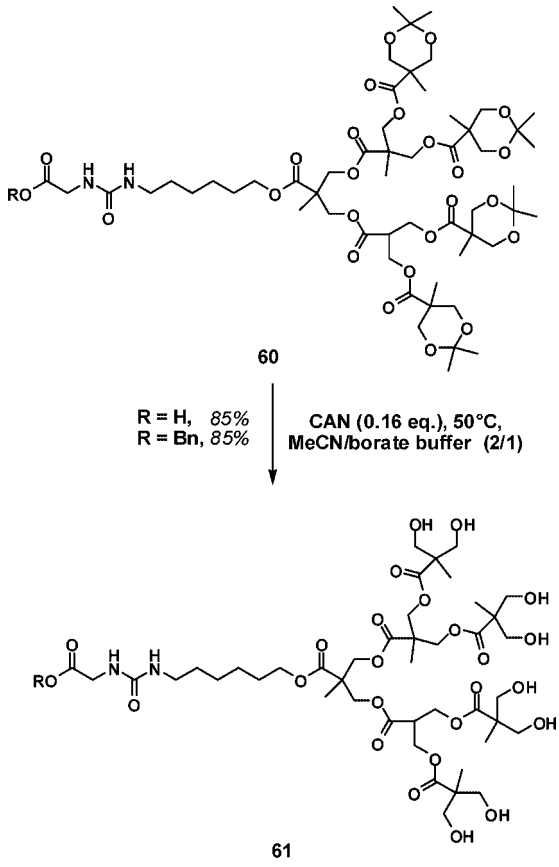


FIGURE 10

The two results described above also highlight the modular nature of this deprotection. Indeed, in the case of slightly hindered or recalcitrant acetals, sluggish reactions may sometimes be observed using the conventional protocol. In such situations, the amount of CAN employed can be increased to enhance the rate and yield of the deprotection.

Mazitschek and Giannis focused on the preparation and biological evaluation of novel fumagillin and ovalicin analogues as potential candidates for the interruption of tumor-induced angiogenesis, the formation of new blood vessels (Figure 11).[20] At the midpoint of their synthetic plan, removal of dioxolane **63** was required. The authors were surprised to find that this ketal protecting group was exceptionally stable, and all standard methods employed for its unraveling resulted in either decomposition or recovery of the starting material. Such a resilient behavior is probably due to the particular concatenation of functional and/or protecting groups present in **63**.

Once again, CAN was the single method among those tested that enabled the deprotection to take place, smoothly yielding ketone **64** in nearly quantitative yield (only the overall yields for the two-step sequence are given; no details concerning the amount of CAN are provided). The authors stated that "an additional advantage of this procedure with regard to the adjacent stereogenic center is the fact that the deprotection can be carried out under neutral conditions". Indeed, sensitive stereogenic centers, formed before the removal of ketal, are preserved throughout the deprotection sequence.

Cossy and co-workers studied the potential of radicals generated by irradiation of alkyl halides in the presence of triethylamine.[21] These radicals underwent smooth addition to neighboring double and triple bonds, yielding interesting bicyclic structures. The authors then applied this reaction to a formal synthesis of (±)-bisabolangelone (Figure 12). Their elegant synthetic plan, leading to the known intermediate **68**, featured a fully diastereoselective cyclization of bromide **65** and a sequential aldol reaction–dehydration sequence to introduce the side chain diene. The final step was the cleavage of the dioxolane in compound **67**. This transformation was achieved by using 0.03 equiv of CAN in buffered acetonitrile, at 60 °C, overnight. The desired ketone **68** was obtained in 60% yield without affecting the diene or the TES-protected alcohol.

One of the most interesting features of the CAN-catalyzed procedure is the ease and reliability of its scale-up. Indeed, Metzner, Brière, and co-workers required access to bulk quantities of tetraol **70** as starting material for their synthesis of conformationally locked sulfides **71** and **72** (Figure 13).[22] These scaffolds are particularly useful catalysts for the enantioselective epoxidation of aldehydes via the corresponding sulfonium ylide derivatives.

Their sequence started with the readily available trisacetonide of D-mannitol. In their hands, the previously described deprotection protocol, using acetic acid, proved to be erratic. However, the use of catalytic amounts of CAN in aqueous acetonitrile reproducibly afforded the desired monoacetonide **70** in 98% crude yield. As observed before, no additional purification was required and the reaction could be performed on an up to 15 g scale.

Selectivity in the Deprotection of Glycosidic Acetals

The smooth conditions involved in the aforementioned CAN-catalyzed deprotections stimulated us to survey the applicability of the process to sugars, the chemistry of glycosides being a domain in which the manipulation of protecting groups is of paramount importance. Our initial essays focused on 1,2-5,6-di-*O*-isopropylidene-α-D-glucofuranose **73** which contains two acetonide functionalities: one located on the side chain and the other directly connected to the anomeric position (Figure 14). Gratifyingly, regioselective excision occured at the 5,6-*O*-isopropylidene position while the anomeric protection remained untouched. As we had observed in many of our previous studies, the triol **74** is obtained in analytically pure form and with an excellent yield, after a simple aqueous workup. Furthermore, when the mixture was heated to 45 °C, the deprotection rate is enhanced without any effect on the regioselectivity or the efficiency.

This deprotection is also efficient in the presence of a benzyl group, smoothly yielding 1,2-*O*-isopropylidene 3-benzyl-α-D-glucofuranose **76** at 45 °C (Figure 15).

The same efficiency could be observed when the unmasking of 1,2-3,5-di-*O*-isopropylidene-α-D-xylofura-

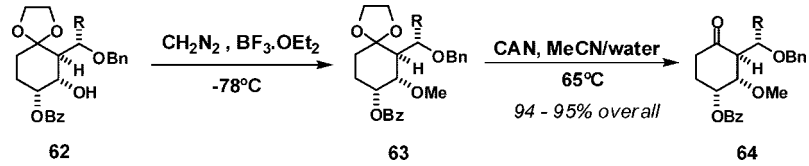


FIGURE 11

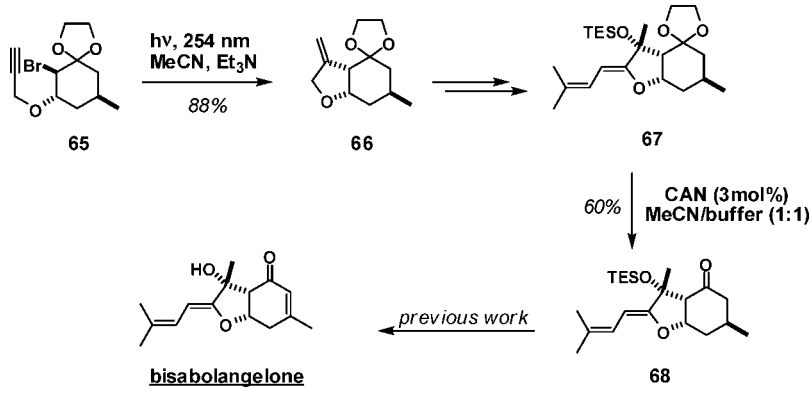


FIGURE 12

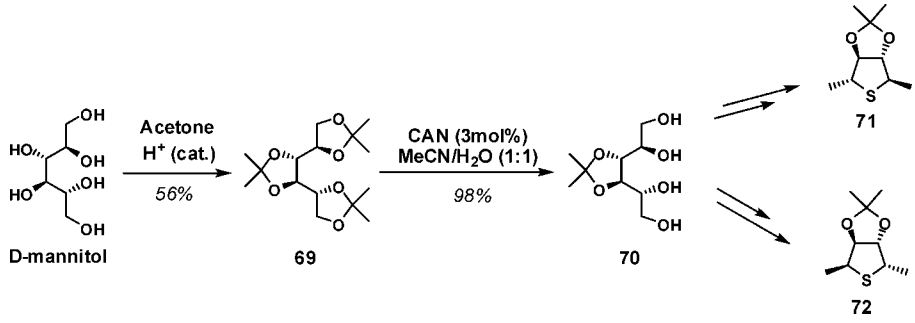


FIGURE 13

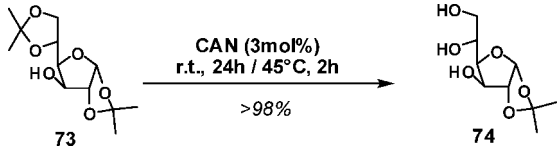


FIGURE 14

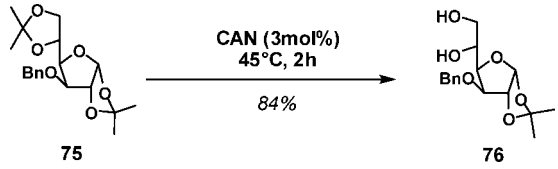


FIGURE 15

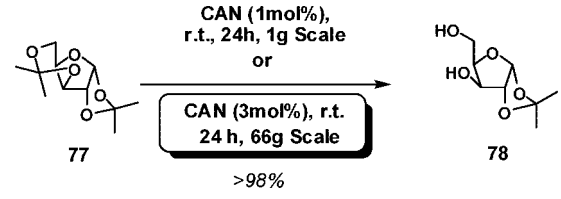


FIGURE 16

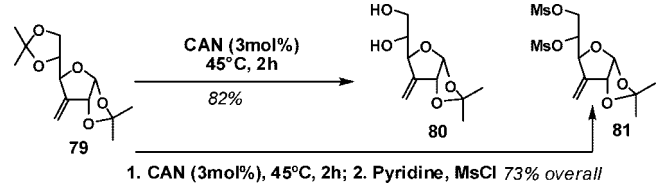


FIGURE 17

nose **77** was performed (Figure 16). Because the 3,5-diol protection is known to display low stability, as little as 1 mol % CAN was enough to ensure a complete reaction. When the reaction was performed on a large scale, better results were obtained using the traditional protocol (3 mol % catalyst). The reliability of this reaction, even on a >50 g scale, is yet another invaluable asset of this procedure.

A C_3 *exo*-methylene functionality is also compatible with the CAN-mediated deprotection protocol (Figure 17). The unstable diol **80** is obtained in 82% yield, once more without affecting the acetonide at the anomeric position. To verify this result, the diol was mesylated directly in the crude mixture, providing bis-mesylate **81** in an overall yield of 73%. No isomerization of the exocyclic double bond could be detected under these conditions.

Finally, during a program devoted to the synthesis of fluorine-modified nucleotides, the 3-deoxy-3-difluoromethylene glycoside **84** was required. Its preparation through direct deprotection of **82** was envisaged. The deprotection product **83** proved to be extremely labile, and none of the acidic conditions employed for the cleavage of the side chain acetonide moiety of **82** proved

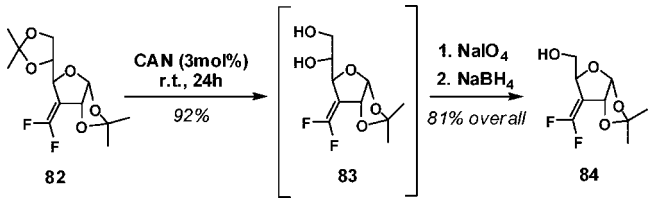
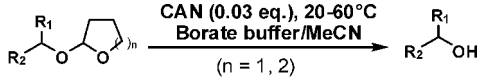
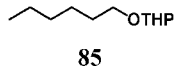
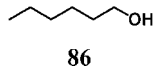
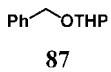
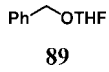
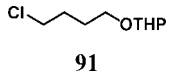
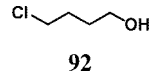
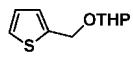
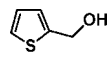
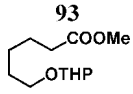
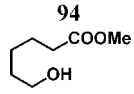


FIGURE 18

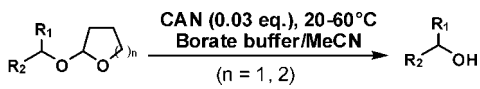
Table 6. Deprotection of THF and THP Ethers with CAN[a]

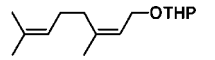
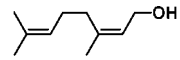
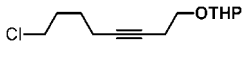
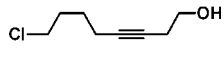
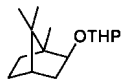
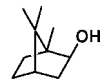
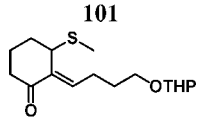
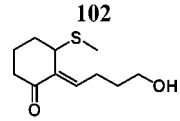
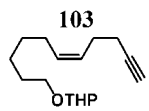
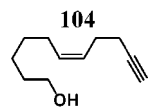


entry	substrate	product	yield (%)
1	 **85**	 **86**	94
2	 **87**	 **88**	87
3	 **89**	 **90**	91
4	 **91**	 **92**	86
5	 **93**	 **94**	91
6	 **95**	 **96**	82

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

Table 7. CAN-Catalyzed Deprotection of Acid-Labile Substrates



entry	substrate	product	yield (%)
1	 **97**	 **98**	86
2	 **99**	 **100**	94
3	 **101**	 **102**	87
4	 **103**	 **104**	99
5	 **105**	 **106**	98

to be viable (including, for example, AcOH, HCl, and H_2SO_4, at various concentrations). Once more, the use of 3 mol % CAN afforded the unstable diol **83** (in 92% yield), which was immediately subjected to an oxidative cleavage–hydride reduction sequence leading to the difluoro alcohol **84** in 81% yield.

From Masked Ketones to Protected Alcohols: THP and THF Deprotection

Given the remarkable success obtained in the deprotection procedure catalyzed by CAN, we were intrigued by the possibility of applying our protocol to the unmasking of other classes of acetals. For instance, the widely used THP and THF protecting groups for alcohols are, in practice, no different than mixed acetals. One of the aspects that stimulated us was the fact that the somewhat harsh conditions that are normally required for excision of these protecting groups are rarely compatible with sensitive substrates.

With the aim of delineating milder and hence more generally applicable reaction conditions, we subjected a range of tetrahydropyranyl and tetrahydrofuranyl ethers to catalytic amounts of CAN, in buffered acetonitrile, at room temperature or 60 °C. Selected examples are collected in Table 6.[23]

A number of interesting features emerged from this study. For instance, no oxidation of benzylic alcohols or aromatic (and even aliphatic, vide infra) sulfides was observed, lending further credit to our proposal that CAN acts exclusively as a powerful Lewis acid under these conditions. Again, the compatibility of these conditions with a variety of functional groups was ascertained (Tables 6 and 7).

Moreover, the exquisite chemoselectivity of this protocol is uniquely highlighted by the deprotection of a number of acid-labile substrates, some of which are compiled in Table 7. In each of these examples, extensive decomposition and/or rearrangement ensued upon exposure to even mild acidic conditions. For the majority of these cases, the CAN-catalyzed protocol was the only solution to a successful unveiling of the product alcohols in high yields. Furthermore, no rearrangement was detected when the camphor-derived THP ether **101** was treated under these conditions, and alcohol **102** was obtained in excellent yield (entry 3). Substrate **103** proved to be impossible to hydrolyze using a wide variety of common acidic procedures (entry 4). Several products, including those resulting from the 1,3-migration of the sulfur substituent or from the Michael addition of the free alcohol onto the enone function, could be detected in these complex mixtures. In stark contrast, CAN-catalyzed deprotection proceeded smoothly and afforded **104** in quantitative yield.

At this juncture, it appeared to be interesting to probe the relative rates of deprotection of different groups, through competition experiments. It was particularly striking to observe that trityl ethers, usually highly labile under acidic conditions, were in fact completely inert when submitted to our CAN protocol. This unconventional behavior enabled, for the first time, the selective

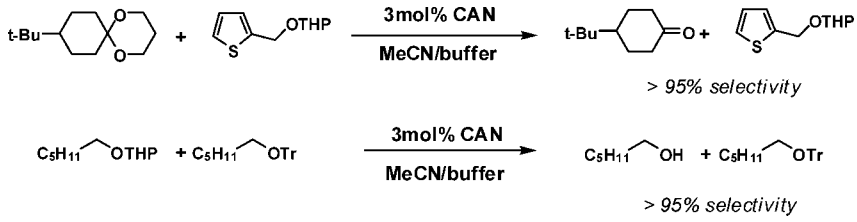


FIGURE 19

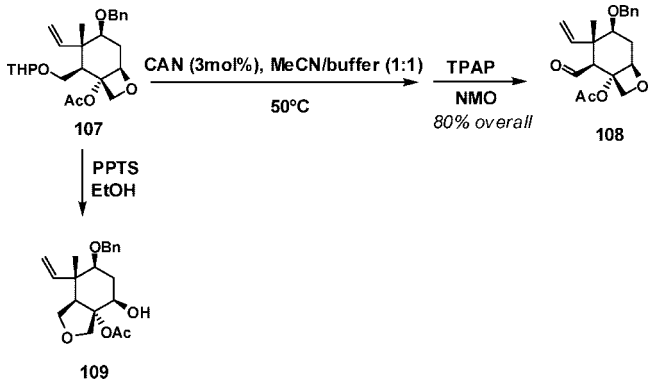


FIGURE 20

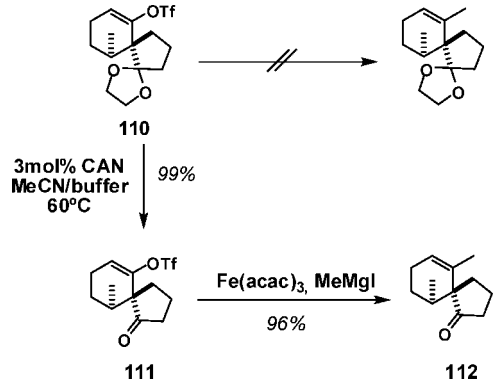


FIGURE 21

unmasking of a THP group in the presence of a trityloxy substituent.

Conceptually more intriguing was the behavior of THP ethers vis-à-vis a protected carbonyl (Figure 19). The remarkable observed selectivity, in favor of the ketal unraveling, could prove to be quite useful in tricky synthetic contexts.

Indeed, these conditions proved to be especially useful in the enantioselective synthesis of the CD ring subunit of paclitaxel, by Chida and co-workers (Figure 20).[24] The authors had foreseen a late-stage crafting of the oxetane ring, followed by liberation of a primary alcohol function and its oxidation to the required aldehyde **108**. In the event, intermediate **107**, bearing three orthogonally protected hydroxyl groups, was to be freed from the THP functionality to complete the synthesis. The CAN-catalyzed procedure fulfilled this task admirably, delivering the crude alcohol which was directly oxidized (TPAP/NMO) to the aldehyde **108** in a respectable 80% overall yield. Interestingly enough, when **107** was exposed to PPTS in ethanol, the unmasked primary hydroxyl group engaged the proximal, sensitive oxetane ring, generating significant amounts of a tetrahydrofuran derivative (whose presumed structure is **109**). Thus, even under these mild acidic conditions, activation of the oxetane moiety is likely to be operating, a problem which is not encountered with the CAN protocol.

Chemoselective Deprotections in the Presence of Enol Triflates: Story of a Synthetic Venture

During our recent total synthesis of members of the spirovetivane family of sesquiterpenes, we have encountered a chemoselectivity issue.[25] The crucial, Fe(III)-catalyzed formation of an elusive endocyclic, trisubstituted double bond was serendipitously shown to proceed smoothly only in the absence of the dioxolane ketal protecting group (Figure 21).[26] Thus, the success of our strategy heavily relied upon the chemoselective and efficient unmasking of the ketone function in the presence of the labile enol triflate moiety of **110**. In the event, the CAN-catalyzed protocol[27] played this role perfectly, delivering the pure, otherwise unavailable keto enol triflate **111** in quantitative yield. In stark contrast, using conventional acidic conditions, rapid hydrolysis of the enol triflate function took place.

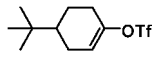
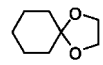
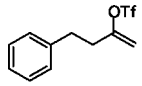
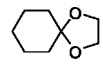
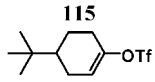
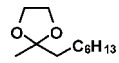
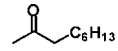
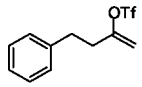
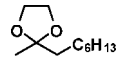
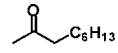
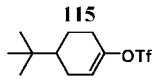
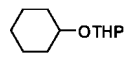
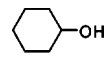
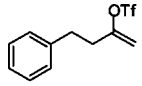
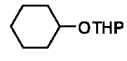
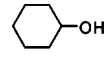
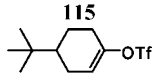
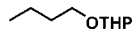
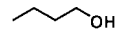
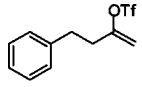
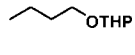
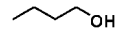
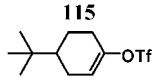
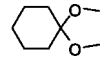
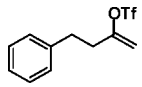
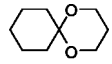
The prominent role played by enol triflates in synthesis, particularly in metal-mediated coupling processes, instigated us to study this reaction.[28]

At the onset, the two model enol triflates **113** and **115** (Table 8)[29] were selected as representative substrates and subjected to the CAN-catalyzed protocol, under typical intermolecular competitive conditions (1:1 ratio), in the presence of suitably protected partners. The results of these experiments are collected in Table 8.

As can be seen from Table 8, dioxolane ketals derived from both cyclic and acylic ketones **114** and **50** were smoothly unraveled under mild conditions (room temperature to 40 °C, 1–2 hours) and in a completely chemoselective manner (entries 1–4). No hydrolysis of the enol triflates, which could be easily recovered after the reaction in quantitative yields, was observed.

The same levels of selectivity were ascertained when the more demanding THP ethers **116** and **117** were employed as the competitive substrates. In these cases (entries 5–8), after 2–3 h at 60 °C, complete deprotection occured without any noticeable decomposition of the enol triflates. Furthermore, the 1,3-dioxane **119** and the more labile dimethylketal **118** were also chemoselectively hydrolyzed under these conditions (entries 9 and 10). Finally, it is noteworthy that the vinyl triflate **113** could be submitted to the deprotection conditions for up to 12 h

Table 8. CAN-Catalyzed Competitive Deprotections in the Presence of Enol Triflates[a]

entry	enol triflate	protected substrate	deprotected product	temperature, time	% enol triflate recovery
1	 **113**	 **114**	 **114a**	25 °C, 3 h; 40 °C, 1 h	>95
2	 **115**	 **114**	 **114a**	40 °C, 1 h	>95
3	 **113**	 **50**	 **51**	40 °C, 1 h	>95
4	 **115**	 **50**	 **51**	40 °C, 1 h	>95
5	 **113**	 **116**	 **116a**	60 °C, 3 h	>95
6	 **115**	 **116**	 **116a**	60 °C, 3 h	>95
7	 **113**	 **117**	 **117a**	60 °C, 2 h	>95
8	 **115**	 **117**	 **117a**	60 °C, 2 h	>95
9	 **113**	 **118**	 **114a**	25 °C, 1 h	>95
10	 **115**	 **119**	 **114a**	40 °C, 2 h	>95

[a] All competition experiments were performed using 3 mol % CAN and a 1:1 ratio of enol triflate **113** or **115** and protected compounds **114–119**.

without any sign of competitive hydrolysis of the enol triflate function.

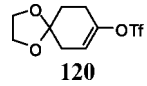
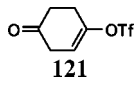
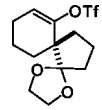
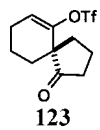
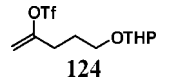
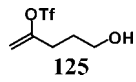
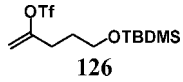
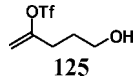
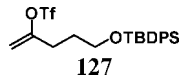
It thus happens that this unique catalytic deprotection procedure is fully compatible even with these sensitive enol moieties, thereby highlighting its synthetic usefulness.

Encouraged by these results, we finally evaluated the chemoselective deprotection of bifunctional substrates, embodying both the protecting group and the enol triflate functionality. Some selected examples are displayed in Table 9.

As can be seen, this protocol offers the exciting possibility of efficiently and selectively constructing keto enol triflates such as **121** and **123** (entries 1 and 2, respectively). Furthermore, the system responds well to an important increase in steric hindrance, as evidenced by the slightly higher temperature required to cleave the ketal function of **122** (entry 2).

Interesting results were obtained when substrates **124–126**, containing a masked alcohol function, were employed. While both the THP-protected compound **124** and its *tert*-butyldimethylsilyl (TBDMS) analogue **126** could be converted to the desired alcohol **125**, derivative **127**, bearing a *tert*-butyldiphenylsilyl (TBDPS) group, remained unaltered under our reaction conditions. In contrast to **121** and **123**, which could be easily purified by rapid column chromatography, enol triflate **125** proved to be particularly labile and decomposed extensively upon attempted purification.[30] CAN had not been employed previously for the catalytic deprotection of silyl ethers and, even in such a stringent scenario, performed quite well.

Table 9. CAN-Catalyzed Deprotections in the Presence of Enol Triflates[a]

entry	substrate	product	temperature, time	yield (%)
1	 **120**	 **121**	40 °C, 2 h	90
2	 **122**	 **123**	60 °C, 2 h	94
3	 **124**	 **125**	60 °C, 3 h	76
4	 **126**	 **125**	60 °C, 3 h	80
5	 **127**	–	60 °C, 3 h	NR[b]

[a] All reactions were performed using 3 mol % CAN in buffered MeCN. [b] No reaction.

Conclusions

The use of CAN as a catalyst for the deprotection of commonly employed protecting groups no longer appears to be a synthetic curiosity. Rather, it has become a powerful methodology bearing a number of advantages over standard procedures. Particularly noteworthy from the examples described in this Account is the exquisite chemoselectivity displayed by CAN as a Lewis acid, leading to a very high tolerance of otherwise acid-labile functionalities. We believe that this selectivity, coupled with the simplicity of the experimental procedures, is bound to provide CAN with a front seat in the arena of deprotection conditions, particularly in the total synthesis of complex and sensitive natural products. We hope that, as time passes, new and exciting applications of this method will be gradually unveiled.

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