Cerium(IV) Ammonium Nitrate as a Catalyst in Organic Synthesis

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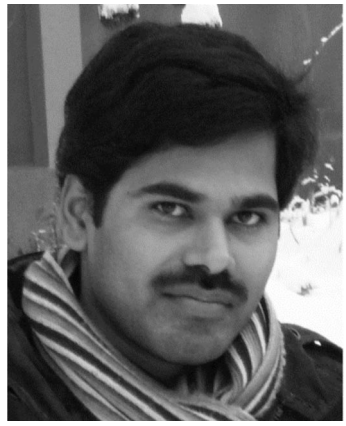
1. Introduction

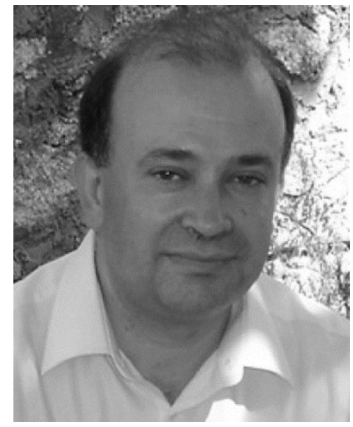
Cerium belongs to the family of the lanthanides, which constitute (together with scandium and yttrium) the so-called rare earth elements. Cerium is the most abundant of these elements and has been estimated to constitute about 0.0046% of the Earth's crust by weight. In fact, cerium cannot be considered "rare" at all, because its abundance is similar to or higher than that of better-known elements such as copper, bromine, cobalt, zinc, and tin.

Cerium has a property, unique among the lanthanides, that explains its ability to participate in one-electron transfer reactions, its ability to exist in two stable, adjacent oxidation states +3 and +4 with configurations $[Xe]4f^1$ and $[Xe]4f^0$, respectively, due to enhanced stabilization of the latter due to the presence of the vacant f shell. The high reduction potential of Ce(IV) (1.61 V vs normal hydrogen electrode) makes Ce(IV) a very efficient oxidizing reagent as compared to other cations, and for this reason its salts, and especially the commercially available cerium(IV) ammonium nitrate (CAN), have found widespread use as one-electron oxidants.[1] More specifically, CAN has been found to be chemically superior in many respects to the widely employed manganese triacetate for the generation of radicals.[2] CAN has the additional advantages of having a low toxicity besides being inexpensive, reasonably soluble in many organic media, air-stable, and easily handled, allowing for a considerable degree of experimental simplicity.

The possibility of employing Ce(IV)-generated radicals for the synthetically useful generation of carbon−carbon bonds was first discovered by Heiba and Dessau[3] and has been subsequently developed to a considerable extent, together with the use of CAN for the generation of carbon−heteroatom bonds. This work has been reviewed,[4] and some accounts of the work of specific groups, most notably the one led by Nair, have also been published.[5] However, although the main current goal in the area of CAN-promoted synthetic chem-



Vellaisamy Sridharan was born in Tamil Nadu, India. He received B.Sc. and M.Sc. Chemistry degrees, together with a Gold medal for university first rank in M.Sc., from Madurai Kamaraj University, Madurai, India. Subsequently, he passed the national level CSIR-NET (JRF) and GATE exams and started doctoral studies in the Department of Organic Chemistry of the same university under the joint guidance of Professors S. Muthusubramanian and S. Sivasubramanian and received the Ph.D. degree in 2005. During his doctoral studies, he was selected by the Department of Science and Technology (DST), New Delhi, Government of India, to participate in the Meeting of Nobel Laureates and students in Chemistry held at Lindau, Germany, in 2002. After his Ph.D., he is continuing his research as a postdoctoral associate, since May 2005, in the group of Professor José Carlos Menéndez in the Department of Organic and Medicinal Chemistry, School of Pharmacy of the Complutense University, Spain, except for a 12 months postdoctoral stay at the University of Paul Cezanne, Marseille, France, where he worked with Professor Jean Rodriguez on sulfoximine chemistry during 2008−2009. Currently, he is working on the development of new synthetic methodologies and multicomponent reactions for the synthesis of biologically relevant molecules including natural products. In his research career, he has coauthored around 35 international publications and presented his work in more than 15 international conferences held in India, Germany, France, the United Kingdom, and Spain.



José Carlos Menéndez was born in Madrid (1960) and obtained degrees in Pharmacy from Universidad Complutense at Madrid, UCM (1982) and Chemistry from UNED (1985), followed by a Ph.D. in Pharmacy from UCM in 1988, under the supervision of Dr. Mónica M. Söllhuber. In August 1988, he joined the group of Professor Steven V. Ley at Imperial College, London, where he worked on the total synthesis of the natural ionophoric antibiotic routiennocin. In September 1989, he returned as a Profesor Titular to the Organic and Medicinal Chemistry Department at UCM, where he has pursued his teaching and research career ever since. He has varied research interests, mostly in connection to synthetic work related to the development of new antitumour drugs, including heterocyclic quinones, antitumour marine natural products and MDR reversors, and, more recently, ligands of prion protein. Other projects pursued in his group place more emphasis on the development of new synthetic methodology, including work on hetero Diels−Alder reactions, microwave-assisted organic synthesis, CAN as a catalyst for organic synthesis, and new domino and multicomponent reactions for the preparation of biologically relevant bicyclic systems and nitrogen heterocycles. This work has been documented in about 130 research papers, reviews, and chapters and 9 patents. He has also some long-standing collaborations with several chemical and pharmaceutical Spanish companies. Additionally, he has coauthored two textbooks in Medicinal Chemistry for McGraw-Hill Interamericana (Introducción a la Química Farmacéutica, 2nd ed., 2001 and Ejercicios de Química Farmacéutica, 1997), and a third one for Elsevier (Medicinal Chemistry of Anticancer Drugs, 2008). He is the head of the Organic Microanalysis service at UCM since its creation in 1991. Since 2004, he is a Corresponding Member of the Spanish Royal Academy of Pharmacy. He was a Visiting Professor at Université Paul Cézanne (Aix-Marseille III) in 2007.

istry is the development of conditions that allow the use of catalytic amounts of CAN, the study of this aspect is quite recent and has never been summarized in the review literature. Therefore, the purpose of the present Review is to provide a comprehensive account of the synthetic applications of reactions promoted by substoichiometric amounts of CAN. Our discussion of the synthetic applications of CAN as a catalyst covers the literature up to the end of 2009. We have also striven to clarify the reaction mechanisms involved, which in principle should belong to one of the following categories, although they are not always easy to interpret from the evidence provided in the literature.

(a) The first is generation of radical and radical-cation species coupled to the reduction of Ce(IV) to Ce(III), with concomitant regeneration of Ce(IV) by an external oxidant. This is the most commonly proposed mechanism, although often without any supporting evidence.

(b) The second is Brønsted acid catalysis, due to the generation of protons by hydrolysis of the nitrate anion of CAN.

(c) The third is Lewis acid catalysis. In this connection, it is interesting to note that CAN may be a useful alternative to the expensive, hygroscopic lanthanide triflates. It is also relevant to mention that, among lanthanides, Ce salts are the ones that have the lowest affinity for oxygen, making them potentially complementary to other, better studied, Lewis acids.[6]

2. Oxidation Reactions

2.1. Introduction

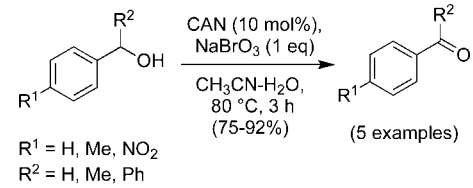
Although Ce(IV) has been well-known as an oxidizing agent for many years, it has several disadvantages, one of which is the large amount of reagent needed because Ce(IV)-containing reagents have relatively high molecular weights, combined with the fact that Ce(IV) cations can accept only one electron at a time. Another problem is the lack of generality of the reaction; for instance, CAN (in stoichiometric amounts) is an excellent reagent for the oxidation of benzylic alcohols[7] and cyclopropylcarbinols[8] to the corresponding carbonyl compounds, but gives cleavage products when applied to other types of substrates such as 1,2-diarylethanols[9] and bicyclo[2.2.1]heptan-2-ol derivatives.[10] These problems have prompted the development of methods where the Ce(IV) species is added in catalytic amounts and recycled from the resulting Ce(III) oxidation level. While this can be achieved electrochemically, the protocols reviewed in this section involve replenishing of Ce(IV) by the action of another, cheaper, oxidant. The most commonly employed one is the bromate anion, which recycles Ce(IV) according to eq 1. Oxygen is another commonly employed co-oxidant for these processes.

$$4\mathrm{Ce(III)} + \mathrm{BrO_3^-} + 5\mathrm{H^+} \rightarrow 4\mathrm{Ce(IV)} + \mathrm{HOBr} + 2\mathrm{H_2O} \quad (1)$$

2.2. Oxidation of Alcohols

One of the earliest examples of the use of CAN as a catalytic oxidant was published by Ho[11] and was based on the consideration of the mechanism of the Belousov−Zhabotinskyi reaction, where Ce(IV) is reduced by bromomalonic acid to Ce(III), which is then reoxidized by the bromate anion. On this basis, it was postulated that it should be possible to carry out the oxidation of organic substrates using only catalytic amounts of Ce(IV) and stoichiometric quantities of bromate. Indeed, this hypothesis was verified by the efficient oxidation of some primary or secondary benzylic alcohols to the corresponding aldehydes or ketones in the presence of the Ce(IV)/BrO_3^- system (Scheme 1). The fact that the bromate anion was not capable of oxidizing arylmethanol derivatives confirmed that the postulated mechanism was the one actually in operation.

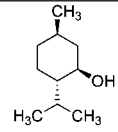
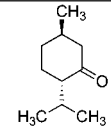
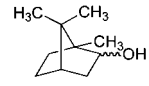
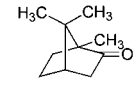
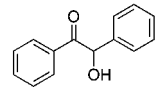
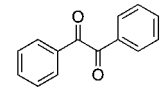
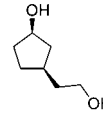
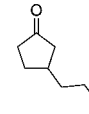
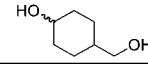
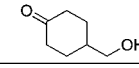
Scheme 1



Subsequent studies on the CAN/bromate system showed that it was also capable of oxidizing secondary alcohols to ketones while, remarkably, leaving primary alcohol groups largely untouched, with the exception of the one in 1-(4-hydroxymethylphenyl)ethanol.[12] It is noteworthy that cerium(IV) sulfate proved to be as efficient as CAN, but cerium(IV) oxide and Ce(III) chloride were inactive. Some representative examples of these transformations are summarized in Table 1, and it should be remarked that some of them (e.g., those in entries 2 and 3) were not possible in the presence of stoichiometric amounts of CAN, as they led to fragmentation products.

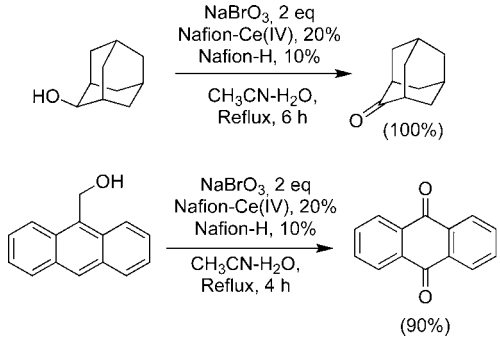
Another development in this area was the use of a Ce(IV)-impregnated Nafion-K catalyst, which is reusable after simple washing, in the presence of sodium bromate. This catalyst was found to be inactive in itself, but it afforded excellent yields when the reaction was carried out in acidic conditions by addition of either nitric acid or 10% Nafion-H.[13] Besides the usual oxidation of benzyl alcohols to aldehydes or ketones, this catalytic system afforded a quantitative yield

Table 1. Oxidation of Secondary Alcohols by CAN (10 mol %) and Sodium Bromate (1 equiv)[a]

entry	starting material	product	yield (%)
1			82
2			77
3			66
4			89
5			83

[a] Reaction conditions: CH_3CN-H_2O, 80 °C, 0.3−1 h.

Scheme 2

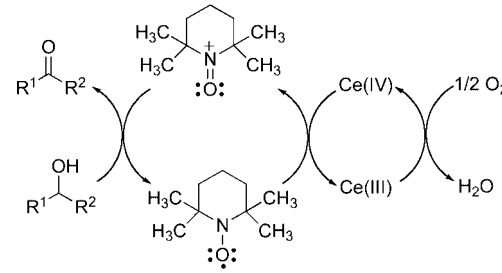


of 2-adamantanone from 2-adamantanol and also transformed 9-hydroxymethylanthracene into anthraquinone in excellent yield (Scheme 2).

As part of a study prompted by the current drive toward more sustainable technologies such as heterogeneous catalysis, the CAN/sodium bromate system has been further modified by immobilizing the cerium catalyst on phosphonate and phosphonic acid-modified silica gel, and indeed the species thus prepared was believed to be the first example of a Ce(IV)-based heterogeneous catalyst. These catalysts were active on primary and secondary alcohols, which were transformed into carboxylic acids and ketones, respectively.[14]

Besides sodium bromate, there has been great interest in the use of air as the ideal environmentally friendly co-oxidant for these Ce(IV)-catalyzed processes. An early study involving the use of CAN adsorbed on charcoal proved the feasibility of this idea, because this catalyst was able to promote the air oxidation of benzyl alcohols and acyloins to the corresponding carbonyl compounds in 68−92% yields by heating a toluene solution of the substrate at 100 °C for 2−20 h in an open vessel.[15] More recently, the aerobic catalytic oxidation of benzylic and allylic alcohols using a catalytic system composed of CAN and 2,2,6,6-tetramethylpiperidinyl-1-oxyl (TEMPO) has been described.[16] Although TEMPO alone is enough to promote the oxidation, the presence of CAN often allows one to carry out the reaction under milder conditions or in shorter reaction times. Some representative examples of these oxidations are listed in Table 2, together with the data for the equivalent reactions carried out in the absence of CAN.

Scheme 3



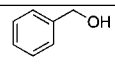
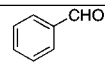
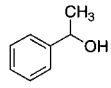
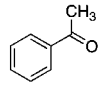
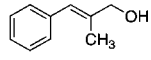
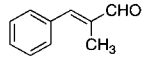
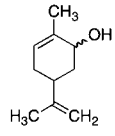
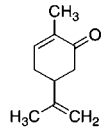
The mechanism of this oxidation can be rationalized as shown in Scheme 3, where the starting alcohol is oxidized to the corresponding carbonyl derivative by the *N*-oxoammonium cation derived from the one-electron oxidation of TEMPO by Ce(IV). Finally, molecular oxygen is reduced to water by the Ce(III) cation generated in this process.

In a related procedure, it has been shown that the oxidation of benzylic and allylic alcohols by air can be catalyzed by combining CAN with *N*-hydroxyphthalimide (NHPI).[17] In this reaction, the species that performs the oxidation is the phthalimide-*N*-oxyl (PINO) radical, derived from NHPI through a mechanism very similar to the one mentioned for the case of the CAN−TEMPO system and which is summarized in Scheme 4. This protocol is a consequence of the previous discovery by Ishii that NHPI efficiently catalyzes the aerobic oxidation of a range of organic compounds.[18]

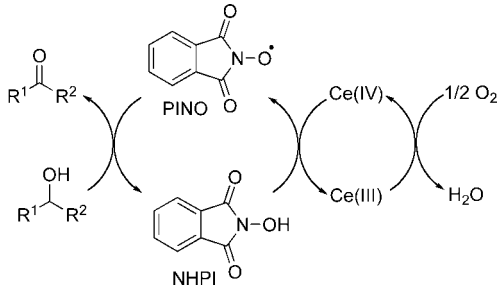
2.3. Oxidation of Thioethers to Sulfoxides

The transformation of thioethers into sulfoxides is of synthetic interest due to the importance of sulfoxides as synthetic intermediates. Work in this area is parallel to the one on the oxidation of alcohols previously mentioned in section 2.2. Again, the seminal work was due to Ho, who

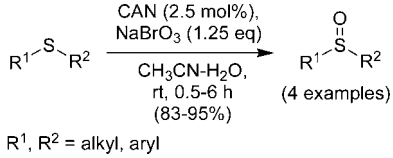
Table 2. Aerobic Oxidation of Benzylic and Allylic Alcohols Catalyzed by the CAN (10−20 mol %)/TEMPO (10 mol %) System in Acetonitrile

entry	starting material	product	TEMPO conditions and yields (%)	CAN-TEMPO conditions and yields (%)
1			100 °C, 6 h (99%)	82 °C, 2 h (92%)
2			100 °C, 4 h (93%)	82 °C, 1 h (99%)
3			100 °C, 2.8 h (88%)	82 °C, 0.5 h (94%)
4			65 °C, 29 h (78%)	82 °C, 1 h (94%)
5			---	82 °C, 7 h (75%)

Scheme 4



Scheme 5



proved that four representative thioethers could be transformed into the corresponding sulfoxides in excellent yields in the presence of CAN (2.5 mol %) and sodium bromate (1.25 equiv) (Scheme 5).[19] This transformation had been previously carried out with stoichiometric amounts of CAN, but under these conditions the oxidation reaction was complicated by a competing Pummerer rearrangement.[20] This problem was not found in the catalytic version, and this difference was attributed to the fact that in this case the reaction medium does not become sufficiently acidic to trigger the Pummerer reaction.

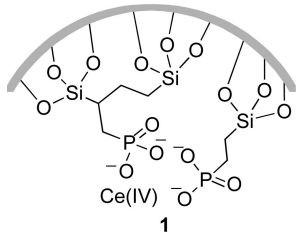
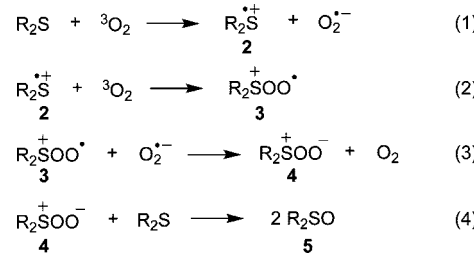


Figure 1.

Scheme 6

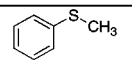
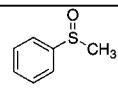
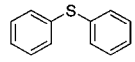
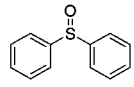
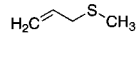
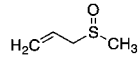


To simplify the reaction workup for the oxidation of thioethers to sulfoxides, some heterogeneous Ce(IV) catalysts have been developed. One of them is an immobilized cerium alkyl phosphonate of structure **1** (Figure 1), which gave good yields of sulfoxides using sodium bromate or *tert*-butyl hydroperoxide as co-oxidants, although the former was considered preferable because it was more selective.[21]

A simpler approach to the development of heterogeneous catalysts capable of oxidizing sulfides to sulfoxides consisted of the use of a silica-gel supported CAN−sodium bromate mixture, which catalyzed the oxidation in yields and scope similar to that of the immobilized cerium alkyl phosphonate catalyst and could be used under much milder reaction conditions.[22] A comparison between both methods for a few representative cases is given in Table 3.

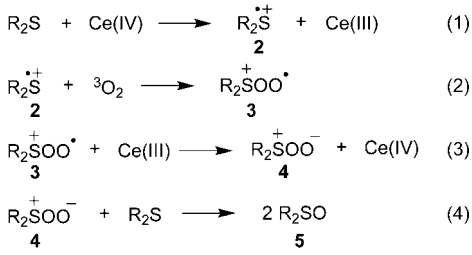
The use of molecular oxygen as a co-oxidant in the CAN-catalyzed preparation of sulfoxides from thioethers has also been investigated. The first study was based on the discovery that thioethers can oxidize to sulfoxides under high temperatures and oxygen concentrations, in the presence of polar solvents, albeit in a slow process.[23] The mechanism of this transformation (Scheme 6) was proposed to involve an initial unfavorable electron transfer step to give a radical cation **2** and superoxide anion (eq 1). This would be trapped by a molecule of triplet oxygen and afford **3** (eq 2). Back-donation of an electron from superoxide anion would transform **3** into the zwitterionic species **4** (eq 3), which is known to yield two molecules of sulfoxide by reaction with a second molecule of thioether (eq 4).

Table 3. Comparison between Two Heterogeneous Catalysts for the Oxidation of Thioethers to Sulfoxides

entry	starting material	product	conditions, yield (%) (Ce alkylphosphonate[a])	conditions, yield (%) (SiO_2-CAN)
1			50 °C, 0.5 h, 0.8 eq $NaBrO_3$ (98%)	rt, 13 min, 0.1 eq CAN, 1.1 eq $NaBrO_3$ (99%)
2			80 °C, 144 h, 2 eq $NaBrO_3$ (97%)	rt, 10 h, 0.1 eq CAN, 1.1 eq $NaBrO_3$ (96%)
3			40 °C, 48 h, 4 eq $NaBrO_3$ (91%)	rt, 27 min, 0.1 eq CAN, 1.1 eq $NaBrO_3$ (70%)
4			40 °C, 4 h, 4 eq $NaBrO_3$ (99%)[b]	rt, 30 min, 0.05 eq CAN, 1.1 eq $NaBrO_3$ (98%)

[a] For 1 mmol of substrate, 0.03 g of cerium alkyl phosphonate, containing 0.7 mmol/g of Ce(IV), was employed. [b] The following conditions were found to give the corresponding sulfone in 99% yield: 70 °C, 24 h, 6 equiv of $NaBrO_3$.

Scheme 7



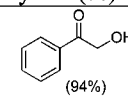
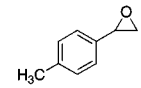
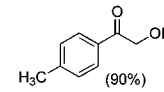
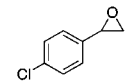
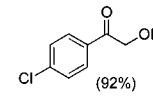
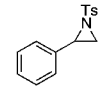
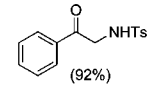
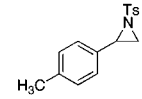
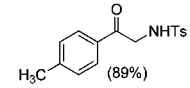
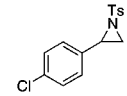
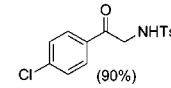
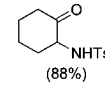
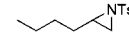
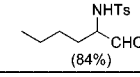
Because the initial unfavorable electron transfer is rate-determining, efforts were made to accelerate it by addition of a suitable one-electron oxidant, which led to the finding that Ce(IV), in the form of catalytic amounts of CAN, was the best promoter for the reaction among many species studied. A mechanistic study led to the proposal summarized in Scheme 7.[24]

Despite the improvements associated with the use of Ce(IV), the conditions required (14 bar O_2, 60−100 °C, 0.5−5.5 h) were still too harsh. Subsequent work has uncovered more active catalysts for the aerobic oxidation of thioethers, such as the Fe-substituted polyoxometalate/hydrogen dinitrate system.[25] A K10-montmorillonite clay-supported CAN catalyst has also been found to give excellent yields for the air oxidation of thioethers to the corresponding sulfoxides, although the scope of the reaction was not studied in detail, and in some cases the major product was a disulfide (Table 4).[26]

2.4. Oxidation of Epoxides and Aziridines

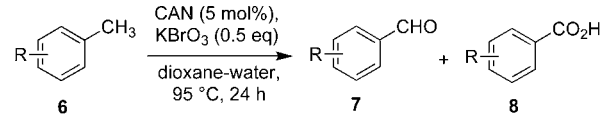
The association of CAN, in catalytic amounts, and *N*-bromosuccinimide (NBS) provides an efficient reagent for the direct transformation of aryl epoxides into α-hydroxyarylketones, although the reaction failed for alkyl and cyclic epoxides. When applied to *N*-tosylaziridines, the reaction proved more general, as shown in Table 5.[27] It was verified that both CAN and NBS were essential for the reaction. Mechanistically, this process was proposed to take place by CAN-catalyzed hydrolysis of the epoxide or aziridine ring (see sections 3.2.6 and 3.2.7), followed by oxidation.

Table 5. Oxidation of Epoxides and Aziridines by CAN (0.2 equiv) and NBS (1 equiv)[a]

entry	starting material	product, yield (%)
1		 (94%)
2		 (90%)
3		 (92%)
4		 (92%)
5		 (89%)
6		 (90%)
7		 (88%)
8		 (84%)

[a] Conditions: CH_3CN-H_2O, room temperature.

Scheme 8



2.5. Oxidation of Alkylbenzenes

The combination of CAN, in catalytic amounts, and potassium bromate can be employed to oxidize some methylbenzenes to mixtures of the corresponding aldehydes and acids, as shown in Scheme 8 and Table 6 for some representative cases.[28] It is noteworthy that oxygen-bearing

Table 4. Air Oxidation of Thioethers to Sulfoxides: Comparison of Conventional Conditions with the Reaction in the Presence of a K10-Montmorillonite Clay-Supported CAN Catalyst (10.2% CAN in Weight)

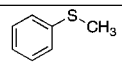
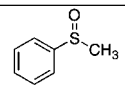
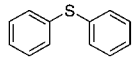
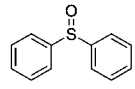
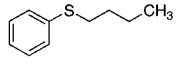
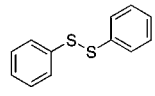
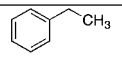
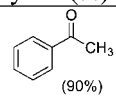
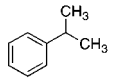
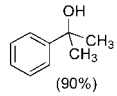
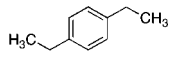
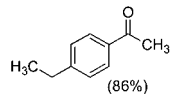
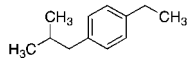
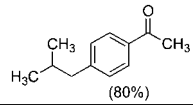
entry	starting material	product	conditions, yield (%)	conditions, yield (%)
1			CAN (stoichiometric), MeOH, rt, 5 h (35%)	CAN-loaded clay, MeOH, rt, 2 h (100%)
2			CAN (stoichiometric), MeOH, rt, 5 h (54%)	CAN-loaded clay, MeOH, rt, 2 h (100%)
3			---	CAN-loaded clay, MeOH, rt, 2 h (yield not given)

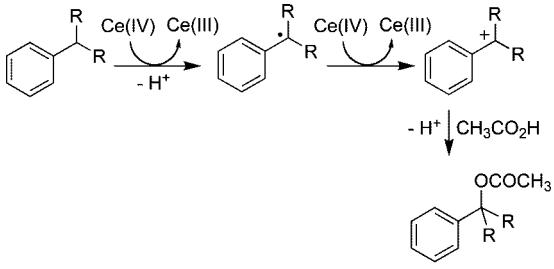
Table 6. Results Obtained in the Oxidation of Methylbenzenes with $CAN/KBrO_3$

entry	R	yield of **7** (%)	yield of **8** (%)
1	H	31	15
2	4-CH_3	70	20
3	4-^{t}Bu	29	26
4	4-Br	25	21
5	4-OCH_3	0	0
6	4-NO_2	0	0

Table 7. Results Obtained in the Oxidation of Alkylbenzenes with $CAN/KBrO_3$

entry	starting material	product, yield (%)
1		 (90%)
2		 (90%)
3		 (86%)
4		 (80%)

Scheme 9



substituents like methoxy or nitro were not compatible with the reaction.

When similar conditions were applied to higher alkylbenzenes, the reaction products were alcohols or ketones, depending on the degree of substitution of the starting materials (Table 7). In the case of dialkylbenzenes, only one of the chains was oxidized.

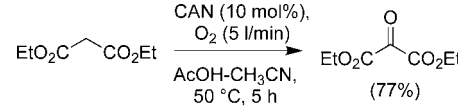
The CAN/bromate combination can also afford esters if the oxidation is carried out in a carboxylic acid (e.g., acetic acid) as solvent, probably through the mechanism shown in Scheme 9 (see also eq 1).[29]

2.6. Oxidation of Active Methylene Compounds

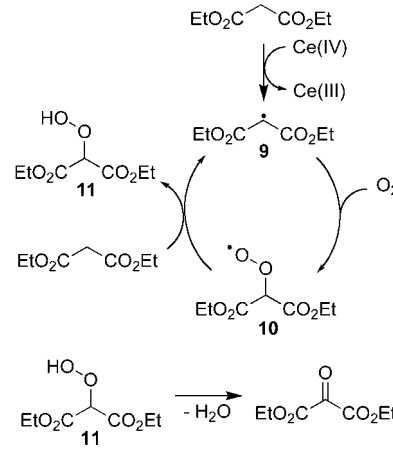
CAN is a good initiator for the direct transformation of diethyl malonate into diethyl ketomalonate by molecular oxygen. The optimal reaction conditions involved bubbling oxygen through a solution of the reactants in acetic acid−acetonitrile (Scheme 10).[30]

The mechanism proposed for this transformation is summarized in Scheme 11 and starts by the generation of malonyl radical **9** by action of CAN on the starting material. The radical **9** is intercepted by molecular oxygen to give the peroxy radical **10**, which can react with another molecule of diethyl malonate to give hydroperoxide **11**. Finally,

Scheme 10



Scheme 11



elimination of a molecule of water from **11** affords the final product (Scheme 11).

2.7. Oxidative Cleavage Reactions

2.7.1. Oxidative Cleavage of Olefins

The acidic K10-montmorillonite clay-supported CAN catalyst mentioned in section 2.3 was also useful for the oxidative degradation of olefins by molecular oxygen, normally in quantitative yields. The mechanism proposed by the authors of this study involves the catalytic cycle summarized in Scheme 12.[26]

2.7.2. Oxidative Cleavage of Alkynes

The oxidative degradation of alkynes by molecular oxygen proceeds slowly under noncatalyzed conditions. However, this reaction is dramatically accelerated in the presence of CAN to give carboxylic acids as major products.[31] Some representative examples are given in Table 8.

The mechanism proposed for this reaction is depicted in Scheme 13. Removal of one electron from the starting alkyne

Scheme 12

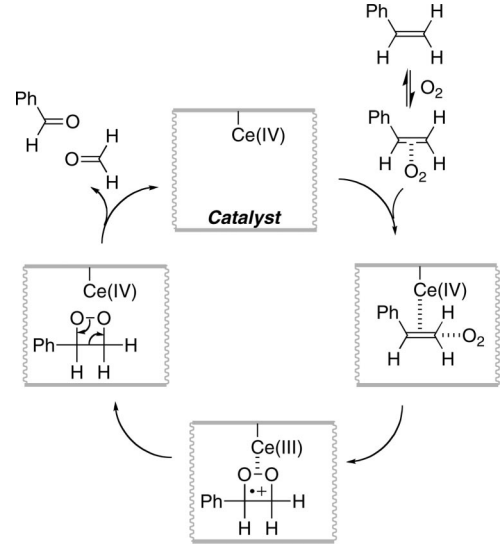
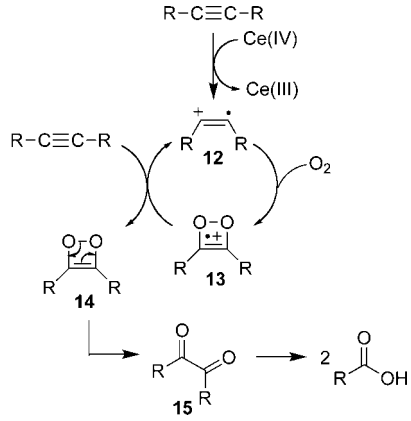


Table 8. Oxidative Degradation of Alkynes by Oxygen in the Presence of CAN (5 mol %)

entry	alkyne	pO_2, bar	product(s), yield (%)
1	Ph—≡—H	70	$PhCO_2H$, 65%
2	Ph—≡—Ph	70	$PhCO_2H$, 61% PhCOCOPh, 23%
3	Ph—≡—^{n}Hex	70	$PhCO_2H$, 65% ^{n}HexCO_2H, 34% PhCOCO^{n}Hex, 12%
4	^{n}Pent—≡—^{n}Pent	15	^{n}PentCO_2H, 84%

Scheme 13



Scheme 14

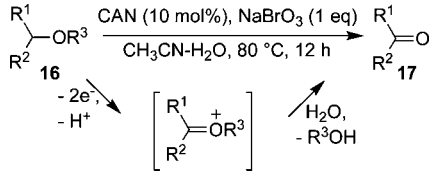


Table 9. Oxidative Cleavage of Ethers by CAN−$NaBrO_3$

entry	R^1	R^2	R^3	yield (%)
1	$(CH_2)_5$		CH_3	81
2	$(CH_2)_5$		$Si(CH_3)_3$	75
3	$(CH_2)_5$		$Si(CH_3)_2{}^t$Bu	65
4	^{n}Pr	^{n}Bu	CH_2CH_3	95
5	$^n C_8H_{17}$	H	CH_3	60
6	C_6H_5	H	$CH_2C_6H_5$	95

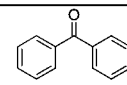
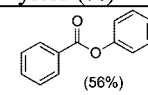
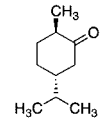
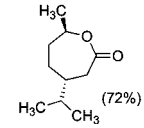
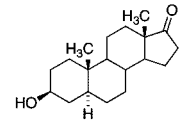
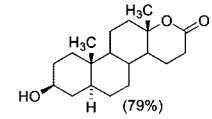
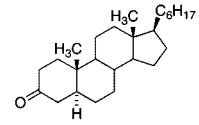
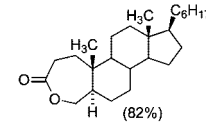
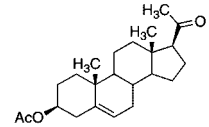
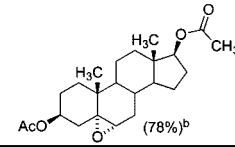
by Ce(IV) affords radical cation **12**, which gives dioxyethane radical cation **13** upon addition of a molecule of oxygen. Intermediate **13** traps a new molecule of alkyne to give another molecule of **12** and **14**, which rearranges to diketone **15**. Although compounds **15** are isolated in some cases, they normally undergo one further oxidative degradation reaction to give the corresponding carboxylic acids.

2.7.3. Oxidative Cleavage of Alkyl and Silyl Ethers

The oxidative cleavage of ethers is a useful synthetic transformation, but existing procedures required very harsh conditions. This prompted Olah to apply Ho's CAN−bromate reagent to this problem, finding that it allowed a simple, mild, and efficient transformation of secondary ethers **16** into ketones **17**, presumably through an intermediate oxonium species. The scope of the reaction was found to include methyl, ethyl, trimethylsilyl, and *t*-butyldimethylsilyl alkyl (or arylalkyl) ethers (Scheme 14, Table 9).[32]

In a variation of this procedure, the oxidative deprotection of trimethylsilyl ethers with CAN supported onto a HZSM-5 zeolite under solvent-free conditions and using microwave irradiation has been described.[33]

Table 10. CAN-Catalyzed Baeyer−Villiger Reactions[a]

entry	starting material	product, yield (%)
1		 (56%)
2		 (72%)
3		 (79%)
4		 (82%)
5		 (78%)[b]

[a] Conditions: CAN (7 mol %), *m*-CPBA (1.3 equiv), CH_2Cl_2, room temperature, 4−6 h. [b] Although not explicitly mentioned in the original publication, this reaction must have required at least 2 equiv of *m*-CPBA.

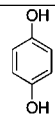
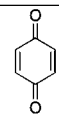
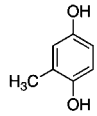
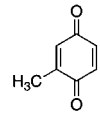
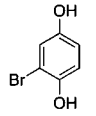
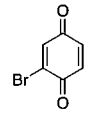
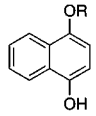
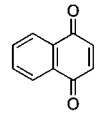
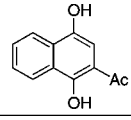
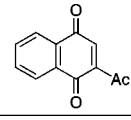
2.8. Baeyer−Villiger Oxidation

CAN is a good catalyst for the reaction between ketones and peracids leading to esters, that is, the Baeyer−Villiger reaction. While most of the examples studied were steroids, the reaction proved to be quite general (Table 10). When the reaction was carried out in a substrate containing a carbon−carbon double bond, the Baeyer−Villiger reaction was accompanied by olefin epoxidation (entry 5). The role of CAN was assumed to be that of a Lewis acid.[34]

2.9. Synthesis of Quinones from Oxygenated Aromatics

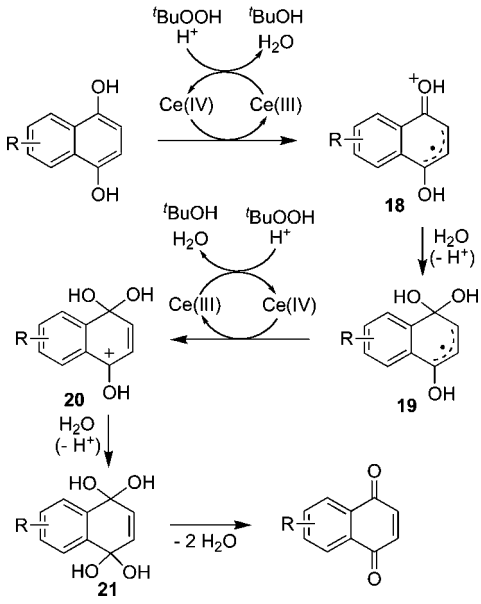
Dual systems containing catalytic amounts of CAN combined with several co-oxidants have been found to afford quinones from hydroquinones. The first of these co-oxidants was sodium bromate, which allowed the preparation of three benzoquinone and naphthoquinone derivatives in 90−96% yields.[19] The combination of CAN and *tert*-butyl hydroperoxide (TBHP) allowed the transformation of a range of 1,4-dihydroxybenzene and 1,4-dihydroxynaphthalene derivatives into the corresponding quinones. Interestingly, the reaction also worked, albeit quite slowly, for one hydroquinone monomethyl ether, but failed to effect the oxidative demethylation of hydroquinone dimethyl ethers.[35] Finally, a catalyst prepared by doping with CAN a Fe^{3+}-exchanged montmorillonite K-10 clay (containing 13.8% Fe) was also successful in the oxidation of some hydroquinones to the corresponding quinones under ultrasound irradiation, while simple montmorillonite K-10 clay, whose Fe content was

Table 11. Comparison between Three Protocols for the CAN-Catalyzed Oxidation of Hydroquinones to Quinines

entry	starting material	product	CAN-$NaBrO_3$,[a] yield (%)	CAN-TBHP,[b] yield (%)	CAN-K10 clay (Fe^{3+}),[c] yield (%)
1			92	84	98
2			---	83	93
3			---	83	97
4			90 (R = H)	91 (R = CH_3)	--
5			---	82	---

[a] CAN (2.5 mol %), $NaBrO_3$ (1.25 equiv), CH_3CN-H_2O, room temperature, 1−2 h. [b] CAN (2 mol %), TBHP (5 equiv), CH_3CN-H_2O, room temperature, 10−18 h (for entry 4, R = CH_3, 50 °C, 11 h). [c] Fe-exchanged clay-CAN (10−50 mol % of CAN), CH_2Cl_2, ultrasound, room temperature, 30−60 min.

Scheme 15



determined to be 10.4%, was not effective.[36] The three methods are compared in Table 11 for some representative examples.

The mechanism of these oxidations is exemplified in Scheme 15 for the transformation of 1,4-dihydroxynaphthalenes into 1,4-naphthoquinones by the CAN/TBHP system. An initial one-electron oxidation of the starting hydroquinone leads to the electrophilic cation-radical **18**, which is attacked by a molecule of water to give **19**. A second one-electron oxidation leads to cation **20**, which is again attacked by water to give **21**, the dihydrate of the final quinone. In both oxidation steps, Ce(IV) is recycled by action of TBHP, which becomes reduced to *tert*-butyl alcohol.[35]

3. Reactions Involving the Generation of Carbon−Heteroatom Bonds

3.1. Introduction

This section will deal with the use of CAN as a catalyst for a very important group of transformations involving the creation of C−O, C−S, C−Se, C−N, and C−halogen bonds.

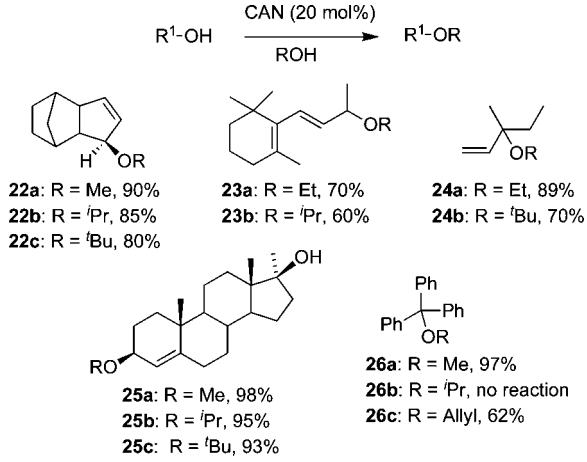
3.2. Reactions Involving C−O Bond Formation

This section will discuss the use of CAN as a catalyst for reactions involving the generation of C−O bonds. While much of this work has been developed in the context of protecting group chemistry of the hydroxy and carbonyl groups, it has also been employed in the wider context of backbone generation.

3.2.1. Ether Formation

3.2.1.1. Generation of Ethers from Alcohols. Iranpoor, one of the researchers who first demonstrated the use of CAN as a catalyst, explored the reaction of several types of allylic and tertiary benzylic alcohols with a variety of primary, secondary, and tertiary alcohols in the presence of catalytic amounts of CAN. This reaction was found to afford ethers in excellent yields,[37] and some representative examples are summarized in Scheme 16.

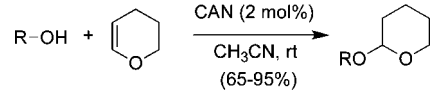
Scheme 16



3.2.1.2. Transetherification. Following the paper on simple etherification mentioned in section 3.2.1.1, the Iran-poor group described an efficient methodology for the CAN-catalyzed alcoholysis of ethers, particularly allylic and tertiary benzylic ethers,[38] with some representative examples being given in Scheme 17. Interestingly, the reaction showed complete chemoselectivity in favor of transetherification on a substrate that contained ether and tertiary hydroxyl functions (compound **25**).

3.2.1.3. THP Protection of Alcohols. Protection of hydroxyl groups is a very common maneuver in organic synthesis. Tetrahydropyranyl ethers were one of the first protecting groups for alcohols, and they are still widely used because of their stability under strongly basic conditions and in the presence of hydride transfer reagents, their easy removal, and also because of the low cost of dihydropyran. The first CAN-catalyzed protection of alcohols by 3,4-dihydro-2*H*-pyran (DHP) was achieved by Maity and Roy,[39] who proved that treatment of a variety of alcohols with DHP in the presence of less than 1 mol % of CAN in acetonitrile at room temperature afforded the protected alcohols in excellent yields. A decade later, Pachamuthu and Venkar extended this methodology to the synthesis of 2-deoxy-*O*-glycosides.[40] These authors first tested the protection of sterically hindered alcohols and alcohols containing additional acid-sensitive groups such as ketal, epoxide, acetal, and cyclopropane moieties in the presence of 2 mol % of CAN and found the reaction to be very effective (Scheme 18, Table 12). Interestingly, CAN adsorbed on silica gel was also equally efficient. It is noteworthy that a TBDMS group was unaffected in these conditions, but use of a stoichiometric amount of CAN in methanol effected its deprotection. For a mechanistic proposal to explain the THP ether formation in a related situation, see section 3.2.1.4.

Scheme 18



3.2.1.4. Glycosidation Reactions, Including the Ferrier Rearrangement. The scope of the above-mentioned THP ether formation reaction was further explored by carrying out the reaction between alcohols and glycals (compounds **31** and **32**) to provide the corresponding 2-deoxy-*O*-glycosides, including a disaccharide (Scheme 19, Table 13).[40] This reaction is important because most of the existing Lewis or protic acids that were tried did not allow the addition of alcohols to glycals due to a competing Ferrier reaction (see below).[41] On the other hand, the CAN-catalyzed methodology allowed the formation of 2-deoxy-*O*-glycosides **33** and **34** as mixtures of two anomers in which the α-anomer was major, in moderate to good yields, along with small amounts of the Ferrier (i.e., allylic displacement) products **35**. It is noteworthy that the Ferrier side products were not observed when 4 equiv of CAN was employed.

The proposed mechanism (Scheme 20) involves the reaction of CAN with alcohols to generate nitric acid, a very strong Brønsted acid, which activates glycals as oxonium cations. This is followed by transfer of the alkoxide moiety from cerium to the cation to give the observed 2-deoxy-*O*-glycosides (or THP ethers).

When the same reaction was carried out under reflux conditions, the Ferrier reaction became the only observed pathway. Thus, treatment of 3,4,6-tri-*O*-acetyl(or benzoyl)-D-glucal with a number of primary, secondary, benzyl, cinnamyl, and propargyl alcohols in the presence of CAN (10 mol %) in refluxing acetonitrile gave the corresponding Ferrier glycosides in excellent yields with high α-selectivity (Scheme 21),[42] which probably arose from thermodynamic control under the anomeric effect. In this case, the authors proposed that the glycosidation of glycals with alcohols in the presence of CAN might proceed through a one-electron transfer with initial formation of a radical cation and an allylic oxonium intermediate.

Scheme 17

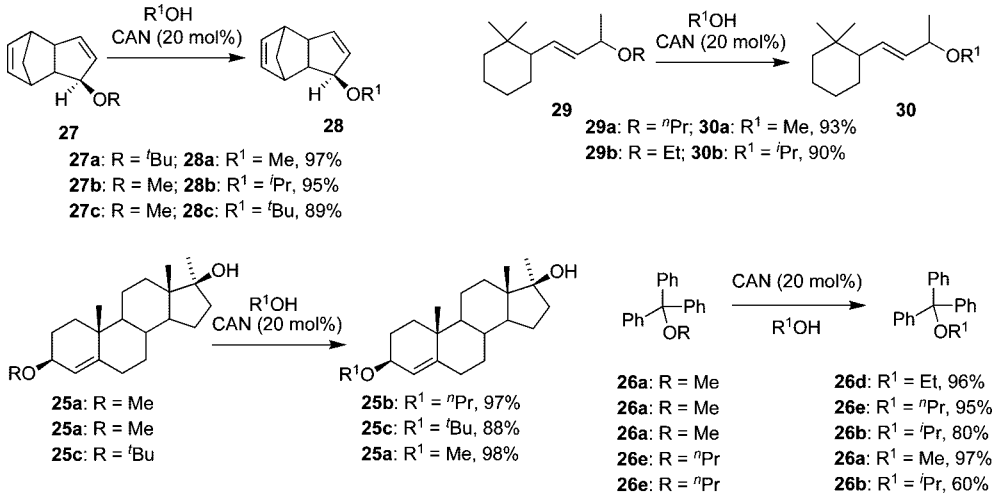
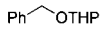
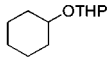
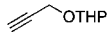
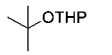
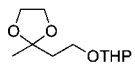
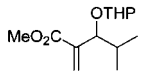
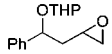
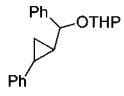
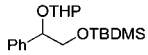
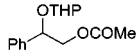
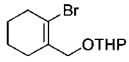
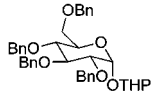
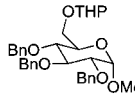
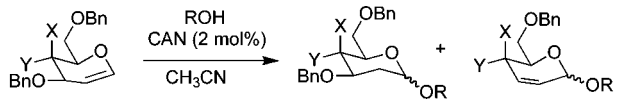


Table 12. Scope and Yields of the CAN-Catalyzed THP Ether Formation

entry	product	yield (%)
1		95
2		92
3		94
4		65
5		69
6		78
7		77
8		91
9		71
10		85
11		80
12		88
13		92[a]
14		95

[a] Mixture of two anomers in a 58/42 ratio.

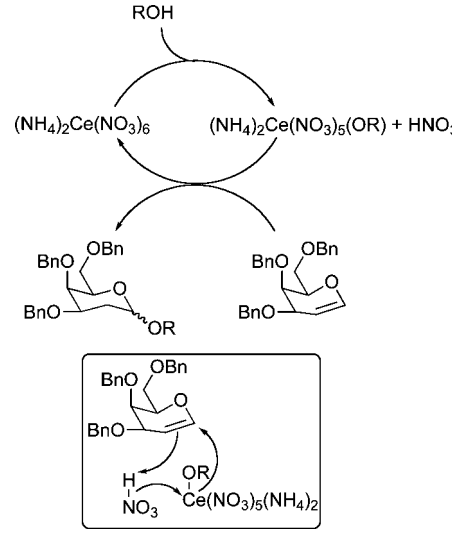
Scheme 19



31: X = OBn; Y = H
32: X = H; Y = OBn
33: X = OBn; Y = H
34: X = H; Y = OBn
35: X = H; Y = OBn

CAN was also a good catalyst for the Ferrier rearrangement in nucleosides, and thus uracil derivative **36a** afforded compounds **37** and **38** upon treatment with 0.02 equiv of CAN in methanol solution at 0 °C (Scheme 22). The formation of **37** can be explained by a Ferrier reaction with methanol as the nucleophile followed by displacement of uracil by a second molecule of methanol, probably with an oxonium species as an intermediate. The conditions needed for this reaction were remarkably mild, in contrast to those required for the related reaction of an adenine derivative **36b**, which required 1.4 equiv of CAN, probably due to coordination of the catalyst to the adenine amino group.[43]

Scheme 20



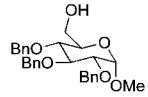
3.2.1.5. MOM Monoprotection of Glycols. The regioselective monoprotection of glycols as MOM ethers was achieved, during the enantioselective synthesis of (+)-neplanocin F, by a CAN-catalyzed reaction of glycols with trimethyl orthoformate followed by DIBAL reduction (Scheme 23).[44] Thus, treatment of glycol **39** with excess trimethyl orthoformate in the presence of 5−10 mol % of CAN afforded the intermediate orthoester **40**, which was subsequently converted into the monoprotected MOM derivative **41** in good overall yield. The orthoester formation failed in the presence of conventional catalysts like camphorsulfonic acid.

A couple of years later, the same group extended the scope of their study to a number of new substrates.[45] Regioselectivity was poor in the monoprotection of **42**, although the yield was 81%, and the reaction furnished products **43** and **44** in a 1.7:1 ratio (Scheme 24), under conditions similar to the ones employed in the initial study. Interestingly, the reaction of **45** with trimethyl orthoformate/CAN and subsequent reduction furnished exclusively the monoprotected derivative **46** (Scheme 25).

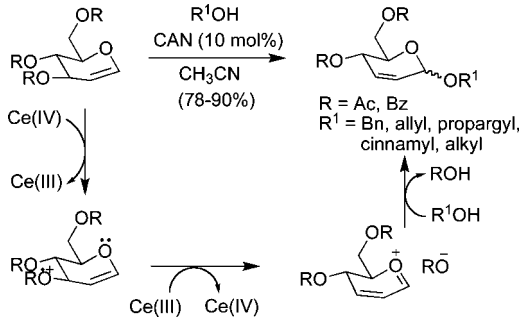
On the other hand, the regioselective introduction of a MOM protecting group to nitrogen-containing substrates was unsuccessful, and thus the one-pot orthoester formation-reduction of **47** gave only the *N*-methyl derivative **49**. This result shows that the presence of the nitrogen atom in the glycol prevents the formation of the corresponding orthoester intermediate, leading, instead, to the *N*-formyl derivative **48**, which was then reduced to the observed product. This mechanism was confirmed by the isolation of **48** before the addition of the reducing agent in a separate reaction (Scheme 26).

Protection of ribofuranose **50** using the same methodology gave a 1:1 mixture of monoprotected MOM products **52a** and **52b** via intermediate **51** (Scheme 27). Interestingly, treatment of the isolated intermediate **51** with DIBAL under the usual conditions did not lead to the products in the absence of CAN, but the reaction proceeded well when this catalyst was added. This result

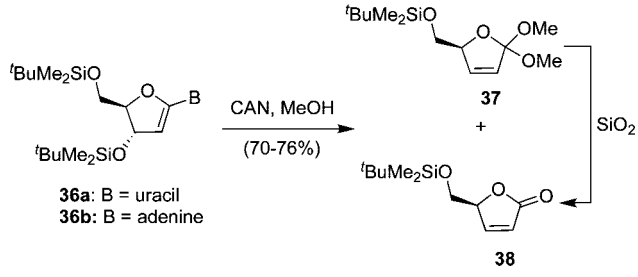
Table 13. Representative Examples of the CAN-Catalyzed Reaction of Glycals with Alcohols

entry	glycal	nucleophile	glycoside	yield (%)	anomer ratio α/β
1	**31**	methanol	**33a**	78	32/1
2	**31**	allyl alcohol	**33b**	74	4/1
3	**31**	cholesterol	**33c**	26	1.5/1
4	**31**	cyclohexanol	**33d**	63	8/1
5	**31**	*t*-butyl alcohol	**33e**	51	1.7/1
6	**31**		**33f**	52	2/1
7	**32**	methanol	**34a** (**35a**)	56 (38)	1.7/1(5/1)
8	**32**	allyl alcohol	**34b** (**35b**)	60 (23)	1.1/1(4.7/1)
9	**32**	cyclohexanol	**34c** (**35c**)	65 (18)	11.5/1 (only α)
10	**32**	*t*-butyl alcohol	**34d** (**35d**)	34 (44)	1.8/1(4.8/1)

Scheme 21



Scheme 22

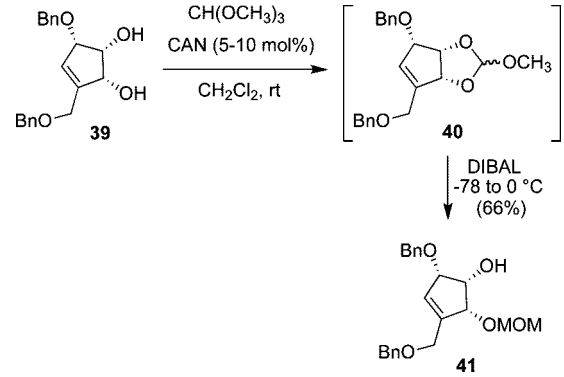


proves that the role of CAN in the selective monoprotection protocol is vital, not only for the orthoester formation step, but also for the subsequent reduction, which it accelerates by acting as a Lewis acid.

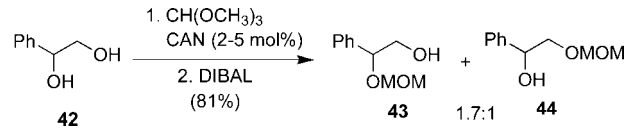
Some steroid-based substrates have also been protected under similar conditions. In the case of diol **53**, a mixture of both possible monoprotected regioisomers **54** was isolated in an excellent overall yield (Scheme 28). The more hindered substrate **55** gave a single MOM-protected product **56**, albeit in poor yield (Scheme 29).

3.2.1.6. Enol Ether Formation. Etherification of the enol form of cyclic 1,3-diketones by a range of alcohols in excellent yields has been reported in the presence of catalytic

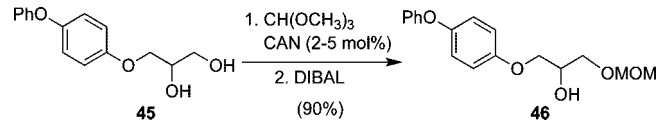
Scheme 23



Scheme 24



Scheme 25

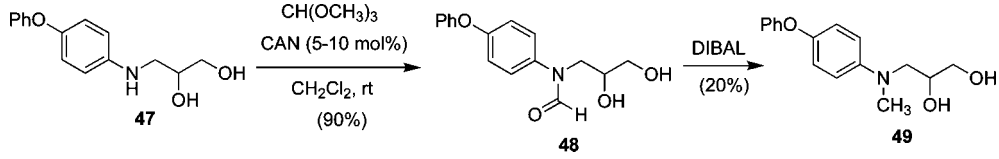


amounts of CAN (10 mol %) under mild conditions and short reaction times (Scheme 30).[46] The reverse deprotection has also been achieved by simply changing the reaction conditions to reflux in an acetonitrile−water mixture with 10 mol % of CAN, again in excellent yields.

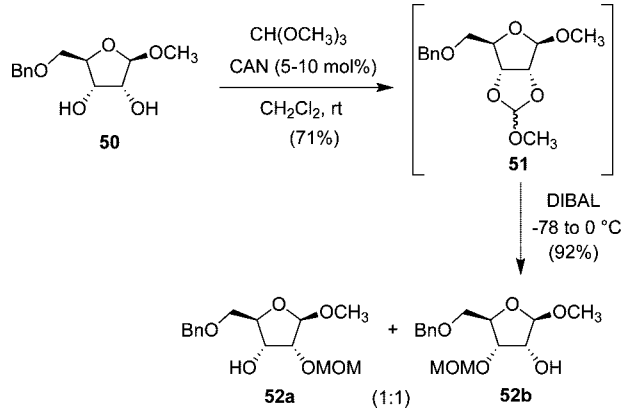
3.2.2. Esterification

Esterification, that is, the transformation of carboxylic acids into esters by treatment with the corresponding alcohols, is one of the classical transformations in organic

Scheme 26



Scheme 27

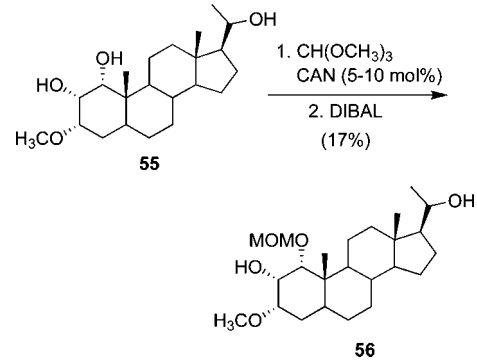


synthesis and is still of great significance. Carboxylic acids have been esterified effectively in the presence of 7 mol % CAN by a number of primary and biologically relevant secondary alcohols containing multifunctional groups (Scheme 31 and Figure 2).[47] Tertiary alcohols and aromatic acids failed to esterify under similar reaction conditions. A plausible mechanism has been proposed for the reaction, as shown in Scheme 31, considering that Ce(IV) acts as a Lewis acid.

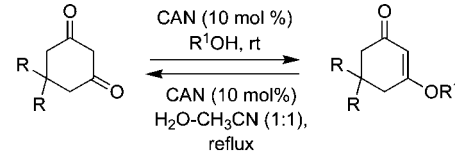
The acetylation of *t*-butyl alcohol with acetic anhydride in the presence of 1 mol % of CAN was first described as an isolated example.[48] A few years later, a variety of primary, secondary, tertiary alcohols, and phenols were effectively acetylated using a similar methodology (Scheme 32).[49] CAN was proposed to act as a Lewis acid by coordination with the acyl moiety of acetic anhydride, thereby increasing the electrophilicity of the carbonyl carbon.

Trimethylsilyl (TMS) is one of the most important protecting groups for alcohols, but it has the disadvantage of being unstable under strongly acidic conditions. On the other hand, unlike silyl groups, acetate tolerates acidic conditions. Hence, the direct conversion of silyl ethers into acetates is an interesting transformation in organic synthesis. Khosropour et al. reported an efficient one-pot conversion of silyl ethers into the corresponding acetates with acetic anhydride in the presence of 10 mol % of CAN immobilized on *n*-butylpyridinium tetrachloroferrate ([nbp]$FeCl_4$) under microwave irradiation (Scheme 33 and Figure 3).[50] The reaction was unsuccessful in the absence of CAN under similar conditions, which indicates that the ionic liquid acts as a solvent but has no catalytical role. The conversion was excellent irrespectively of the nature of the substituents on the aromatic ring. However, *t*-butyl trimethylsilyl ether

Scheme 29



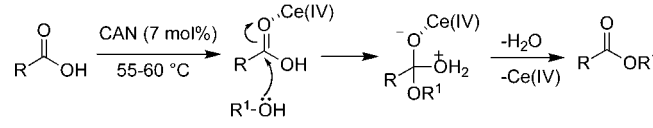
Scheme 30



a: R = H; R^1 = Me, 93%(91%); **b**: R = H; R^1 = Et, 91%(92%);
c: R = H; R^1 = $CH_3(CH_2)_2CH_2$, 88%(90%);
d: R = H; R^1 = $CH_3(CH_2)_4CH_2$, 86%(84%);
e: R = H; R^1 = Bn, 90%(88%); **f**: R = H; R^1 = $BnCH_2$, 89%(83%);
g: R = Me; R^1 = Propargyl, 89%(84%); **h**: R = Me; R^1 = Me, 92%(90%);
i: R = Me; R^1 = Et, 90%(89%); **j**: R = Me; R^1 = Allyl, 90%(87%);
k: R = H; R^1 = ^{i}Pr, 70%(80%); **l**: R = Me; R^1 = 3-methylcyclohexyl, 62%(75%)

Yields in brackets refer to the deprotection reaction

Scheme 31

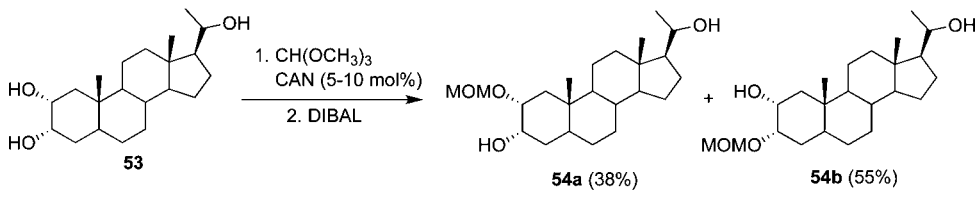


underwent deprotection to the corresponding alcohol without producing any acetate. A mixture of aryl-OTMS and alkyl-OTMS provided selectively the alkyl ester. It is important to note that the CAN−[nbp]$FeCl_4$ system could be recycled once without loss of its catalytic properties.

The mechanism proposed by the authors to explain this transformation is summarized in Scheme 34 and involves the temporary generation of a molecule of trimethylsilyl chloride.

In an article mainly related to the synthesis of chloroesters catalyzed by bismuth nitrate, one example of the effect of CAN as a catalyst in this transformation has also been described. Thus, acetyl chloride was found to react with

Scheme 28



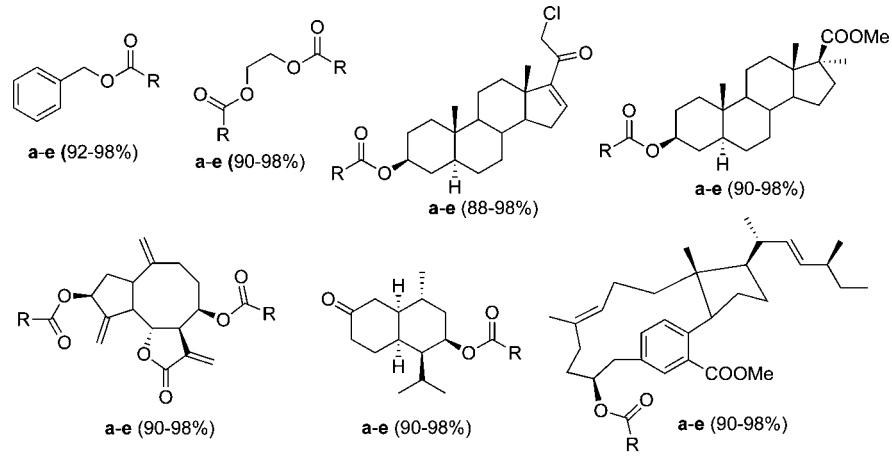
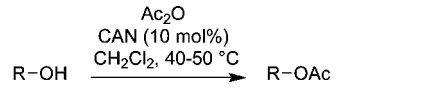


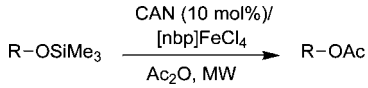
Figure 2.

Scheme 32



a: R = Bn, 86%; **b**: R = 2-chlorophenyl, 98%;
c: R = 4-methylphenyl, 95%; **d**: R = ^{n}decyl, 86%;
e: R = menthyl, 89%; **f**: R = cyclohexylmethyl, 86%;
g: R = $PhCHCH_3$, 89%; **h**: R = 4-nitrophenyl, 96%;
i: R = 2-naphthyl, 90%; **j**: R = $CH_3(CH_2)_9C(CH_3)_2$, 88%

Scheme 33



tetrahydrofuran in the presence of 5 mol % of CAN to afford the corresponding 4-chlorobutyl acetate in 85% yield (Scheme 35).[51]

3.2.3. Acylal Formation

Geminal diacetates (acylals) are excellent carbonyl protecting groups due to their stability in neutral, basic, and acidic media. Moreover, acylals are important precursors for the preparation of some interesting synthetic intermediates such as acyloxydienes and vinyl acetates, besides their industrial application as cross-linking reagents for cellulose in cotton. Roy and Banerjee reported

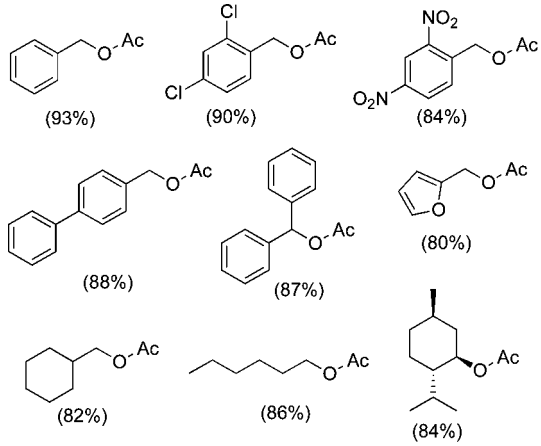
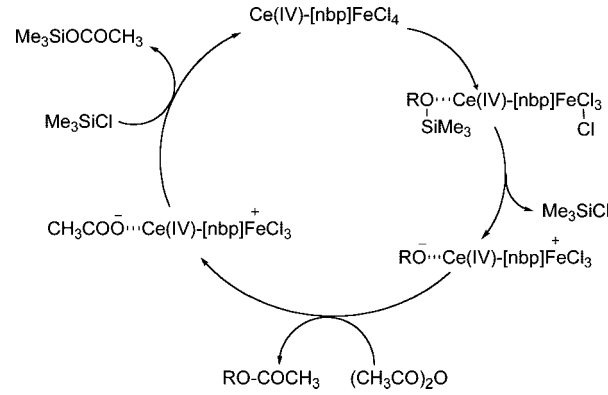
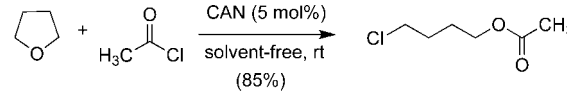


Figure 3.

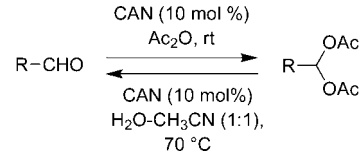
Scheme 34



Scheme 35



Scheme 36



an efficient method for the synthesis of acylals of aldehydes using CAN as the catalyst (10 mol %) under solvent-free conditions at room temperature (Scheme 36).[52] A number of aromatic and aliphatic aldehydes afforded the corresponding acylals in excellent yields, while the reaction involving cyclic and acylic ketones failed (Figure 4). The authors also reported a deprotection procedure for acylals using a catalytic amount of CAN in an acetonitrile−water solvent system under elevated temperature, which is also shown in Scheme 36 and Figure 4.

Shingare et al. employed the same methodology for the chemoselective protection and deprotection of 4-oxo-4*H*-1-benzopyran-3-carboxylates using 6 mol % of CAN (Scheme 37).[53] This reaction proceeded with complete chemoselectivity, because the ketone functionality remained unaffected, whereas the aldehyde group underwent the transformation into acylal in excellent yields.

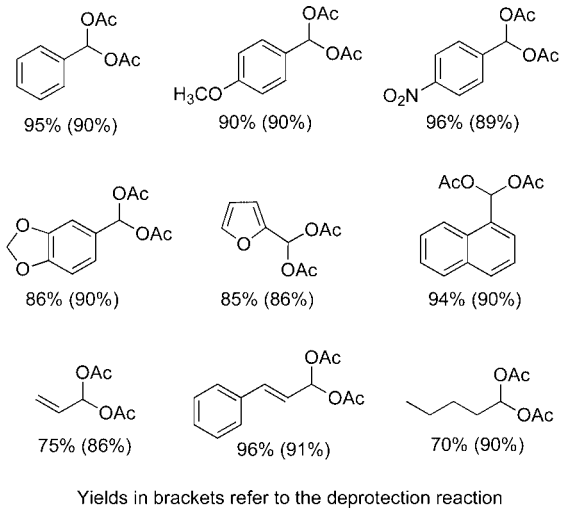
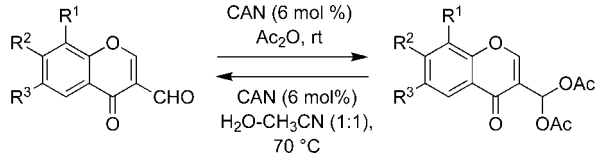


Figure 4.

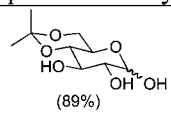
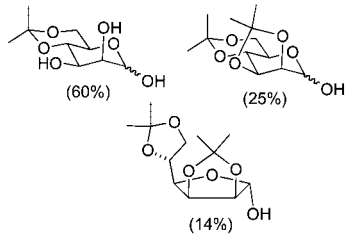
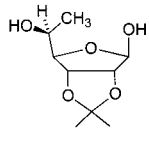
Scheme 37



a: $R^1 = R^2 = H$, $R^3 = Me$, 88%(88%); **b**: $R^1 = R^2 = H$, $R^3 = Cl$, 82%(91%); **c**: $R^1 = H$, $R^2 = Me$, $R^3 = H$, 81%(92%); **d**: $R^1 = R^2 = R^3 = H$, 89%(90%); **e**: $R^1 = R^3 = Cl$, $R^2 = H$, 90%(90%); **f**: $R^1 = Me$, $R^2 = H$, $R^3 = Cl$, 85%(90%); **g**: $R^1 = R^2 = H$, $R^3 = Br$, 85%(90%); **h**: $R^1 = R^2 = H$, $R^3 = F$, 87%(92%)

The yields in brackets refer to the deprotection reaction

Table 14. CAN-Catalyzed Acetonide Synthesis: Selected Examples

entry	substrate	products and yields (%)
1	D-glucose	 (89%)
2	D-mannose	 (60%), (25%), (14%)
3	L-rhamnose	 (88%)

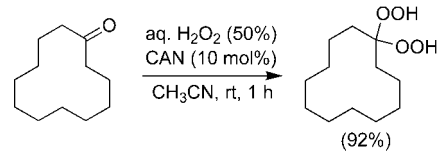
3.2.4. Acetonide Formation

CAN (20 mol %) effectively catalyzed the generation of carbohydrate acetonides in anhydrous DMF.[54] Although the reaction was useful for many substrates, the selectivity of the method was low in some cases when unprotected sugars were employed as starting materials. The results obtained in the protection of some representative monosaccharides are shown in Table 14.

Regarding disaccharide protection, the reaction of sucrose under the same conditions gave a mixture of a mono- and a diacetonide, which was the major product, as shown in Scheme 38.

Regarding the mechanism for the acylal formation, the authors first considered the possible role of CAN as a one-electron oxidant, but found that the reaction was not modified by the addition of radical traps (e.g., 2,4,6-tri-*tert*-butylphenol). The reaction did not proceed after the addition of potassium carbonate or pyridine, which could suggest catalysis by a protic acid, but on the other hand the reaction was found to take place in the presence of the more crowded 2,6-di-*tert*-butyl-4-methylpyridine. This ruled out acid catalysis by the ammonium cation or by protons arising from the hydrolysis of CAN, which in any case was improbable because of the anhydrous conditions employed. Therefore, the authors suggest that CAN acts as a Lewis acid, and that pyridine or the carbonate anion decreasees reactivity by forming a stable complex with Ce(IV).

Scheme 39



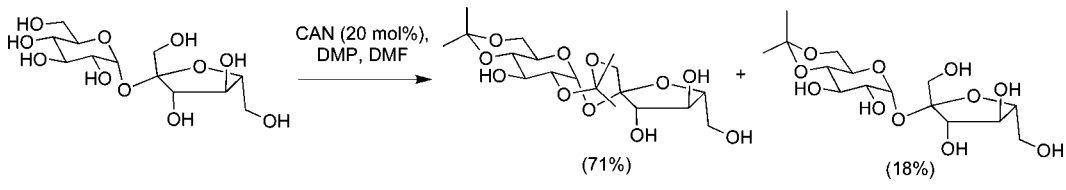
3.2.5. Dihydroperoxidation

Ketones have been converted into the corresponding *gem*-dihydroperoxides with aqueous hydrogen peroxide in the presence of CAN under mild conditions (Scheme 39).[55] CAN was proposed to act as a Lewis acid, activating the carbonyl group and increasing the electrophilic character of the carbonyl carbon atom. The reactions were excellent with both cyclic and acylic ketones, and in the case of aryl ketones and benzaldehyde derivatives, the presence of electron-withdrawing substituents was shown to be detrimental for yield.

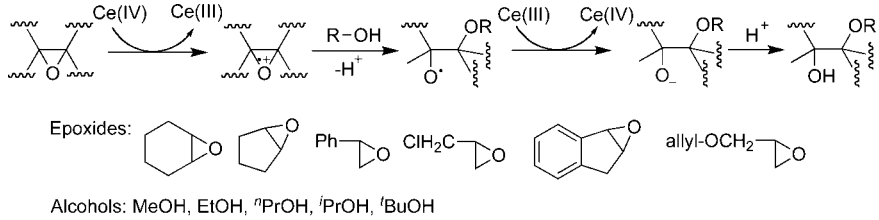
3.2.6. Epoxide Opening by Oxygen Nucleophiles

One of the best methods for the synthesis of protected 1,2-diol systems is the ring-opening of epoxides by alcohols. Generally, the ring-opening of epoxides has been achieved under acidic conditions, but these have disadvantages such as low regioselectivity and a possibility for polymerization. Lewis acids are the main alternative to carry out these transformations, and in this context Iranpoor and Baltork developed the conditions for opening the epoxide ring system by a range of alcohols in the presence of substoichiometric amounts of CAN with excellent selectivity and in very high

Scheme 38



Scheme 40



yields (Scheme 40).[56] A year later, the same group extended the scope of their method to include the use of water, acetic acid, and thiols as nucleophiles.[57] The authors proposed that the reaction occurred through a one-electron transfer reaction with the initial formation of the epoxonium radical cation. The formation of a radical cation was initially believed to be confirmed by the loss in yield observed in the presence of large excess of acrylamide as a radical trap, together with the generation of polyacrylamide. However, this proposal was ruled out by subsequent studies that proved that CAN itself may catalyze the polymerization of acrylamide (see below).

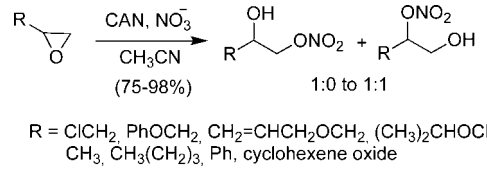
Lessard et al. carried out a set of experiments to explore the mechanism of the alcoholysis of allylic and benzylic alcohols and of epoxides in the presence of CAN.[58] As previously mentioned, Iranpoor had proposed for these reactions a radical mechanism, which was supported in principle by experiments involving use of acrylamide as a radical trap.[56] They found that the reactions gave similar yields when using 5 mol % of CAN instead of 20−60 mol % as described in the Iranpoor methodology. Furthermore, very similar results were obtained with 5−20 mol % of sulfuric acid. Potentiometric titration studies revealed that the molar fraction of Ce(IV) continuously decreased during the reaction to reach zero after 4 h irrespective of the presence of the substrate, which clearly suggested that the reaction is not catalytic with respect to Ce(IV). The reason for the consumption of CAN was identified to be the formation of formaldehyde by oxidation of methanol by CAN, which was confirmed by trapping the aldehyde with 5,5-dimethyl-1,3-cyclohexanedione in the absence or in the presence of the organic substrate.

The evidence for the radical mechanism given by Iranpoor was that the addition of acrylamide (a radical trap) prevented the reaction, but it was proved by Lessard that CAN effectively catalyzed the polymerization of acrylamide, and therefore the acrylamide experiments cannot be taken as evidence for the mechanism proposed by Iranpoor. Lewis acids such as $AlCl_3$ also catalyzed the polymerization reaction with excellent yields. On the basis of the above evidence, Lessard ruled out Iranpoor's radical mechanism and proposed that the reaction was catalyzed by protons generated from the oxidation of methanol in the presence of CAN, and not directly by CAN.

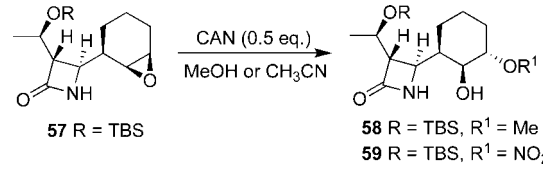
Epoxides containing either activating or deactivating groups have been converted into the corresponding alkyl nitrates with CAN alone or with catalytic CAN in the presence of excess nitrate ion in the form of ammonium nitrate or tetrabutyl ammonium nitrate (Scheme 41).[59] The yields were excellent in most cases, but the reactions showed poor regioselectivity.

The key step for the synthesis of precursor of 4-alkoxytrinems, a family of tricyclic natural β-lactam derivatives, has been carried out by means of a CAN-catalyzed epoxide opening reaction. The reaction of compound **57** with 0.5 equiv of CAN furnished the 1,2-diol derivatives **58** and/or **59**, depending on the solvent used, where the nitro group in **59** arises from CAN. In methanol, a mixture of both compounds were isolated, but in acetonitrile **59** was formed exclusively (Scheme 42).[60]

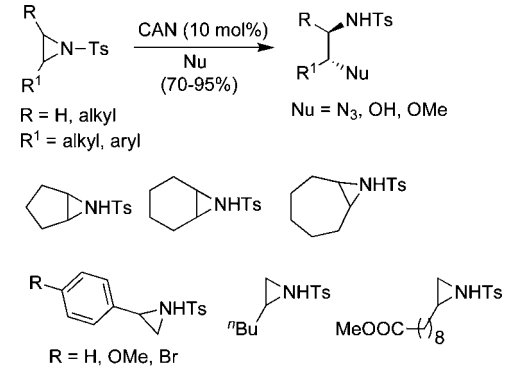
Scheme 41



Scheme 42



Scheme 43



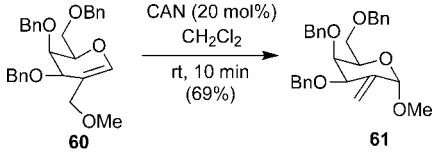
3.2.7. Aziridine Opening by Oxygen Nucleophiles

Ring-opening of aziridines provides a valuable method for the preparation of β-functionalized amines. Chandrasekhar et al. demonstrated the ring-opening of *N*-tosylaziridines by nucleophiles such as water and methanol in the presence of CAN (Scheme 43).[61] With a few exceptions, excellent regioselectivities were observed irrespective of the nature of the nucleophiles. Nitrogen nucleophiles, such as the azide anion, were also employed. In the same period, another article appeared dealing with similar chemistry where water and aliphatic primary amines were employed as nucleophiles.[62]

3.2.8. 1,3-Alkoxy Migration in Glycal Ethers

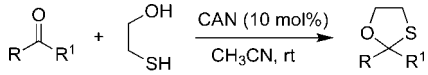
One example of a CAN-catalyzed 1,3-alkoxy migration that leads to Ferrier-type products bearing an exocyclic rather than the usual endocyclic C═C bond has been described, although indium trichloride was subsequently identified as

Scheme 44



60 61

Scheme 45



a better catalyst for this transformation. Thus, treatment of compound **60** with CAN in dry dichloromethane induced a 1,3-shift of the methoxy group to afford compound **61** in 69% yield in just 10 min at room temperature (Scheme 44).[63]

3.3. Reactions Involving the Formation of C−S and C−Se Bonds

3.3.1. 1,3-Oxathiane Synthesis and Thioacetylation

Similarly to acetal and acylal formation, protection of carbonyl compounds to thioacetals is also important in multistep organic synthesis. Maiti and Roy reported a mild procedure for the formation of thioacetals from carbonyl compounds in acetonitrile using CAN as a catalyst (Scheme 45 and Figure 5),[64] finding that the reaction can be performed successfully on aromatic and aliphatic aldehydes, and also on ketones.

The Roy group also reported a thioacetalization method for carbonyl compounds in the presence of catalytic amount of CAN in chloroform (Scheme 46).[65] The reaction showed complete chemoselectivity for the aldehyde when carried out on a mixture of benzaldehyde and acetophenone.

3.3.2. Thioglycosidation

Using a procedure related to the glycosidation mentioned in section 3.2.1.4, the thioglycosidation of glycals has also been attained using a CAN-catalyzed reaction. Reaction of glycals **62** with 10 mol % of CAN and ethanethiol in acetonitrile afforded the 2-deoxy-1-thioglycosides **63** as

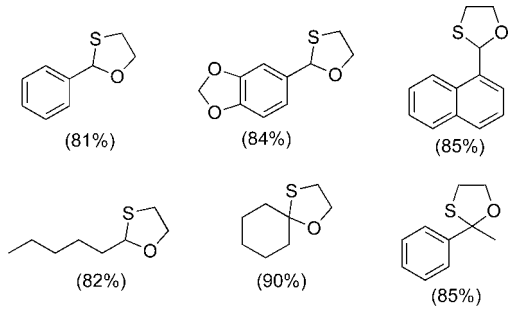
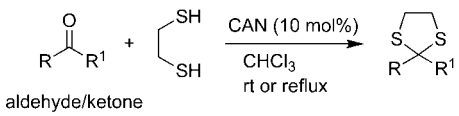


Figure 5.

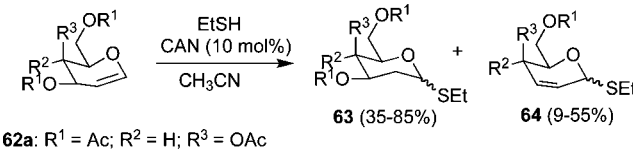
Scheme 46



aldehyde/ketone

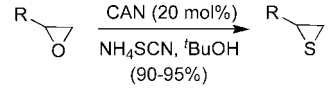
a: benzaldehyde, 85%; **b**: 3,4-dimethoxybenzaldehyde, 75%; **c**: 3-OMe-4-OCH_2Ph-C_6H_3CHO, 96%; **d**: ^{n}hexanal, 80%; **e**: 2-methylpropanal, 80%; **f**: crotonaldehyde, 70%; **g**: cyclopentanone, 82%; **h**: cyclohexanone, 87%

Scheme 47



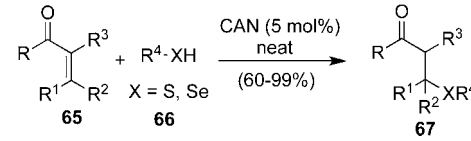
62a: R^1 = Ac; R^2 = H; R^3 = OAc
62b: R^1 = Ac; R^2 = OAc; R^3 = H
62c: R^1 = Bn; R^2 = H; R^3 = OBn
62d: R^1 = Bn; R^2 = OBn; R^3 = H

Scheme 48



R = Ph, CH_3, $CH_3(CH_2)_3$, $ClCH_2$, $PhOCH_2$, CH_2=$CHCH_2OCH_2$, $(CH_3)_2CHOCH_2$, $HOCH_2$
Also for cylopentene, cyclohexene, cyclooctene oxides

Scheme 49



65 66 67

mixtures of α- and β-anomers (Scheme 47).[66] Apart from the thioglycosides, Ferrier products **64** were also formed under the reaction conditions as minor products, especially in the case of glucals in comparison with galactals. All attempts to minimize or avoid the Ferrier products by changing reaction conditions, solvents, and catalyst load were unsuccessful.

3.3.3. Epoxide Opening by Sulfur Nucleophiles

Following the work described in ref 57, which first demonstrated the use of thiols as nucleophiles for epoxide opening, the same group reported the synthesis of thiiranes from epoxides using thiocyanate as nucleophile (Scheme 48).[67] Reactions of different epoxides with ammonium thiocyanate in *t*-butyl alcohol in the presence of 20 mol % CAN afforded excellent yields of the thiiranes in short reaction times.

Thiourea has been used as the source of sulfur for the CAN-catalyzed conversion of epoxides to thiiranes. The reaction was carried out under both conventional heating and microwave conditions, and a considerable rate enhancement was observed in the case of microwave irradiation.[68]

3.3.4. Michael Additions of S and Se Nucleophiles

1,4-Additions of thiols and benzeneselenol to α,β-unsaturated ketones in the presence of CAN under solvent-free conditions have been extensively studied by the Yao group (Scheme 49 and Figure 6).[69] The reaction of a variety of cyclic and acylic α,β-unsaturated ketones **65** with thiols and benzeneselenol **66** in the presence of 10 mol % of CAN afforded the Michael adducts **67** in excellent yields and very short reaction times.

The mechanism proposed for this transformation was based on the single-electron transfer ability of Ce(IV). According to this proposal, the reaction of the starting thiol with CAN would lead to the corresponding thiyl radical cation, and subsequently to a thiyl radical from the fragmentation of the radical cation. This thiyl radical then would undergo a radical chain addition to the enone to form the final 1,4-addition

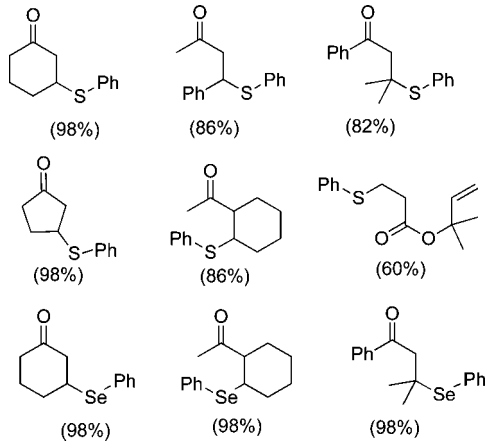
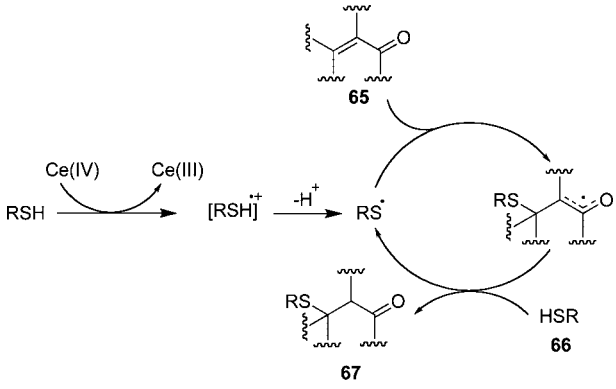


Figure 6.

Scheme 50



product. However, no solid evidence was given to prove the formation of radical or radical cation intermediates (Scheme 50).

3.4. Reactions Involving C−N Bond Formation

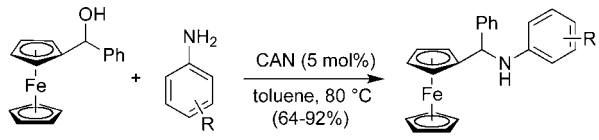
3.4.1. Nucleophilic Substitution Reactions Involving Nitrogen Nucleophiles

The reaction of (ferrocenyl)(phenyl)methanol with a variety of arylamines in toluene at 80 °C furnished the amination products in very good yields in the presence of CAN (Scheme 51).[70] However, other Lewis acids such as $InCl_3$, I_2, $CeCl_3$, and $Bi(NO_3)_3 \cdot 5H_2O$ and solvents like 1,4-dioxane, nitromethane, and acetonitrile were also found to be equally effective. The authors proposed a mechanism involving the formation of a carbocation intermediate followed by nucleophilic substitution by amines. For the related reactions of ferrocenyl alcohols and C-nucleophiles and for a more detailed mechanistic discussion, see section 6.2.

3.4.2. Epoxide Opening by Nitrogen Nucleophiles

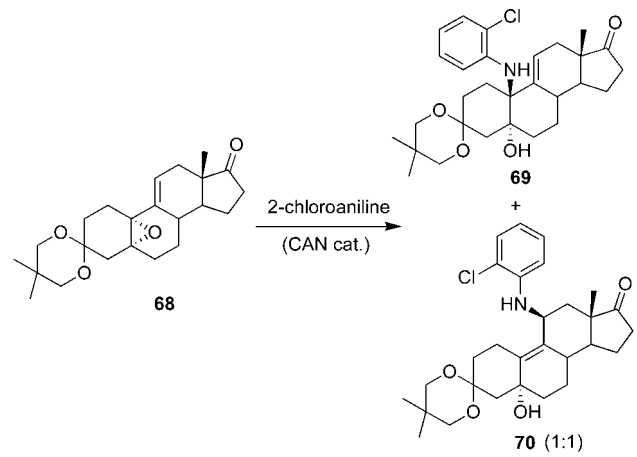
Neef et al. reported the reaction of 2-chloroaniline with the steroidal epoxide **68** in the presence of a substoichiometric amount of CAN. S_N2 and S_N2' products **69** and **70**

Scheme 51

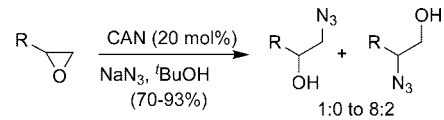


R = H, OMe, Me, Cl, Br

Scheme 52

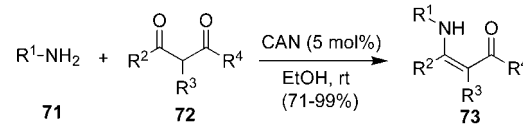


Scheme 53



R = Ph, $ClCH_2$, $PhOCH_2$, $CH_2{=}CHCH_2OCH_2$, $(CH_3)_2CHOCH_2$, ^{n}Bu and cyclohexene oxide

Scheme 54



71: R^1 = aryl, alkyl, Bn
72: cyclic and acyclic1,3-dicarbonyls

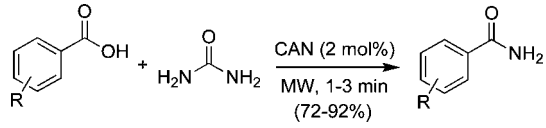
were isolated in a 1:1 ratio (Scheme 52).[71] Nevertheless, the reaction of **68** with methanol gave almost exclusively the S_N2 product.

The regioselective azidolysis of epoxides has been reported by Iranpoor.[72] Excellent conversions and selectivities were observed in the reaction of epoxides and sodium azide in the presence of 20 mol % of CAN in *t*-butyl alcohol under mild conditions (Scheme 53).

3.4.3. β-Enaminone Generation

The wide range of synthetic applications of β-enaminones,[73] such as the preparation of heterocycles, including alkaloids, α- and β-amino acids, peptides, and other synthetically relevant compounds, made their preparation from β-dicarbonyl derivatives attractive. The first report on the CAN-catalyzed synthesis of β-enaminones appeared in 2006 and had two important limitations, the need for sonication to enhance the reaction and the fact that it was restricted to acetylacetone as substrate.[74] A few months later, we reported a general, mild, and efficient synthesis of β-enaminones from β-dicarbonyl compounds and primary amines using CAN as a catalyst in ethanol at room temperature.[75] The reactions tolerate aliphatic amines, aryl amines containing both electron-withdrawing and -donating substituents, acyclic and cyclic β-ketoesters, β-ketothioesters, and β-diketones (Scheme 54). Another interesting feature of this method is the fact that a large number of solvents were effective in this reaction, including DCM, 1,4-dioxane, THF, methanol, acetonitrile, chloroform, and water. Almost simultaneously, Mo et al.

Scheme 55



described the application of a very similar methodology for the synthesis of β-enaminones,[76] and another paper describing the same methodology was published in 2008 with additional examples but without any significant improvements.[77]

3.4.4. Amide Formation

Microwave irradiation was found to be useful for the CAN-promoted synthesis of amides from carboxylic acids and urea under solvent-free conditions (Scheme 55 and Figure 7).[78] The generality and scope of the reaction was demonstrated by conducting it with a number of structurally diverse substrates such as simple carboxylic acids, hetero aromatic acids, α,β-unsaturated acids, phenylacetic acids, and sterically hindered aliphatic acids. It was found that compounds containing electron-withdrawing groups reacted at a relatively slower rate.

3.4.5. Aza-Michael Reactions

CAN-effectively catalyzed the Michael-type addition of aliphatic amines to α,β-unsaturated carbonyl compounds in water.[79] Acetonitrile and methanol were also found to be very effective as solvents in terms of yields and reaction time. Several aliphatic secondary amines gave the aza-Michael adducts in excellent yields, while the aliphatic primary amine, cyclohexylamine, afforded the bis-adducts. Anilines failed to react with Michael acceptors under similar conditions (Scheme 56).

In the same period, Duan et al. reported an aza-Michael addition protocol suitable for arylamines.[80] A variety of aryl, aliphatic primary, and secondary amines reacted with ethyl acrylate and acrylonitrile in THF at 60 °C in the presence

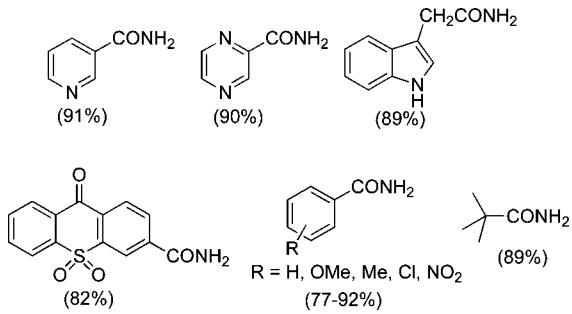
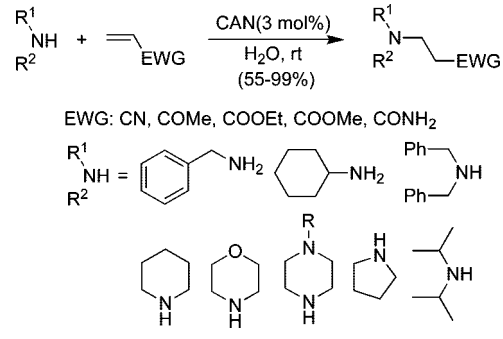
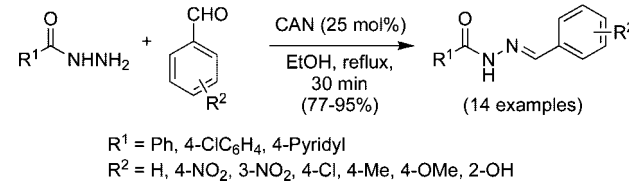


Figure 7.

Scheme 56



Scheme 57



of 10 mol % of CAN to give the Michael adducts in very good to excellent yields. Primary aromatic amines with electron-donating group gave better results, and a strongly electron-withdrawing group (NO_2) gave no conversion. The reaction of *N*-methylaniline with ethyl acrylate failed to give the product under the standard experimental conditions, but ultrasound irradiation led to the desired product in 83% yield. Application of sonication to all other reactions significantly reduced the reaction time without decreasing the yields.

3.4.6. Synthesis of Acyl Hydrazones

The reaction between acyl hydrazides and aryl aldehydes in the presence of 25 mol % of CAN in refluxing ethanol afforded the acyl hydrazones in excellent yields. These compounds were subsequently converted into 1,3,4-oxadiazoles in the presence of CAN, but this transformation required an equimolecular quantity of the cerium salt (Scheme 57). The reaction tolerated a variety of functional groups on both the hydrazide and the aldehyde partners.[81a]

3.4.7. Azobenzene Synthesis

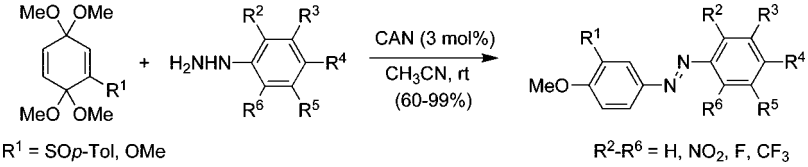
Azobenzenes have been synthesized by a direct reaction between quinone bisacetals and arylhydrazines (Scheme 58).[81b] The excellent yields and short reaction times reached in the presence of CAN were shown to be general for many quinone bisacetals and arylhydrazines. For instance, the 2-(*p*-tolylsulfinyl)-substituted bisacetal reacted with arylhydrazines in acetonitrile to furnish the azo derivatives. This excellent procedure was extended to other types of quinone-derived compounds. Thus, 4-azophenol was prepared in 88% yield by reacting *p*-benzoquinone with 4-trifluoromethyl-2,3,5,6-tetrafluorophenylhydrazine **74** in the presence of 3 mol % of CAN (Scheme 59). The *p*-quinol derivative **75** was also found to be a good substrate (Scheme 60). This report described the first mild and high-yielding methodology for the synthesis of azocompounds from commercially available or easily accessible starting materials.

3.5. Reactions Involving C−Halogen Bond Formation

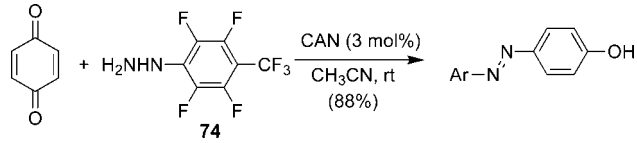
3.5.1. Aromatic Halogenation

In the presence of CAN, acetyl chloride, which is a well-known acetylating agent and had never been previously reported to chlorinate aromatic compounds, was found to be an effective reagent for the chlorination of activated aromatic compounds.[82] Thus, stoichiometric amounts of acetyl chloride reacted with activated aryl compounds bearing methyl, methoxy, and *N*,*N*-disubstituted amino groups in the presence of 10 mol % of CAN to give monochlorinated compounds in very good yields (Scheme 61). As expected, aniline and phenol gave the acetylated products, while acetanilide furnished the chlorinated product. The reaction failed in the case of deactivated aromatics such as nitrobenzene, benzaldehyde, ethyl benzoate, and benzoic acid.

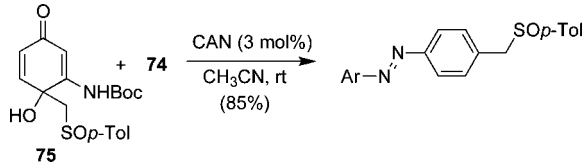
Scheme 58



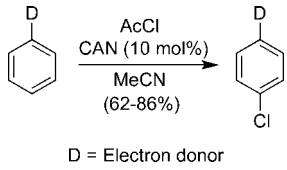
Scheme 59



Scheme 60



Scheme 61

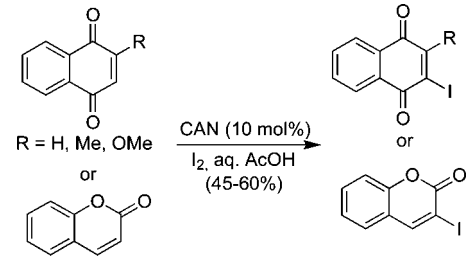


Scheme 62

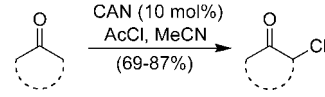
Aromatic aldehydes have been effectively brominated by Br_2 in the presence of a SiO_2/CAN catalyst.[83] Although a method was already available for the bromination of phenols using silica gel as a catalyst,[84] a new catalytic system was developed by mixing CAN with silica gel that was found to overcome previous limitations and to improve the scope of the reaction in terms of yield and selectivity. This system was tested in the reaction of a number of aromatic aldehydes with bromine, finding that two electron-releasing groups in the substrate were ideal and that the reactions involving substrates with electron-withdrawing groups failed. The best example to prove the selectivity of the method was the bromination of 2-hydroxy-5-methylbenzaldehyde (Scheme 62). A mixture of products arising from aromatic mono-, di-, and trihalogenation, together with another one from benzylic bromination, was observed in the reaction catalyzed by silica gel alone. Surprisingly, the CAN/SiO_2-catalyzed reaction furnished only a monobrominated product, 3-bromo-2-hydroxy-5-methylbenzaldehyde, in 95% yield. The reason for this excellent selectivity was proposed to be the coordination of Ce(IV) as a Lewis acid with the carbonyl group in the substrate, leading to a lower electron density in the aromatic ring. These coordination phenomena were confirmed by infrared spectral studies.

The generation of bromine radical and bromine cation from bromine can take place with the help of the Lewis and Brønsted acidic sites on silica gel, and these species can be stabilized by groups behaving as Lewis bases at the silica gel surface.[53,85] CAN acts both as a Lewis acid and as an oxidant that transforms the bromine radical to bromine cation.

Scheme 63



Scheme 64



Das et al. reported a mild and efficient procedure for the iodination of activated aromatic compounds by molecular iodine in the presence of catalytic amount of CAN.[86] The reaction was highly regioselective, and only monoiodination products were isolated, always in excellent yields. High *para*-selectivity was observed in the presence of alkoxy and amino groups, while *ortho*-products were the major ones for phenolic compounds. *ortho*-Iodination was also observed when the *para*-position was blocked with substituents other than hydroxy.

3.5.2. α-Halogenation of Carbonyl Compounds

Naphthoquinones and coumarin have been iodinated in moderate yields by molecular iodine with 10 mol % of CAN in aqueous acetic acid (Scheme 63).[87]

As an extension of the work described in ref 82, the same authors reported the *ortho*-chlorination of a number of cyclic and acyclic ketones by acetyl chloride and CAN (Scheme 64).[88]

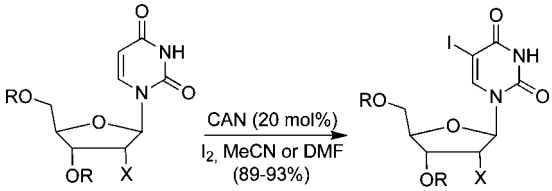
3.5.3. α-Halogenation of Enaminones

5-Iodo-2-deoxyuridine has an excellent antiviral activity,[89] which motivated organic chemists to prepare other 5-iodo-uracil nucleosides. Asakura and Robins reported a facile C_5-iodination of uracil nucleosides by molecular iodine and 20 mol % of CAN in acetonitrile or DMF, in excellent yields (Scheme 65).[90]

3.5.4. Epoxide Opening by Halides

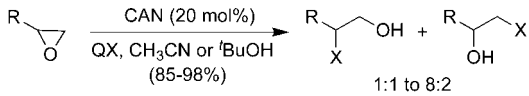
A synthesis of β-halohydrins has been achieved by a CAN-catalyzed ring-opening of epoxides with quaternary ammonium chlorides and bromides in acetonitrile or in *tert*-butyl alcohol (Scheme 66).[91]

Scheme 65



a: R = Ac, X = OAc; **b**: R = Bz, X = OBz;
c: R = Ac, X = H; **d**: R = H, X = OH

Scheme 66



QX = ^{n}Bu$_3$BnNCl, NH$_4$Cl, ^{n}Bu$_4$NBr, NH$_4$Br

R = Ph, CH$_3$, ClCH$_2$, PhOCH$_2$, CH$_2$=CHCH$_2$OCH$_2$, (CH$_3$)$_2$CHOCH$_2$, cyclohexene oxide

4. Reactions Involving the Cleavage of Carbon−Heteroatom Bonds

4.1. Introduction

Breaking carbon−heteroatom bonds is essential in deprotection reactions. The recent introduction of CAN as a catalyst in this type of transformations has introduced a very useful tool for the practitioner of organic synthesis, as will be shown in this section.

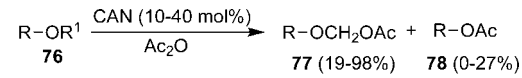
4.2. Functional Group Deprotection Involving the Cleavage of C−O and C−N Bonds

4.2.1. Cleavage of Ethers and Secondary Amines

The special features of the 2-methoxyethoxymethyl (MEM) group, including comparatively good stability to protic acids, make this group attractive for the protection of hydroxyl groups. While MEM can be removed by Lewis acids such as $ZnBr_2$ or $TiCl_4$, the development of a deprotection protocol involving a more stable, easily handled reagent was considered important, and CAN was found suitable for this purpose. Thus, the reaction of MEM ethers **76** with a catalytic amount of CAN and acetic anhydride furnished mixed acetal esters **77** and acetates **78**, which could be easily converted into the corresponding alcohols by alkaline hydrolysis.[92] Cyclododecyl MEM ether reacted with 10 mol % of CAN in acetic anhydride at room temperature to afford cyclododecyloxymethyl acetate in 82% yield in 24 h. An increase of the catalytic load to 40 mol % decreased the reaction time to 5 h. Many other secondary and tertiary MEM ethers gave the mixed acetal esters **77**, while primary MEM ethers provided **77** together with a small amount of acetates **78** (Scheme 67, Table 15). Compounds **77** and **78** were quantitatively converted into their corresponding alcohols by NaOMe/MeOH treatment.[93] This protocol was extended to the methoxymethyl (MOM) group and was also successfully carried out in the presence of other protecting groups such as silyl ethers.

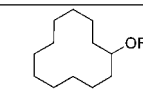
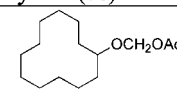
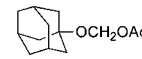
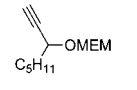
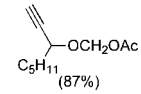
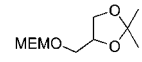
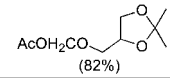
The authors proposed the formation of NO_2^+ cation as the reaction catalyst, citing as evidence the fact that the reaction

Scheme 67



R^1 = MEM or MOM

Table 15. Selected Examples of the Exchange of the MEM or MOM Protections with an Acetyl Group

entry	substrate **76**	product(s) **77**, **78** yield (%)
1	 R = MEM or MOM	 (82-86%)
2		 (90%)
3		 (87%)
4	$C_{12}H_{25}$−OR R = MEM or MOM	$C_{12}H_{25}$−OCH_2OAc (66-72%) $C_{12}H_{25}$−OAc (21-27%)
5		 (82%)

could be also catalyzed by NO_2BF_4, although the results were not completely identical to those observed in the presence of CAN. They proposed that CAN, acting as a Lewis acid, reacts with acetic anhydride to produce acetyl nitrate, which could then generate the NO_2^+ species according to the mechanism described in Scheme 68. The possibility of generation of protic acids from the hydrolysis of CAN was ruled out because silyl ethers are stable in the experimental conditions.

Hwu et al. reported an efficient CAN-catalyzed deprotection of trityl and monomethoxytrityl groups in the context of nucleoside and nucleotide chemistry.[94] For instance, the tritylated adenosine 3′,5′-monophosphoramide **79** reacted with 10 mol % of CAN in a wet acetonitrile/DMF mixture to give the deprotected nucleotide **80** in 90% yield (Scheme 69).

This method was subsequently found to be general and was applied to a variety of nucleosides bearing a tritylated hydroxyl or amino group (Scheme 70 and Figure 8).

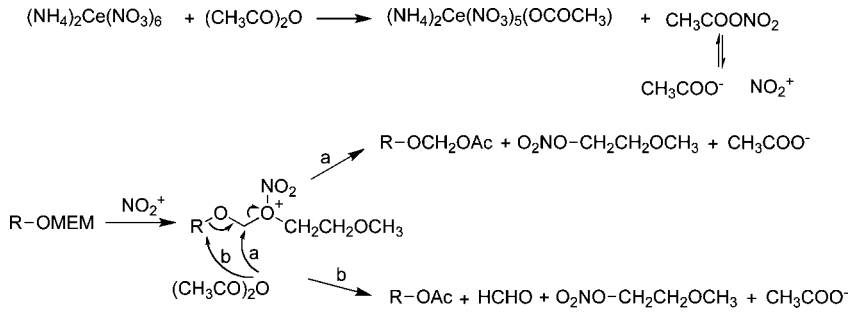
The related 5′-*O*-mono(*p*-methoxy)-trityl group (MMTr) has also been removed in similar conditions. For instance, treatment of dinucleotide **81** with CAN in acetonitrile afforded 91% yield of the deprotected compound **82**, while leaving intact the *tert*-butyldimethylsilyl protections (Scheme 71).

A few years later, the same group extended their study to a large number and variety of substrates[95] and proved that CAN alone or CAN adsorbed on silica effectively catalyzed the deprotection of the trityl (Tr), monomethoxytrityl (MMTr), dimethoxytrityl (DMTr), TBDMS, and TIPS groups from alcohols or amines, while leaving intact the acetonide group, as shown in Scheme 72 for the reaction that affords compound **84** starting from **83**. On the other hand, the use of CAN/SiO_2 led to the fully deprotected compound **85** in almost quantitative yield (Scheme 72; regarding acetonide cleavage, see also section 4.2.4).

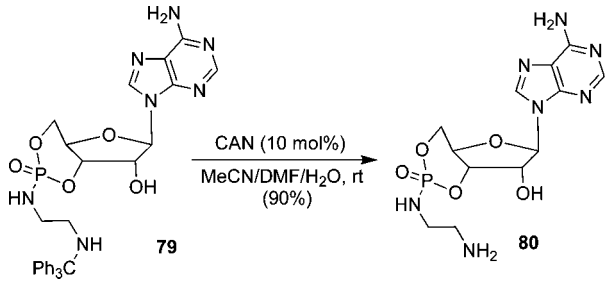
Both *N*- and *O*-protected trityl groups have been successfully removed in one synthetic operation by this methodology (Scheme 73). The reaction time was reduced significantly, and the yields were improved by the use of CAN adsorbed on silica gel.

This deprotection protocol tolerated well the presence of acid-sensitive groups. For example, detritylation of 1-benzoyl-3-(tryphenylmethyl)glycerol **86** using CAN or CAN/SiO_2 (10 mol %) afforded the deprotected product **87** in

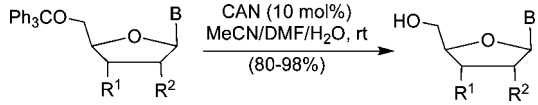
Scheme 68



Scheme 69



Scheme 70



excellent yield without affecting the benzoyl group, while the same reaction gave a mixture of products when the deprotection was performed with 5% TFA (Scheme 74). This methodology was also extended to the deprotection of silyl groups (see section 5).

Concerning the mechanism of the silica-supported CAN-catalyzed reaction, formation of nitric acid from CAN was ruled out because the pH values of the solutions remained constant during the course of the reaction. The authors proposed a radical mechanism where cerium(IV) would oxidize the $ROCPh_3$ moiety to the corresponding radical cation while cerium is reduced to the Ce(III) state. The rate of the reaction depended upon the stability of the resultant carbocation, as evidenced by the fact that the deprotection of dinucleotide **81** occurred about 10 times faster than the deprotection of 5′-*O*-trityladenosine because the MMTr cation is more stable than the CPh_3^+ cation (Scheme 75).

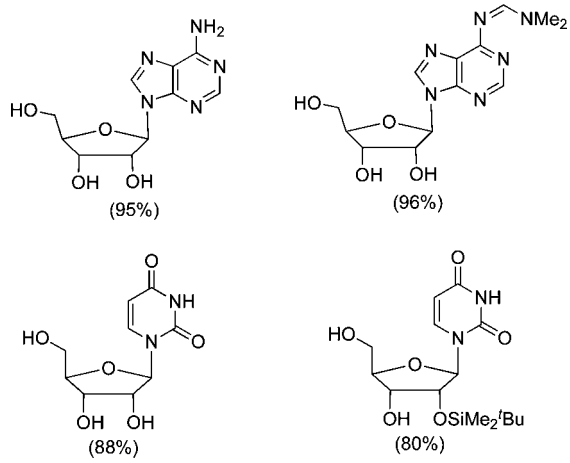
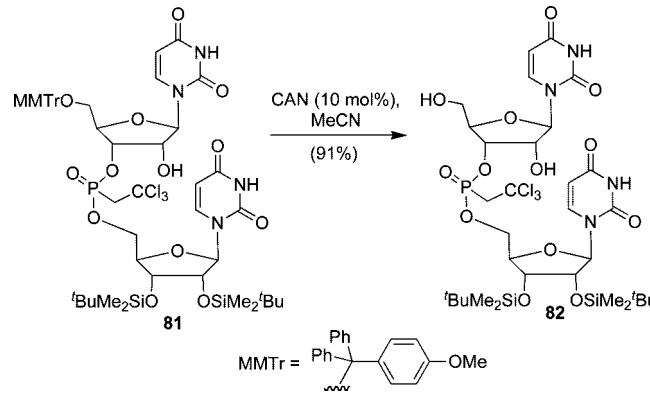
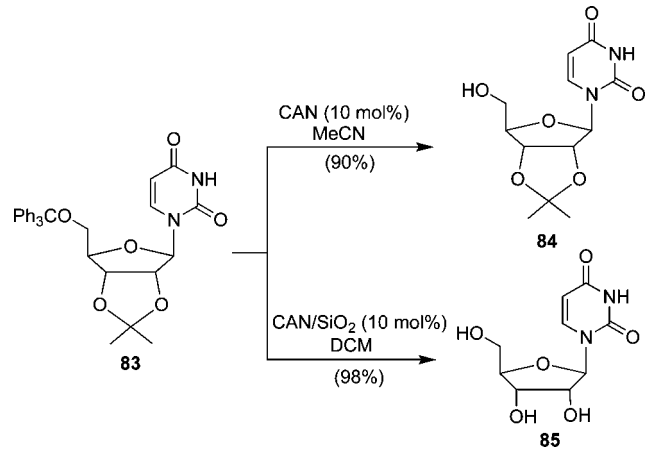


Figure 8.

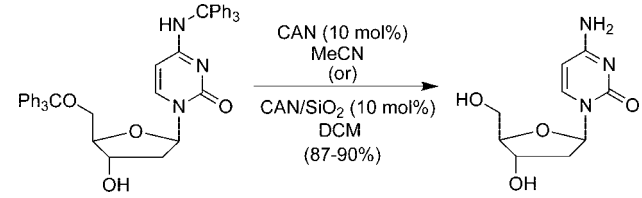
Scheme 71



Scheme 72



Scheme 73

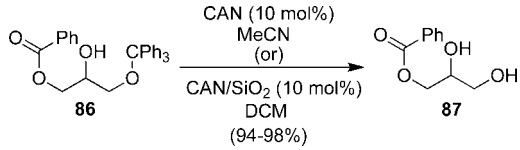


For the CAN-catalyzed deprotection of tetrahydrofuryl and tetrahydropyranyl ethers, see section 4.2.3.

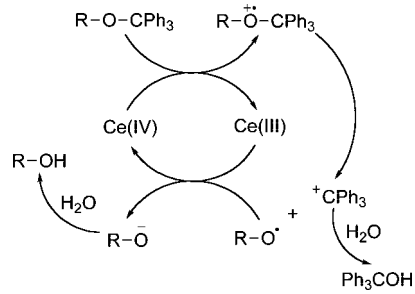
4.2.2. t-Butoxycarbonyl Group Cleavage

The *t*-butoxycarbonyl (BOC, *t*-Boc) group is one of the main protecting groups for amines, alcohols, and thiols. Removal of this group from a variety of substrates including carbamates, carbonates, carbonothioates, and simple esters has been achieved, in nearly quantitative yields, by treatment with 20 mol % of CAN in acetonitrile under reflux conditions

Scheme 74



Scheme 75



Scheme 76

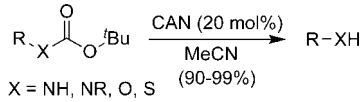
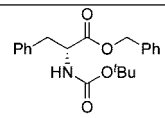
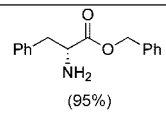
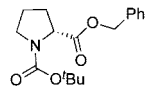
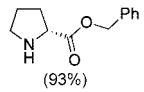
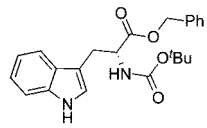
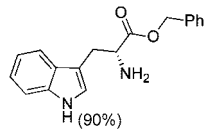
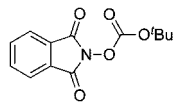
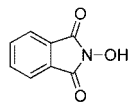
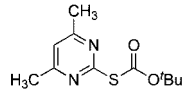
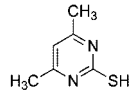
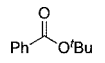


Table 16. Representative Examples of the CAN-Catalyzed BOC Deprotection

entry	substrate	product, yield (%)
1		 (95%)
2		 (93%)
3		 (90%)
4		 (99%)
5		 (96%)
6		 (98%)

(Scheme 76, Table 16).[96] A radical mechanism similar to the one previously discussed has been proposed.

The same authors also observed the removal of *t*-Boc group using silica gel supported CAN as a catalyst, finding that this modification of their method considerably reduced the reaction time.[97]

Scheme 77

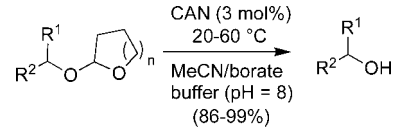
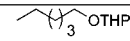
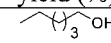
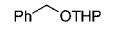
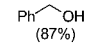
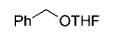
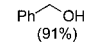
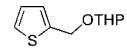
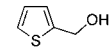
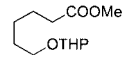
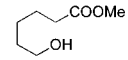
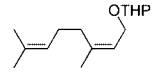
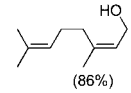
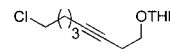
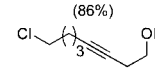
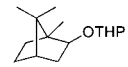
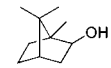
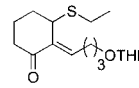
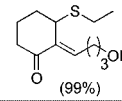


Table 17. Representative Examples of CAN-Catalyzed Deprotections of THF and THP Ethers

entry	substrate	product, yield (%)
1		 (94%)
2		 (87%)
3		 (91%)
4		 (91%)
5		 (82%)
6		 (86%)
7		 (94%)
8		 (87%)
9		 (99%)

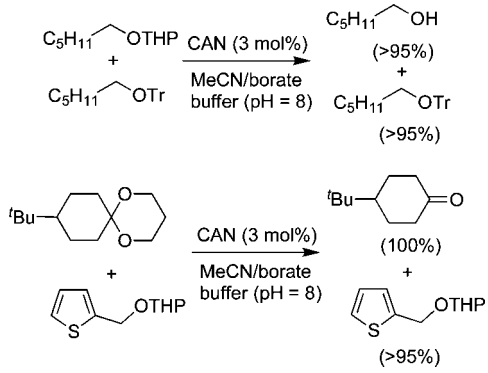
4.2.3. Acetal Cleavage

Markó et al. reported the deprotection of cyclic acetals in the presence of 2.5 equiv of CAN in acetonitrile−water solution.[98] Subsequent work by the same group proved that acetal cleavage could be carried out in the presence of catalytic amounts of CAN, and these conditions were first applied to the case of THP and THF ethers, which were efficiently transformed into the corresponding alcohols under neutral conditions.[99] A wide range of such ethers, containing a variety of functional groups including esters, nitriles, ketones, enones, halides, sulfides, alkenes, and alkynes, were quantitatively deprotected with CAN in borate buffer (pH = 8) (Scheme 77, Table 17).

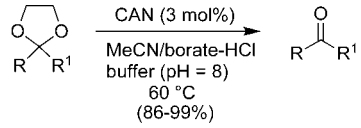
This potential application of this methodology in synthesis was increased by its remarkable chemoselectivity. Thus, it allowed a selective deprotection of a THP ether in the presence of a trityloxy group and also the deprotection of a ketal in the presence of a OTHP group (Scheme 78).

Subsequent work by the Markó group demonstrated the role of CAN as a Lewis acid in the deprotection of ketals.[100] A variety of cyclic acetals and ketals reacted with 3 mol % of CAN in borate−HCl buffer to furnish the deprotected products in excellent yields and short reaction times (Scheme 79, Table 18). Again, the reaction showed a remarkable chemoselectivity because it tolerated the presence of a number of functional groups, including ketones, enones, and triisopropylsilyl (TIPS) ethers. Furthermore, secondary and tertiary alcohols did not undergo elimination reactions, even in cases where they would have led to conjugated systems (e.g., entry 5). The deprotection of an α-substituted chiral

Scheme 78



Scheme 79



acetate could be performed without epimerization, which could not be avoided in the presence of stoichiometric CAN (entry 8). Interestingly, aldehydes obtained in the deprotection of acetals were stable, and they were not further oxidized to carboxylic acids. On the other hand, a pinacol-derived ketal failed to be deprotected under the reaction conditions (entry 10).

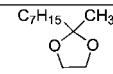
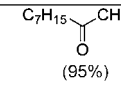
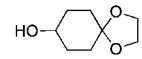
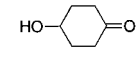
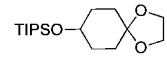
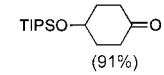
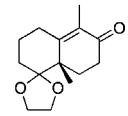
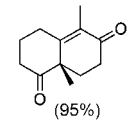
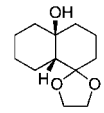
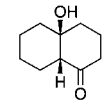
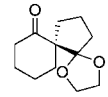
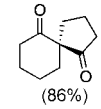
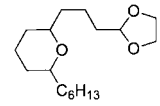
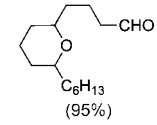
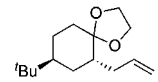
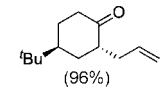
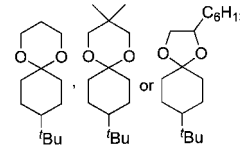
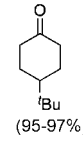
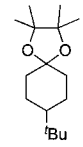
The reaction of ketal **88** with 3 mol % of CAN and 1.5 equiv of $NaBrO_3$ furnished not only the expected ketone **89**, but also the unmodified diol side product (Scheme 80). This was interpreted as evidence that CAN did not act as an oxidant in the deprotection reaction. Furthermore, when the reaction was monitored by cyclic voltammetry, only Ce(IV) species were detected throughout the reaction, which clearly indicates that the oxidation state of CAN was not modified and hence that it acts as a Lewis acid that activates the acetal or ketal groups toward hydrolysis (see below for a more detailed mechanistic discussion).[101] A couple of years later, Parrilli and co-workers carried out a detailed study on the CAN-catalyzed cleavage of cyclic ketals and confirmed the Lewis acidic properties of CAN under mildly acidic conditions (pH 4.4), but concluded that for the nonbuffered reactions initially reported by Markó[98] the deprotection arises from the protic acid environment arising from CAN hydrolysis.[102]

Maulide and Markó have also proved that CAN is a suitable catalyst for the deprotection of ketals and THP ethers in the presence of enol triflates.[103] For instance, compound **90** was quantitatively converted into the corresponding ketone **91** without disturbing the enol triflate functionality (Scheme 81). Furthermore, a variety of ketals and THP ethers listed in Figure 9 were successfully deprotected in the presence of equimolar amounts of compounds containing an enol triflate function (**92** and **93**) under CAN catalyzed conditions. A few bifunctional substrates were also successfully deprotected.

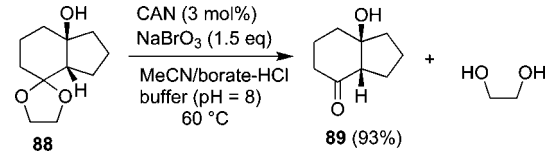
The Markó group also published an elaborate full article[104] and an account[101] summarizing their work on the deprotection of ketals and acetals, and giving further proof of the role of CAN as a Lewis acid. The initial results obtained using 2.5 equiv of CAN were first explained through a radical mechanism that is summarized in Scheme 82.

However, the subsequent development of the catalytic version cast doubt on this initial proposal, and further studies

Table 18. CAN-Catalyzed Deprotection of Cyclic Acetals and Ketals

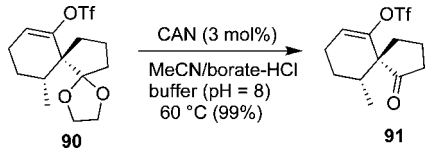
entry	substrate	product, yield (%)
1		 (95%)
2		 (92%)
3		 (91%)
4		 (95%)
5		 (99%)
6		 (86%)
7		 (95%)
8		 (96%)
9		 (95-97%)
10		No reaction

Scheme 80



were performed to confirm the role of CAN in the process. The oxidation level of Ce(IV) throughout the deprotection was studied by cyclic voltamperometry. Using a sweep rate of 100 mV/s, reduction to Ce(III) occurred at −485.7 mV and reoxidation took place at −357.2 mV versus SCE. Neither the shape of the curve nor the position of the

Scheme 81



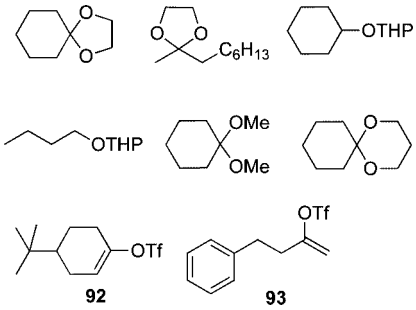
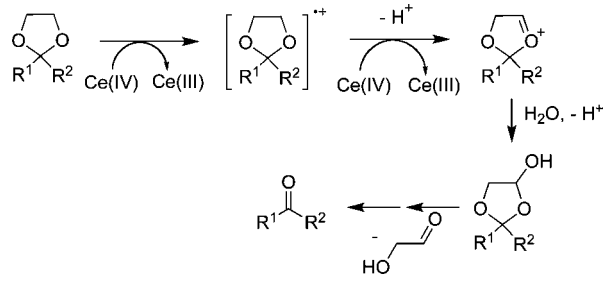


Figure 9.

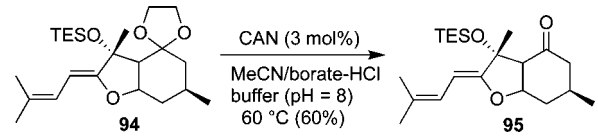
Scheme 82



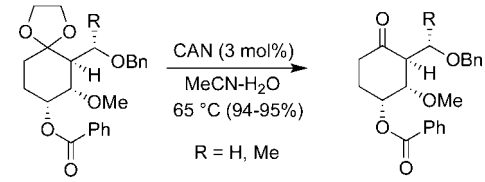
reduction peaks changed upon addition of the deprotection substrate, and the only species detected during the reaction was Ce(IV), proving that in this case CAN did not act as a redox catalyst. For this reason, the mechanism summarized in Scheme 83 was proposed, where coordination of Ce(IV), acting as a Lewis acid, to one of the oxygen atoms of the starting ketal triggers intramolecular delivery of nitrate with concomitant ring-opening to give a hemiacetal, followed to evolution to carbonyl with release of Ce(IV) and the protecting group as a nitrate monoester, which would then be hydrolyzed to regenerate CAN. This mechanism does not have oxonium intermediates, and hence it can explain the previously mentioned absence of epimerization observed for one case that was known to be very sensitive to acid (Table 18, entry 8).[100,101]

Markó's methodology has found application in the context of the total synthesis of natural products. For instance, it was used for the deprotection of the ketal **94** during the total synthesis of (±)-bisabolangelone by the Cossy group (Scheme 84),[105] and also by Mazitschek et al. in a key step of the

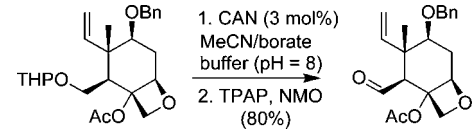
Scheme 84



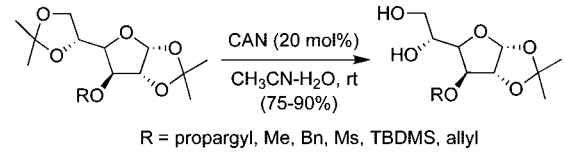
Scheme 85



Scheme 86



Scheme 87



synthesis of fumagillin analogues (Scheme 85).[106] Chida and co-workers also used CAN as a catalyst for the deprotection of a THP ether during the synthesis of an enantiomerically pure CD ring unit of paclitaxel (Scheme 86).[107]

4.2.4. Acetonide Cleavage

In a closely related process, efficient cleavage of acetonides has been achieved by their treatment with 20 mol % of CAN under room temperature conditions (Scheme 87).[108]

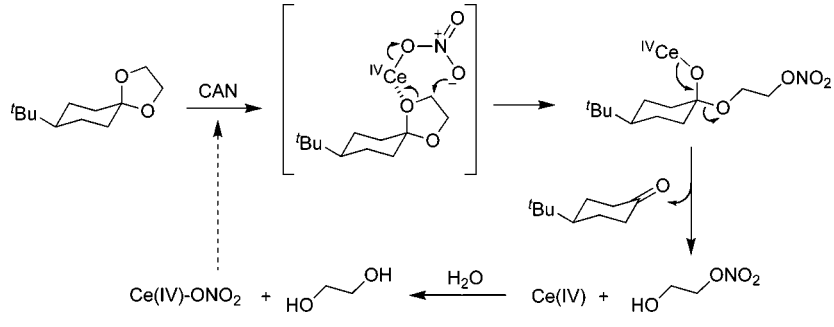
4.3. Disaccharide Hydrolysis

CAN efficiently catalyzed the hydrolysis of some disaccharides in pH 7 buffered solutions at 40−100 °C with turnover numbers 20 and 100 for the case of sucrose (Figure 10).[109]

5. Reactions Involving the Cleavage of Si−O Bonds

tert-Butyldimethylsilyl ethers from either primary or secondary alcohols could be deprotected in the presence of 10 mol % of CAN at 0 °C, in reaction times ranging from 1.5 to 8 h (table 19).[110]

Scheme 83



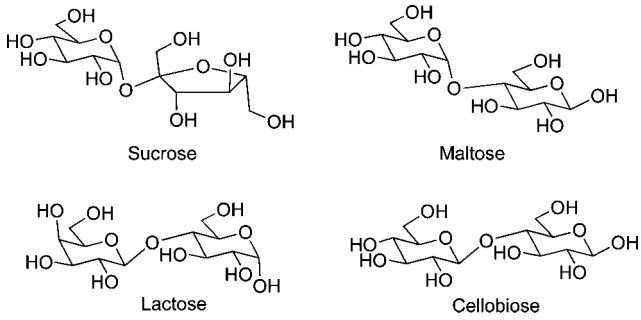
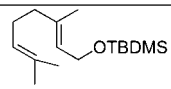
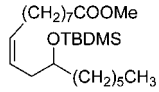
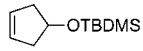
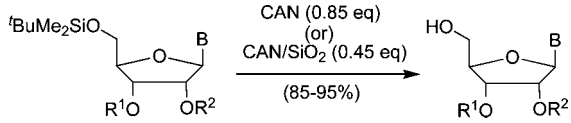


Figure 10.

Table 19. Representative Examples of the CAN-Catalyzed Deprotection of TBDMS Ethers

entry	starting material	time (h)	yield (%)
1		1.5	97
2		8	95
3		1.5	92

Scheme 88



Simultaneously with the previously mentioned work on the deprotection of trityl and monomethoxytrityl groups, Hwu et al. reported an efficient CAN-catalyzed deprotection of trialkylsilyl ethers.[95] In their initial experiments, almost stoichiometric amounts (0.85 equiv) of CAN were required to remove efficiently the TBDMS or TIPS groups, but they subsequently discovered that this amount could be reduced in the presence of silica, and indeed they found that 0.45 equiv of CAN/SiO_2 was enough to achieve similar yields. Interestingly, the TBDMS group on a secondary alcohol did not react, allowing differential deprotection (Scheme 88 and Figure 11).

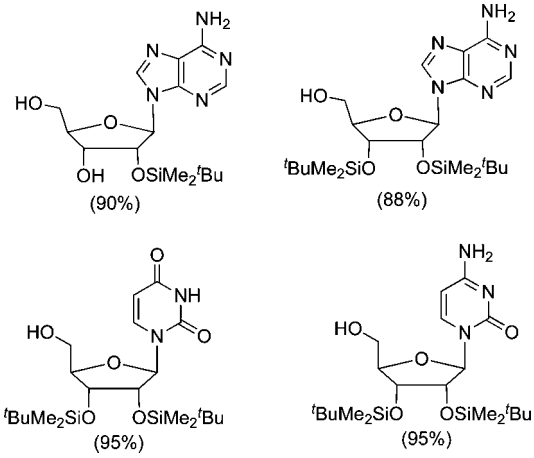
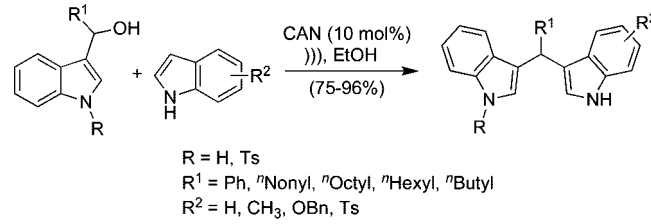
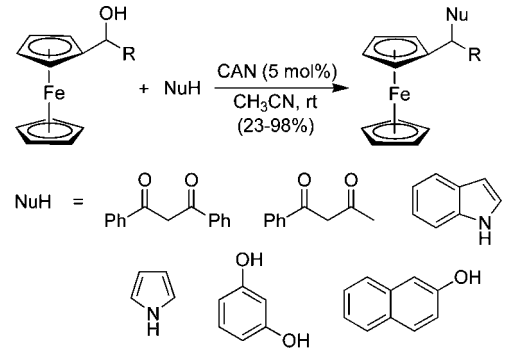


Figure 11.

Scheme 89



Scheme 90



6. Reactions Involving the Generation of Carbon−Carbon Bonds

6.1. Introduction

Carbon−carbon bond formation is probably the most essential maneuver in synthetic organic chemistry. The CAN-induced generation of C−C bonds has been for some time an important aspect of the synthetic application of Ce(IV) species. The development in recent years of catalytic methods, which is summarized in this section, can be considered as the key development that will contribute to the widespread use of these methods.

6.2. Nucleophilic Substitution Reactions

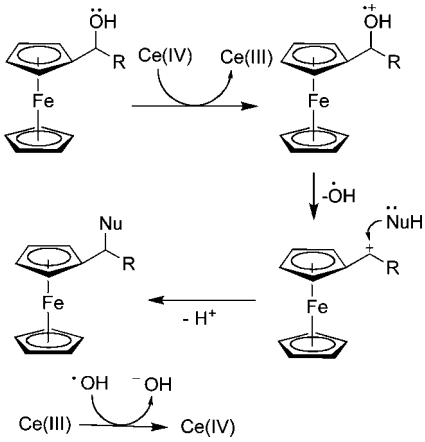
The synthesis of unsymmetrical bis(indolyl)alkanes was achieved by a CAN-catalyzed, ultrasound-accelerated reaction between indoles and (1*H*-indol-3-yl)(alkyl/aryl)methanol (Scheme 89).[111] Among the tested Lewis acids such as $Ce(NO_3)_3$, $Ce_2(C_2O_4)_3$, and $Bi(NO_3)_3$, CAN was found to be more efficient in anhydrous ethanol.

The reaction of ferrocenyl alcohols with C-nucleophiles, including 1,3-dicarbonyl compounds, indole, pyrrole, resorcinol, and 2-naphthol, in the presence of 5 mol % of CAN in acetonitrile afforded the corresponding substitution products in excellent yields (Scheme 90).[112] Among the solvents tested, acetonitrile was found to be most effective one, while THF and ether led to lower conversion. The reaction gave excellent yields with most nucleophiles, including 1,3-dicarbonyl compounds, indole, pyrrole, and resorcinol. For the related reaction between *N*-nucleophiles and ferrocenyl alcohols, see section 3.4.1.

Regarding the mechanism of the reaction, the authors proposed radical cation and carbocation intermediates as depicted in Scheme 91.

The nucleophilic substitution of indoles and pyrrole to xanthene derivatives has been accomplished by treatment with catalytic amounts of CAN under ultrasound irradiation. The reaction of xanthene derivatives **96** with indole furnished the substitution products **97**, and no traces of the Michael

Scheme 91



addition products were noticed (Scheme 92).[113] The product structure was unambiguously assigned by single crystal X-ray analysis. Pyrrole gave the adduct substituted in 2-position with similar reactivity. A plausible mechanism was proposed on the basis of the CAN-catalyzed elimination of the alkoxy group in **96** to give a pyrillium intermediate, which is then attacked by the nucleophile.

Similarly, xanthen-9-ol also reacted with a variety of indole derivatives in the presence of CAN, furnishing the corresponding 9-substituted products in very good yields. As expected, 3-unsubstituted indoles reacted by their C-3 position (Scheme 93), and the only 3-substituted indole that was studied afforded the products substituted in C-2 without any loss in yield.

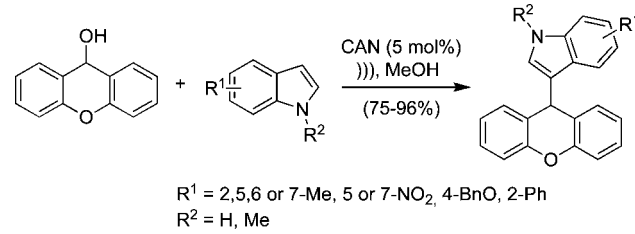
The acetates of Baylis−Hillman adducts reacted with primary aryl, alkyl, and benzyl amines to afford α-dehydro-*β*-amino esters, predominantly as the *E*-isomers, in the presence of CAN (10 mol %).[114] The *E*-selectivity could be explained by the formation of a chelated intermediate **98** with Ce(IV) and the acetoxy group (Scheme 94).

6.3. Michael Additions

The synthesis of *β*-(3-indolyl)ketones by an ultrasound-accelerated, CAN-catalyzed, Michael addition of indoles to α,*β*-unsaturated ketones has been reported by Ji and Wang[115] (Scheme 95). Among the solvents tested, anhydrous methanol was the best one. Other cerium salts such as $Ce(NO_3)_3 \cdot 6H_2O$ and $Ce_2(C_2O_4)_3 \cdot 9H_2O$ failed to catalyze the reaction.

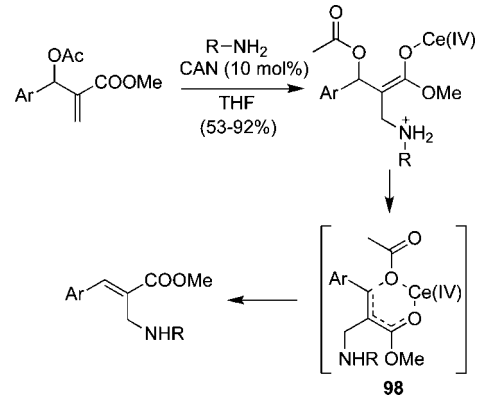
Ko et al. reported the reaction between indoles and α,*β*-unsaturated ketones and aldehydes in the presence of CAN in DMSO/water.[116] Cyclohex-2-enone and indole reacted with 10 mol % of CAN to afford 14% of **99** and 85% of **100** in 12 h, but an increase of the catalyst load to 30 mol % allowed to isolate exclusively compound **100** in 99% yield (Scheme 96). However, other acceptors such as cyclopent-2-enone, but-3-en-2-one, 1-cyclohexenylethanone, and 4-(4-methoxyphenyl)but-3-en-2-one gave only product **99**. The formation of different products depending on the structure of the enone was explained by the authors of the study through the effect of torsional strain. Thus, the addition of the first equivalent of indole to cyclohex-2-enone forms 3-indolylcyclohexanone **99**. When further reaction occurs, the conversion of the sp^2 carbonyl carbon of **99** to a sp^3 carbon in the six-membered ring of **100** leads to a completely staggered chair arrangement and reduces the torsional strain. In the other cases (e.g., from cyclopent-2-enone), the

Scheme 93



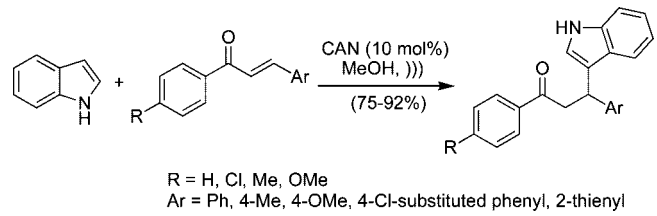
R^1 = 2,5,6 or 7-Me, 5 or 7-NO_2, 4-BnO, 2-Ph
R^2 = H, Me

Scheme 94



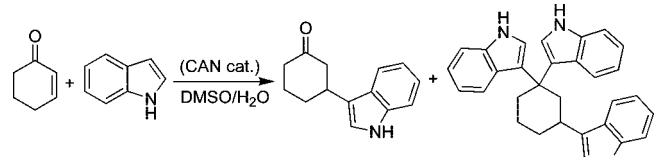
98

Scheme 95



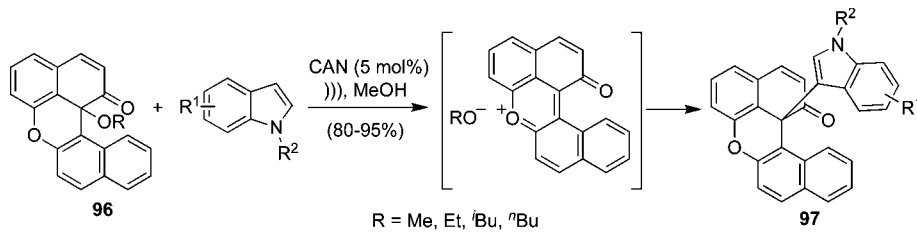
R = H, Cl, Me, OMe
Ar = Ph, 4-Me, 4-OMe, 4-Cl-substituted phenyl, 2-thienyl

Scheme 96



99 (0 to 14%) **100** (77 to 99%)

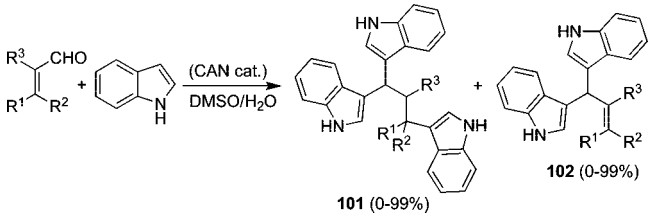
Scheme 92



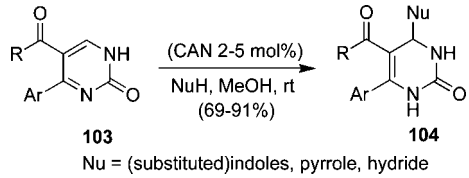
96 **97**

R = Me, Et, *i*Bu, *n*Bu
R^1 = Me, NO_2; R^2 = H, Me

Scheme 97



Scheme 98



torsional strain is increased because of the increase in the number of eclipsing interactions.

The reaction of indole with crotonaldehyde in the presence of 10 mol % of CAN furnished 99% of **101**. A mixture of products **101** and **102** was obtained in the case of 3-methylbut-2-enal, cinnamaldehyde, and cyclohex-1-enecarbaldehyde, whereas quantitative conversion of **102** was achieved for 3,3-diphenylacrylaldehyde (Scheme 97). The above observations were explained through steric effects.

Perumal and co-workers have demonstrated a novel CAN-catalyzed 1,4-addition of nucleophiles to pyrimidin-2(1*H*)-ones.[117] Thus, pyrimidin-2(1*H*)-ones **103** reacted with several indole and pyrrole derivatives, and also with hydride donors, in anhydrous methanol in the presence of 2−5 mol % of CAN to furnish the highly functionalized 3,4-dihydropyrimidin-2(1*H*)-ones **104** in very good yields (Scheme 98 and Figure 12). 3-Substituted indoles, 2-(3-indolyl)ethylamine, and indoles bearing strong electron-withdrawing groups failed to afford the adducts.

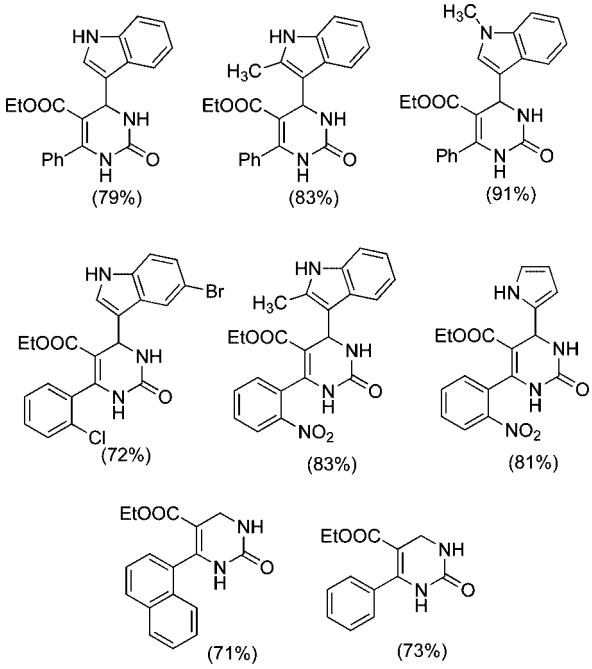


Figure 12.

Scheme 99

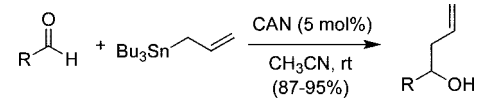
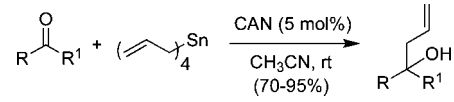


Table 20. Representative Examples of the Preparation of Homoallyl Alcohols by CAN-Catalyzed Allylation of Aldehydes with Allyltributyltin

entry	aldehyde	product, yield (%)
1	Ph−CHO	(95%)
2		(92%)
3		(90%)
4		(87%)
5		(89%)
6		(90%)
7		(91%)
8		(90%)

Scheme 100



6.4. Addition to Carbonyl Groups

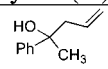
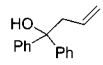
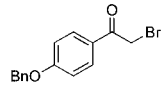
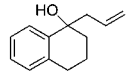
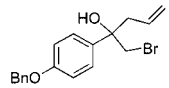
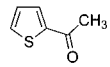
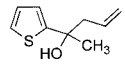
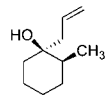
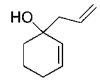
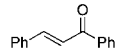
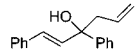
Aldehydes have been successfully allylated by allyltributylstannane in the presence of CAN (5 mol %) with no bis-allylation being observed. This is an important result, because bis-allylation is a problem often observed with other reagents.[118] Acid-sensitive aldehydes like furfural, 2-phenylacetaldehyde, and cinnamaldehyde were also allylated in excellent yields (Scheme 99 and Table 20). These conditions were chemoselective and did not affect ketone groups.

Subsequent work proved that ketones could also be allylated in excellent yields by tetraallyltin reagents, again in the presence of 5 mol % CAN (Scheme 100 and Table 21).[119]

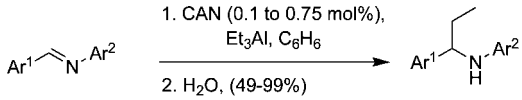
6.5. Addition to Imines

The reaction between *N*-arylaldimines and triethylaluminium, acting as a nucleophilic ethyl donor, was studied in hydrocarbon solvents in the presence of a variety of Lewis acids, among which CAN was found to give the best results. Although lower amounts of the catalyst could be employed, in most cases the authors used 0.75 equiv of the catalyst to

Table 21. Representative Examples of the Preparation of Homoallyl Alcohols by CAN-Catalyzed Allylation of Ketones with Tetraallyltin

entry	ketone	product, yield (%)
1		 (95%)
2		 (89%)
3		 (88%)
4		 (87%)
5		 (90%)
6		 (89%)
7		 (85%)
8		 (70%)

Scheme 101



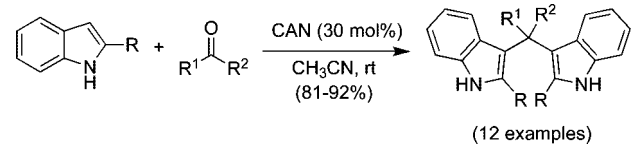
Ar^1 = Ph, 4-MeC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-CNC_6H_4, 4-OHC_6H_4, 2-C_5H_4N
Ar^2 = Ph, 4-$OMeC_6H_4$, 4-ClC_6H_4, 2-$C_{10}H_7$

achieve shorter reaction times (Scheme 101).[120] While the substitution pattern of the *N*-aryl substituent did not affect the reaction, the authors found that electron-releasing groups at the other aryl substituent led to better yields than electron-withdrawing ones, an effect that is opposite to the one normally found by previous authors in lanthanide(III) halide-catalyzed additions of triethylaluminium to imines. For these slower reactions, aldehydes arising from the hydrolysis of the starting imines were observed. Because moisture was rigorously excluded from the reaction media, the water necessary for this side reaction was assumed to come from a redox reaction between nitrate anions and the aluminum hydride species Et_nAlH_{3-n} arising from elimination of ethylene from triethylaluminium.[121]

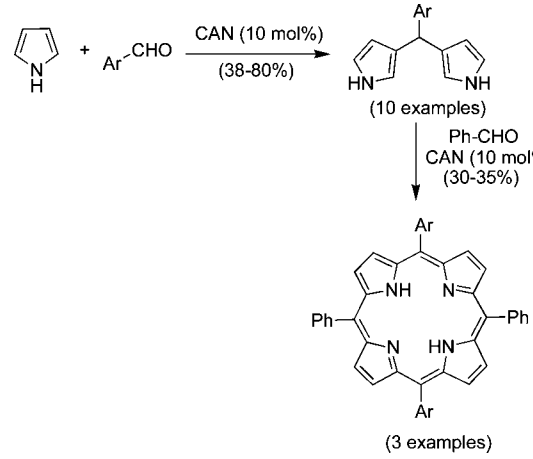
6.6. Domino Nucleophilic Addition−Nucleophilic Substitutions

Addition of indoles to carbonyl compounds followed by in situ nucleophilic substitution of the initially generated alcohol by a second molecule of indole was carried out efficiently in the presence of 30 mol % CAN, leading to di- and triindolylmethane derivatives (Scheme 102).[122] See section 6.3 for an additional example of this reaction.

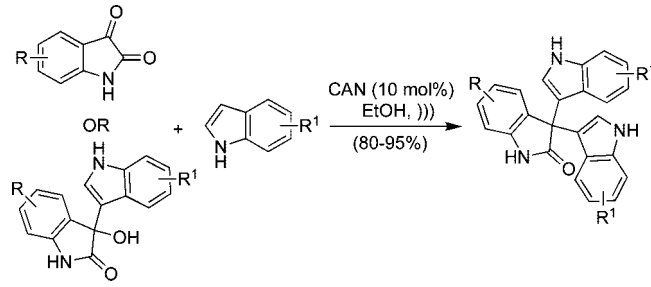
Scheme 102



Scheme 103



Scheme 104



A similar domino transformation has been described for pyrroles, leading to a variety of dipyrrolylmethanes in moderate to good yields. Interestingly, CAN was also found to catalyze the reaction between dipyrrolylmethanes and aldehydes to give porphyrins (Scheme 103).[123]

The Wang group described the synthesis of 3,3-di(indolyl)-indolin-2-ones from indoles and isatin using similar methodology, this time under ultrasound irradiation (Scheme 104).[124]

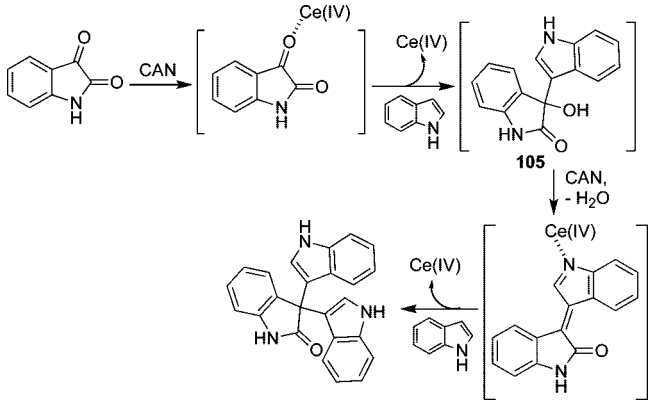
The catalyst was proposed to act as a Lewis acid, which activates the carbonyl group of isatin to generate the intermediate **105** after addition of a molecule of indole. This intermediate undergoes water elimination followed by a second CAN-catalyzed reaction with another molecule of indole to afford the final product (Scheme 105). To prove this mechanism, the authors prepared compound **105** according to a reported method and showed that it also led to the observed products when submitted to the standard reaction conditions.

The use of isolated compounds **105** as starting materials allowed one to employ a second nucleophile different from the starting indole, including pyrroles and 3-substituted indoles, both of which were found to react by their C-2 position (Scheme 106).

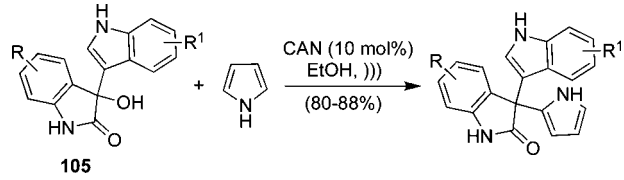
6.7. Domino Knoevenagel−Michael Additions

A library of 4,4′-(arylmethylene)bis(3-methyl-1-phenylpyrazol-5-ols) showing excellent activity against the "peste des petits ruminants" virus (PPRV) was synthesized from

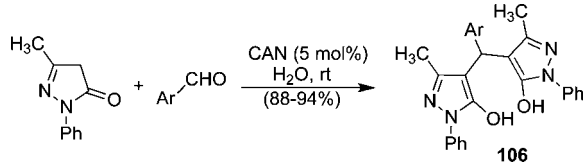
Scheme 105



Scheme 106



Scheme 107



1-phenyl-3-methyl-5-pyrazolone and aromatic aldehydes in water containing 5% CAN.[125] The mechanism for this transformation probably involves an initial CAN-catalyzed Knoevenagel reaction followed by a Michael addition (Scheme 107 and Figure 13, Scheme 108).

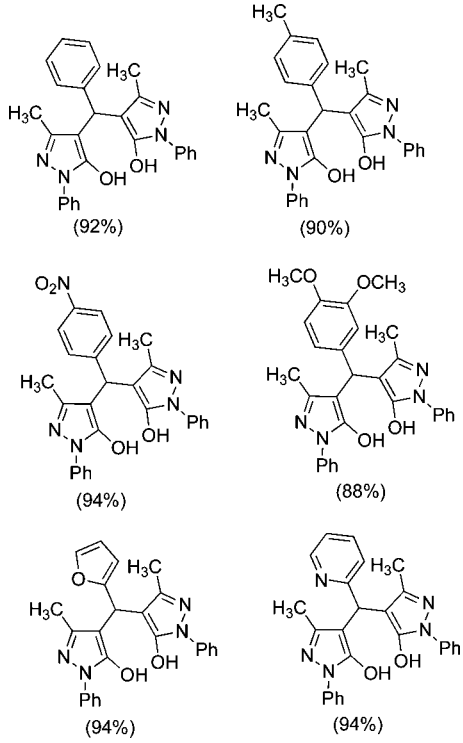
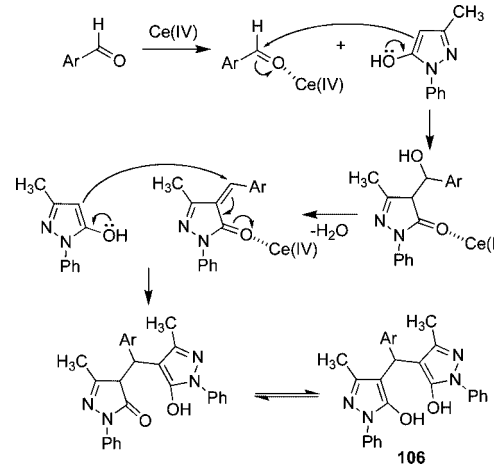
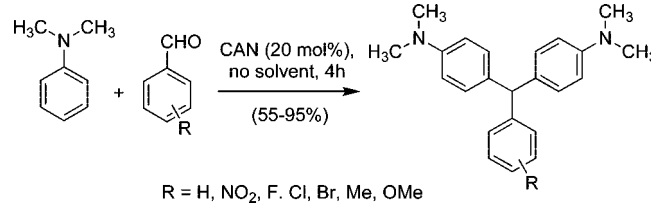


Figure 13.

Scheme 108



Scheme 109



6.8. Electrophilic Aromatic Substitutions

The synthesis of some triarylmethane dyes belonging to the leuco malachite class was achieved by treatment of 2 equiv of *N*,*N*-dimethylaniline with one of an aromatic aldehyde in the presence of 20 mol % CAN, under solvent-free conditions (Scheme 109).[126] Substituent effects were those expected from an electrophilic substitution mechanism; that is, electron-withdrawing groups at the aldehyde component increased the yields.

7. Synthesis of Heterocycles

7.1. Introduction

Heterocycles are the single most important class of organic compounds from an industrial point of view, being essential in the pharmaceutical and agrochemical industries, and therefore inexpensive and stable catalysts that can be used in their construction are in high demand. This section will deal with the use of CAN-catalyzed reactions as key steps for the synthesis of heterocycles, with the exception of heterocyclic synthesis involving multicomponent reactions, which will be treated separately in section 8.

7.2. Synthesis of Five-Membered Heterocycles

7.2.1. Fischer Indole Synthesis

The Fischer reaction consists of the treatment of arylhydrazones with acids to yield indoles. It is one of the classical methods for indole synthesis and has been widely employed in the synthesis of natural products and bioactive compounds, including drugs. CAN, in refluxing methanol, has proved to be an excellent catalyst for the Fischer reaction. It allows the synthesis of indoles **111** from hydrazines **107** and ketones **108** in one pot, with hydrazones **109** and their tautomers **110** as intermediates (Scheme 110).[127]

Scheme 110

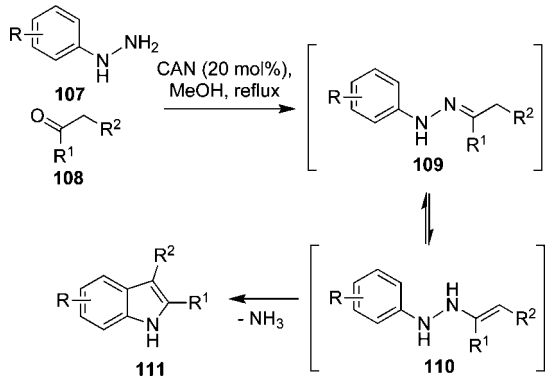
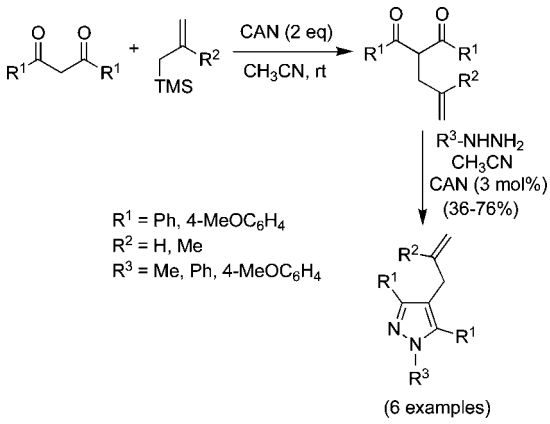


Table 22. CAN-Catalyzed Synthesis of Indoles and Tetrahydrocarbazoles: Selected Examples

entry	R	R^1	R^2	time (h)	yield of **111** (%)
1	H	CH_3	CH_3	2	95
2	4-F	CH_3	CH_3	2	90
3	4-OCH_3	CH_3	CH_3	0.25	90
4	2-NO_2	CH_3	CH_3	3	70
5	2,5-Cl_2	CH_3	CH_3	3.5	70
6	H	H	$CH_2C_6H_5$	3	60
7	H		$(CH_2)_4$	2	95
8	2-CH_3		$(CH_2)_4$	1	85

Scheme 111



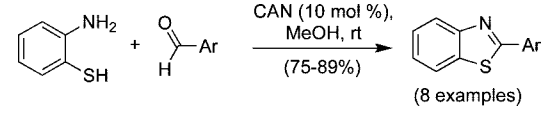
The scope of the indole synthesis is summarized in the examples collected in Table 22 and includes indoles with both electron-releasing and electron-withdrawing substituents at the C4−7 positions, and alkyl or arylalkyl substituents at C-2,3. By using cyclohexanones as starting materials, the procedure could also be adapted to the synthesis of tetrahydrocarbazoles (entries 7,8).

7.2.2. Synthesis of Pyrazoles

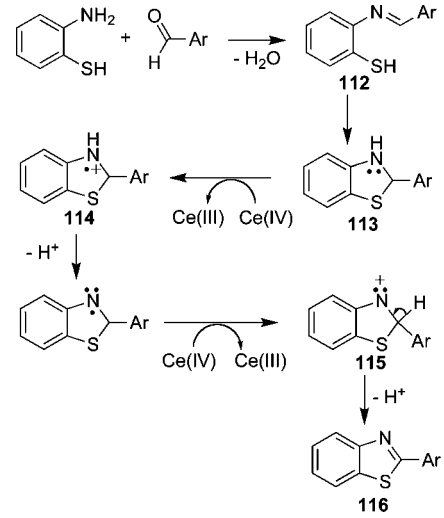
The reaction of 2-allyl-1,3-diketones with methyl- or arylhydrazines in acetonitrile containing 3 mol % of CAN was found to afford the corresponding tetrasubstituted pyrazoles in good yields (Scheme 111). When an unsymmetric 1,3-diketone derivative (i.e., 2-allylbenzoylacetone) and 4-methoxyphenylhydrazine were employed, an excellent 16:1 chemoselectivity was observed in favor of the expected 1-substituted-5-phenylpyrazole. The 2-allyl substituent was found to play an important role in this selectivity, because a similar reaction starting from 2-methylbenzoylacetone was found to give both possible regioisomeric pyrazoles in a 6:1 ratio in favor of the 1-substituted-5-phenylpyrazole.[128] This methodology was applied to the synthesis of propylpyrazoletriol (PPT), an estrogen receptor agonist, starting from 1,3-bis(4-methoxyphenyl)-1,3-propanedione.

In the presence of 2 equiv of CAN, the allylation of 1,3-diketones by allyltrimethylsilanes and the final double condensation with hydrazines can be performed as a one-pot procedure, although this transformation was not general.

Scheme 112



Scheme 113



7.2.3. Synthesis of Benzothiazoles

CAN catalyzes the reaction between *o*-mercaptoaniline and aromatic aldehydes at room temperature to give 2-arylbenzothiazoles (Scheme 112).[129]

The mechanism of this transformation must involve CAN acting both as a Lewis acid and as an oxidant and was proposed to take place as summarized in Scheme 113. Imine **112**, arising from an initial condensation between the starting materials, undergoes cyclization to **113**. This is followed by two one-electron oxidation steps and a final deprotonation, leading to the observed product **116**. It must be assumed that Ce(IV) is regenerated by air oxidation of Ce(III).

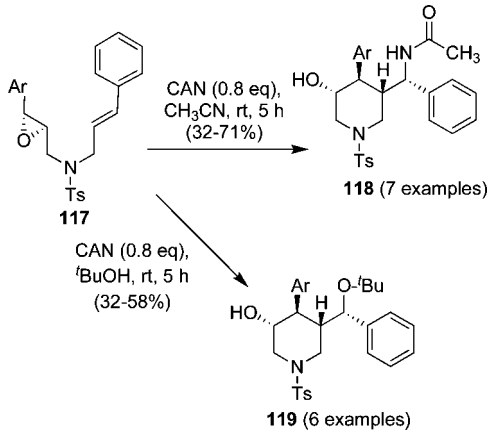
7.3. Synthesis of Six-Membered Heterocycles

7.3.1. Synthesis of Piperidines

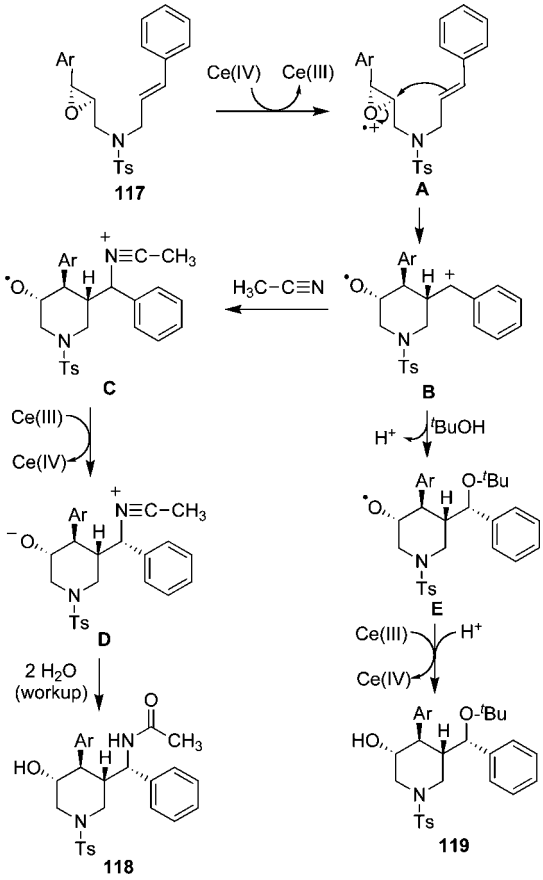
Nair has described a very interesting domino transformation of epoxypropylamines **117** into piperidines **118** as single diastereoisomers by exposure to CAN in dry acetonitrile, in one of the first examples of an intramolecular CAN-catalyzed C−C bond forming process (Scheme 114). Although the reaction needs 0.8 equiv of CAN, this can be considered as a substoichiometric amount, especially taking into account that reactions mediated by CAN often require up to 2.5 equiv of this reagent. The incorporation of one molecule of acetonitrile into the reaction product in a Ritter-like process prompted the investigation of the use of other solvents, and this led to the discovery that the reaction could also be carried out in *tert*-butyl alcohol to give ethers **119**.[130]

Nair rationalized the reaction through the mechanism summarized in Scheme 115. Assuming that the action of

Scheme 114



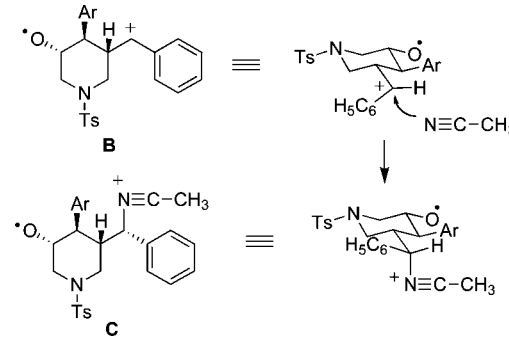
Scheme 115



CAN involves an oxidative process (see also section 7.3.5 in this regard), he proposed that the starting epoxide **117** underwent a single-electron transfer oxidation to give cation radical **A**. A 6-*exo-tet* cycloisomerization of this intermediate affords **B**, which reacts with one molecule of the acetonitrile solvent to furnish radical **C**. A reductive one-electron transfer transforms **C** into anion **D** and regenerates the Ce(IV) cation, and the reaction of **D** with water during the workup process affords the final product **118**. In the reactions carried out in *tert*-butyl alcohol, addition of a molecule of solvent to **B** yields intermediate **E**, which is transformed into the final product **119** by one-electron reduction and proton transfer (Scheme 115).

The remarkable diastereoselectivity of this domino process was explained by proposing that the cycloisomerization that leads to radical cation **B** takes place in such a way that this

Scheme 116



Scheme 117

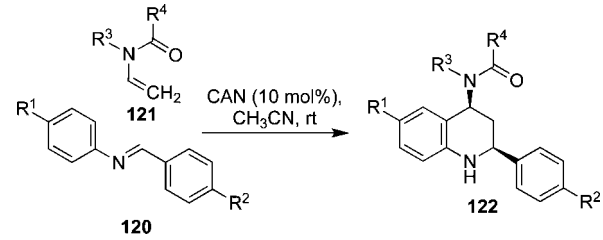


Table 23. Scope of the CAN-Catalyzed Povarov Reaction between Imines and Vinylamides

entry	R^1	R^2	R^3	R^4	yield (%)
1	H	H	CH_3	CH_3	68
2	Cl	NO_2	CH_3	CH_3	77
3	H	OCH_3	CH_3	CH_3	52
4	H	H	$(CH_2)_3$		80
5	Br	H	$(CH_2)_3$		81
6	H	OCH_3	$(CH_2)_3$		63

intermediate has a chairlike geometry, with all substituents in equatorial positions. The benzylic cation is attacked by the nucleophilic solvent from the face opposing the sterically demanding aryl ring placed at the C-4 position (Scheme 116).

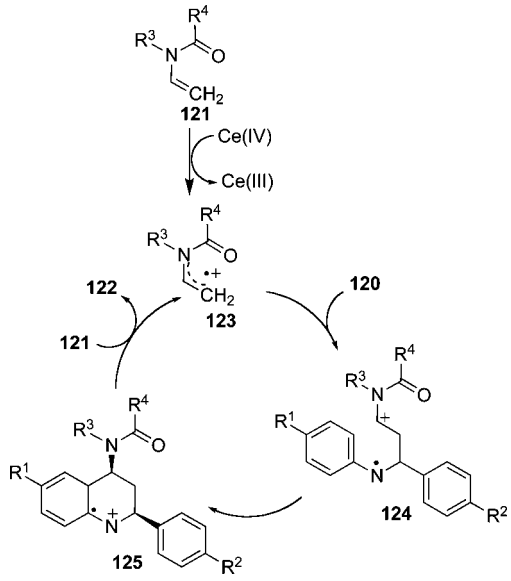
7.3.2. Synthesis of Tetrahydroquinolines via the Povarov Reaction

The Diels−Alder reaction is one of the mainstays in organic synthesis and is widely employed in the preparation of natural and unnatural systems that contain six-membered carbocyclic structural fragments.[131] The application of the Diels−Alder methodology to the construction of six-membered heretocycles has led to the development of hetero-Diels−Alder reactions,[132] which can belong to two subtypes, the oxa-Diels−Alder reactions, which make use of carbonyl compounds, and the imino-Diels−Alder reactions (also known as aza-Diels−Alder reactions), in which imines are involved either in the diene or in the dienophile component of the reaction. The [4 + 2] imino-Diels−Alder reaction between *N*-arylimines and electron-rich olefins is also known as the Povarov reaction[133] and is one of the most convenient modern methods for the preparation of quinoline derivatives.[134]

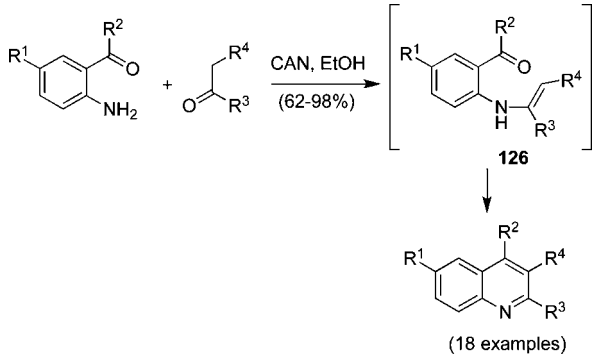
One example of a Povarov reaction that has been found to be catalyzed by CAN is depicted in Scheme 117. It involves the use of *N*-vinylamides as dienophiles and leads diastereoselectively to the *cis*-2,4-disubstituted-1,2,3,4-tetrahydroquinolines **122**. Some representative examples that indicate the scope of the reaction are shown in Table 23.[135]

The authors propose that Ce(IV) oxidizes the electron-rich olefin, and indeed they mention that "Ce(IV) was

Scheme 118



Scheme 119



reduced to Ce(III) in the reaction", although they offer no further details or evidence. Accordingly, they propose a cation radical-mediated nonsincronous cycloaddition initiated by a single-electron transfer reaction that transforms **121** into cation-radical **123**, which reacts with imine **120** to give **124**. This intermediate undergoes the cyclization and is transformed into **125**, which finally reacts with another molecule of the starting material **121** to give the final product and close the cycle (Scheme 118).

CAN-catalyzed three-component Povarov reactions will be discussed in section 8.8.

7.3.3. Synthesis of Quinolines via the Friedländer and Friedländer−Borsche Reactions

The Friedländer reaction is the basis for one of the classical quinoline syntheses.[136] It involves the reaction between 2-aminoaryl aldehydes or ketones and carbonyl compounds containing active methylene functionality under acidic or basic conditions, and allows the creation of the quinoline moiety in a single operation. Mechanistically, the Friedländer reaction may have as intermediates an aldol adduct or a β-enaminone.

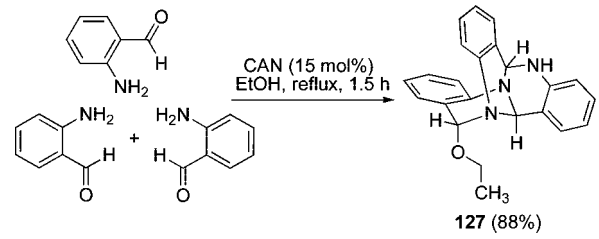
The very mild and efficient catalysis by CAN of the formation of β-enaminones from imines and β-dicarbonyl compounds[75] prompted a systematic study of its effects on the simple Friedländer annulations, with excellent results (Scheme 119). Because of the mentioned ease of formation of enaminones in the presence of CAN, the reaction was assumed to have **126** as an intermediate. Table 24 provides a brief summary of the scope of the reaction.[137]

Table 24. Representative Examples of the Synthesis of Quinoline Derivatives via CAN-Catalyzed Friedländer Annulations[a]

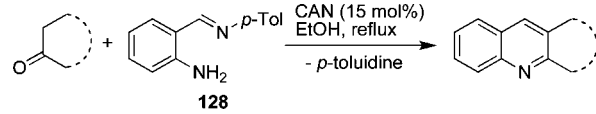
entry	R^1	R^2	R^3	R^4	time (h)	yield (%)
1	H	CH_3	CH_3	CO_2Et	8	98
2	H	CH_3	^{n}Pr	CO_2Et	13	91
3	H	CH_3	CH_3	COPh	8	83
4	H	CH_3	$-(CH_2)_3-$		16	97
5	H	Ph	CH_3	CO_2Et	6	97
6	Cl	Ph	$-(CH_2)_3-$		4	97
7	H	CH_3	CH_3	$COS-^tBu$	6	96
8	H	Ph	$-(CH_2)_4-$		8	98

[a] Conditions: 15 mol % CAN, EtOH, reflux.

Scheme 120



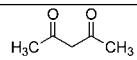
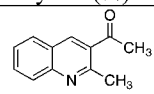
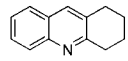
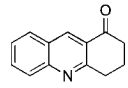
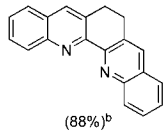
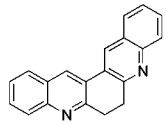
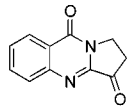
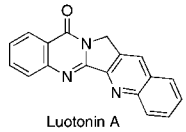
Scheme 121



Friedländer reactions involving 2-aminobenzaldehyde allow the synthesis of quinolines possessing an unsubstituted C-4 carbon, an important moiety that is present in many naturally occurring quinolines. However, the low stability of 2-aminobenzaldehyde makes this reaction quite challenging. In the case of the CAN-catalyzed reaction, the use of 2-aminobenzaldehyde was complicated by the isolation of a side product **127**, arising from a diastereoselective four-component reaction between three molecules of 2-aminobenzaldehyde and a molecule of ethanol. This was confirmed by conducting the reaction in the absence of the active methylene substrate (Scheme 120).

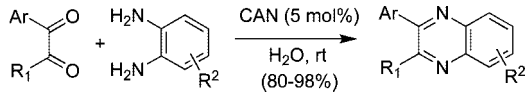
This problem was solved through the use of a Schiff base as a 2-aminobenzaldehyde equivalent, in this case *N*-(2-aminobenzylidene)-4-methylaniline (**128**). This is known as the Borsche variation of the Friedländer reaction (Scheme 121). Representative examples of the results obtained in this study are given in Table 25, and it is relevant to note the possibility of achieving three-component processes involving double Friedländer−Borsche reactions, which had not been previously studied under Lewis acid catalysis (entries 4 and 5). These conditions were also applied to the synthesis of the naturally occurring cytotoxic alkaloid luotonin A, which is able to stabilize the binary complex between human DNA and topoisomerase I.[138] A number of routes have been developed for the synthesis of luotonin A and its analogues,[139] some of which involve the use of the Friedländer reaction as a key step to generate the quinoline unit from the known compound **129**,[140] but the cyclocondensation reaction gave poor yields, never higher than 36%.[141−143] Within this context, it is noteworthy that the CAN-catalyzed Friedländer−Borsche reaction between compound **129** and imine **128** afforded luotonin A in a remarkable 82% yield (entry 6).

Table 25. Examples of the Synthesis of Quinoline Derivatives via CAN-Catalyzed Friedländer−Borsche Annulations

entry	substrate	product, yield (%)
1		 (95%)[a]
2		 (83%)[a]
3		 (94%)[a,b]
4		 (88%)[b]
5		 (87%)[b]
6	 129	 Luotonin A (82%)[a,c]

[a] One equivalent of **128**. [b] Two equivalents of **128**. [c] Literature yields, 36% (triton B, ethanol, reflux, 2 h)[142] or 30% (*p*-toluenesulfonic acid, xylene, reflux, 20 h).[143]

Scheme 122



7.3.4. Synthesis of Quinoxalines

Several studies have been undertaken aiming at the CAN-catalyzed synthesis of quinoxalines, prompted by their importance as building blocks in the pharmaceutical and other chemical industries. Thus, treatment of 1,2-diketones with 1,2-phenylenediamines in the presence of CAN, with tap water as solvent, afforded good to excellent yields of the corresponding quinoxalines. CAN was proposed to coordinate to the carbonyl groups, acting as a Lewis acid. Electron-releasing groups in the amine part led to increased yields, as expected. The reaction lacked chemoselectivity in the case of 1-phenyl-1,2-propanedione, an unsymmetrical ketone, with substituted *o*-phenylenediamines (Scheme 122 and Table 26).[144]

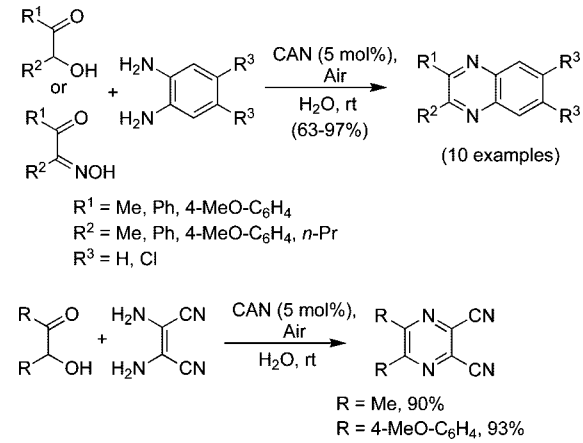
This protocol for quinoxaline synthesis was further developed by combining it with the preparation of the starting 1,2-diketones by the CAN-catalyzed in situ oxidation of the corresponding α-hydroxyketones. To proceed efficiently, this oxidation required bubbling air through the aqueous reaction media. Both the oxidation and the condensation steps could be performed at room temperature (Scheme 123), and the use of other starting diamines such as 1,2-diaminomalononitrile, which afforded pyrazine-2,3-dicarbonitriles, was also

Table 26. Selected Examples of CAN-Catalyzed Quinoxaline Syntheses

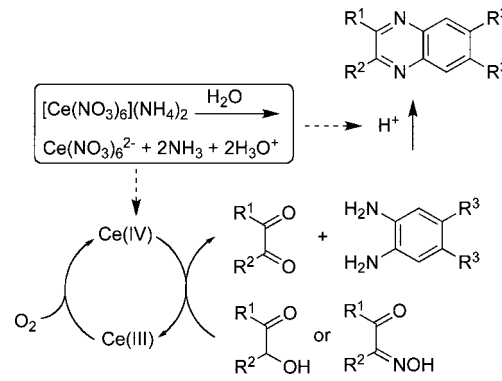
entry	Ar	R^1	R^2	reaction time (min)	yield (%)
1	Ph	Ph	H	10	98
2	Ph	Ph	3-CH_3	10	90
3	Ph	Ph	3-Cl	25	90
4	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	H	10	94
5	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	3-CH_3	20	92
6	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	3-Cl	30	90
7	2-furyl	2-furyl	H	10	95
8	2-furyl	2-furyl	3-CH_3	15	93
9	Ph	CH_3	3-CH_3	10	86[a]
10	Ph	CH_3	3-Cl	30	83[a]

[a] A 1:1 ratio of regioisomers was isolated.

Scheme 123



Scheme 124



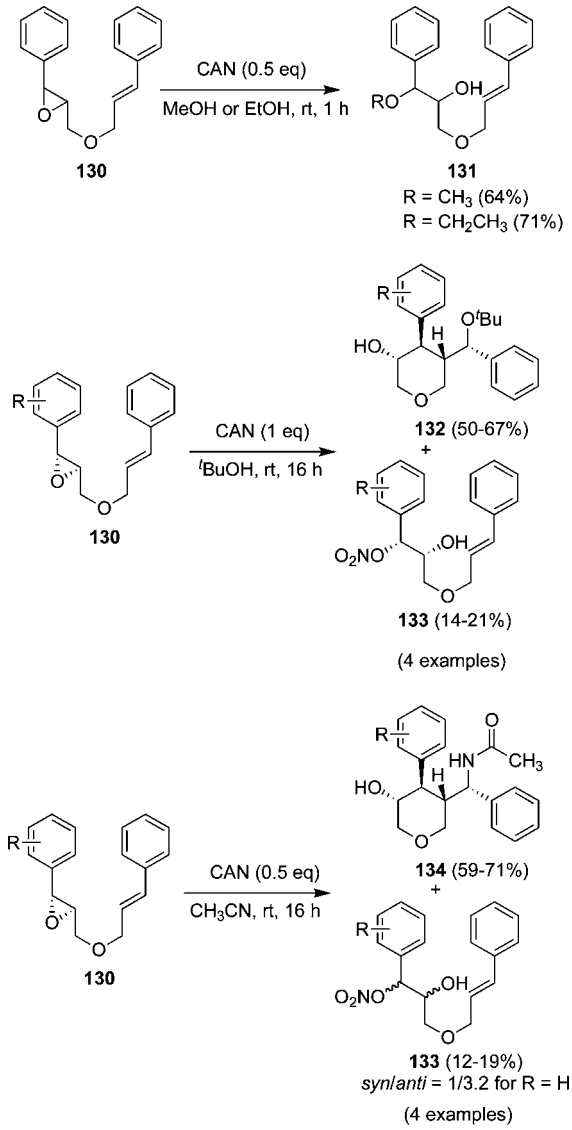
briefly examined. It was also found that α-ketooximes were also suitable starting materials for the quinoxaline synthesis.[145]

The mechanistic proposal summarized in Scheme 124 was put forward by the authors, where Ce(IV) first promotes the oxidation of the starting 2-hydroxyketone to the corresponding 1,2-diketone, being recycled by oxygen from the Ce(III) oxidation state. Subsequently, Ce(IV) catalyzes the condensation reactions, leading to the final product.

7.3.5. Synthesis of Tetrahydropyrans

In a protocol closely related to the one described in section 7.3.1 for the synthesis of piperidines, the group of Nair described the diastereoselective preparation of 3,4,5-trisubstituted tetrahydropyrans from derivatives of 3-phenyl-2,3-epoxypropyl cinnamyl ether (Scheme 125).[146]

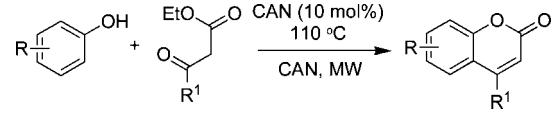
Scheme 125



In the initial study, treatment of compound **130** with a substoichiometric amount of CAN in methanol or ethanol did not lead to cyclized products, but only to compounds **131**, from solvolysis of the starting material. This indicated that fast quenching of the intermediate cationic species by the solvent precluded the intramolecular attack of the styryl side chain, and suggested the use of a less nucleophilic solvent. Indeed, when the reaction was carried out in *tert*-butyl alcohol, the major products were the desired tetrahydropyran derivatives **132**, together with small amounts of *syn*-nitrates **133**. In this case, the reaction was much slower, leading to some consumption of CAN from oxidation of the solvent and hence to the need for a full equivalent of the cerium species. When the reaction was performed in acetonitrile, the results were very similar regarding the isolation of **134**, and only substoichiometric amounts of CAN were again needed.

The mechanism proposed for this transformation is parallel to the one previously discussed for the case of the piperidine synthesis developed by the same group (see Scheme 115), and the same arguments can be used to explain its diastereoselectivity. One interesting remark that was explicitly made in this case was that the reason for assuming a radical process was that the reaction failed in the presence of a number of well-known Lewis acids.

Scheme 126



7.3.6. Synthesis of Coumarins

CAN (10 mol %) was identified as a suitable catalyst for the Pechmann reaction between phenols and β-ketoesters to give coumarins under solvent-free conditions, promoted either by conventional heating or under microwave irradiation using a domestic microwave oven (Scheme 126 and Table 27).[147]

8. CAN-Catalyzed Multicomponent Reactions

8.1. Introduction

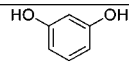
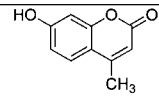
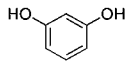
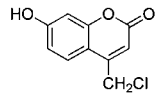
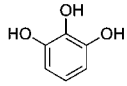
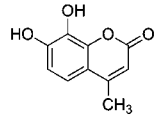
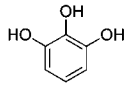
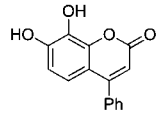
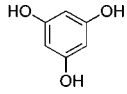
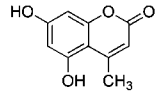
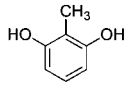
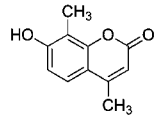
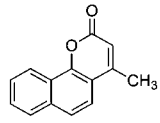
The creation of molecular diversity and complexity from simple and readily available substrates is one of the major current challenges of organic synthesis. The length of a synthetic route depends on the molecular complexity generated, and hence on the number of bonds created in each step. Therefore, the development of processes that allow the creation of several bonds in a single operation has become one of the most attractive goals of organic synthesis. Multicomponent reactions, which can be defined as convergent reactions where three or more reagents are combined in such a way that the final product retains significant portions of all starting materials, are one of the most promising technologies toward achieving this end.[148,149] Besides their exceptional synthetic efficiency, the development of new multicomponent processes will also be crucial to advances in diversity-oriented,[150] combinatorial, and parallel synthesis and hence to the contribution of these methodologies to the generation of new chemical entities (NCEs) in pharmaceutical and agrochemical industries. The possibility of carrying out several synthetic transformations in one operation and without intermediate purification stages is also relevant from an environmental point of view as it involves a drastic reduction in the use of organic solvents and chromatographic stationery phases. For all of these reasons, the development of new multicomponent reactions can be considered as one of the new frontiers in organic synthesis, and this section will be devoted to a discussion of use of CAN as a catalyst for these processes.

8.2. Mannich Reaction

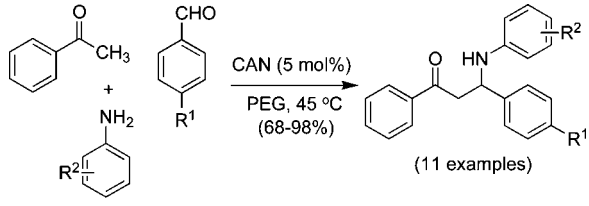
The Mannich reaction between acetophenone, aryl aldehydes, and anilines was found to be catalyzed by 5% CAN. While the reaction proceeded at room temperature, the authors chose to perform it at 45 °C to decrease the reaction time. Higher CAN loadings (e.g., 10%) were found to be detrimental for yield, probably due to decomposition of the reaction product (Scheme 127).[151] Although other solvents like ethanol, acetonitrile, and toluene were equally effective, the authors chose polyethyleneglycol as the reaction medium because of better solubilizing properties, together with its biodegradability and well-known toxicological profile in comparison with ionic liquids and micellar media,[152] and the possibility of recycling.

The nucleophilic addition of phosphite to imines, promoted by alkali metal alkoxides or Lewis acids ($SnCl_2$, $SnCl_4$, $BF_3 \cdot Et_2O$, $ZnCl_2$, $ZrCl_4$), is one of the best methods to access α-aminophosphonates. However, one-pot protocols are not

Table 27. Selected Examples of CAN-Catalyzed Pechmann Syntheses of Coumarins

entry	phenol	coumarin	conventional heating		microwave irradiation	
			time (min)	yield (%)	time (min)	yield (%)
1			10	94	2	96
2			10	92	3	95
3			10	95	2	96
4			15	92	3	94
5			10	95	3	96
6			10	96	3	97
7			15	94	3	95

Scheme 127

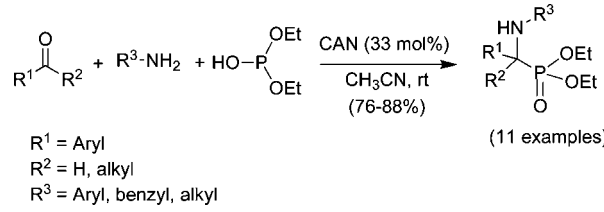


possible because the water liberated during imine formation can decompose the above-mentioned catalysts. The use of lanthanide triflates or $InCl_3$ as water-stable Lewis acids allowed the process to be performed in one pot, but the reactions involving ketones did not proceed well. In this context, it was found that CAN provided a good catalyst for this Mannich-type reaction, allowing the transformation of aliphatic, aromatic, and α,β-unsaturated aldehydes, and also ketones, into the corresponding α-aminophosphonates under very mild reaction conditions (Scheme 128).[153]

8.3. Synthesis of Cyclic β-Aminoesters

β-Amino acids and their esters have great biological and pharmacological relevance due to their presence as structural fragments of a considerable number of bioactive natural

Scheme 128



products including, among many others, the β-lactam antibiotics and antitumor compounds such as taxol and dolastatin 11. In addition, β-amino acids are very important in medicinal chemistry because they allow the creation of peptidomimetics that are resistant to proteolysis[154] and hence have improved pharmacokinetic properties with regard to the natural peptides. In connection with the development of new synthetic routes to cyclic β-amino acids, it was found that the reaction at room temperature between primary amines, β-ketoesters, and chalcones, in the presence of a catalytic amount (5 mol %) of CAN, afforded 2-aminocyclohex-1-ene-1-carboxylic esters **135** in good yields and complete diastereoselectivity, with a molecule of water as the only byproduct. The carbon−carbon double bond of these compounds was reduced with sodium triacetoxyborohydride, again with complete diastereoselectivity. This two-step route allowed the transformation of very simple acyclic starting materials into tetrasubstituted cyclohexane derivatives bear-

Scheme 129

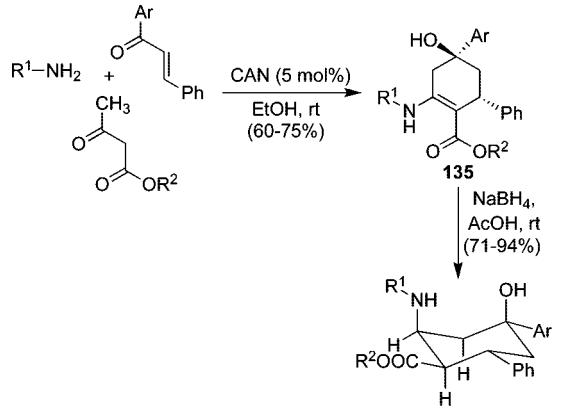


Table 28. CAN-Catalyzed Three-Component Reaction between Primary Amines, β-Ketoesters, and Chalcones

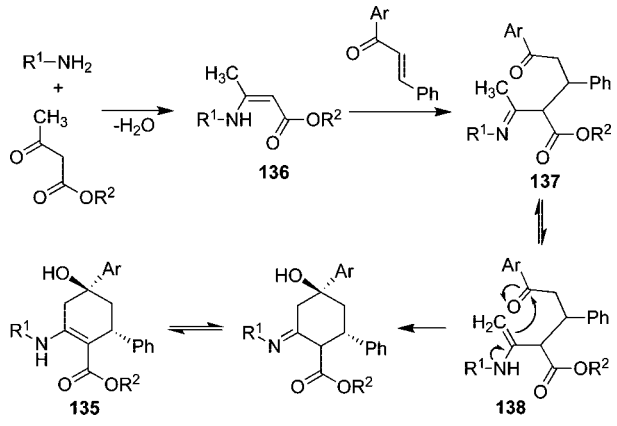
entry	R^1	R^2	Ar	reaction time (h)	yield of **135** (%)
1	^{n}Bu	Et	Ph	30	63
2	^{n}Bu	Et	Ph	42	77
3	^{n}Bu	Et	4-ClC_6H_4	42	73
4	^{n}Bu	^{t}Bu	Ph	42	80
5	^{n}Bu	^{t}Bu	4-ClC_6H_4	42	81
6	$^n C_6H_{13}$	Et	Ph	45	71
7	$^n C_7H_{15}$	Et	Ph	45	73
8	$^n C_6H_{13}$	Et	4-ClC_6H_4	42	68
9	$^n C_7H_{15}$	Et	4-ClC_6H_4	42	72
10[a]	(±)-2-Me−Bu	Et	Ph	45	71
11[a]	(*S*)-2-Me−Bu	Et	Ph	48	74
12[a]	(±)-*sec*-Bu	Et	Ph	96	74
13[a]	(*R*)-*sec*-Bu	Et	Ph	96	72

[a] As a 1:1 diastereomeric mixture.

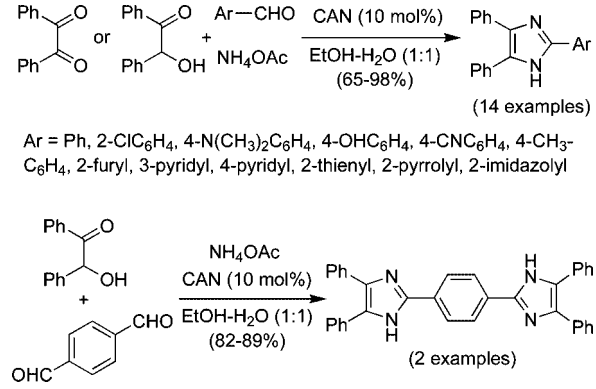
ing four functional groups, including a *cis*-β-aminoester moiety, and generates four stereocenters, three of which are adjacent, including one that is quaternary (Scheme 129 and Table 28).[155]

Cyclohexene derivatives **135** were proposed to arise from an initial CAN-catalyzed reaction between amines and β-ketoesters to give β-enaminones **136** and a Michael addition to the enone system in chalcone substrates to give **137**, followed by imine−enamine tautomerism to **138** and a final cyclization step, where the tendency of both aromatic substituents to sit in equatorial positions controls the stereochemistry of the final products (Scheme 130). A control experiment run from an isolated enaminone gave a result identical to that of the corresponding three-component reaction.

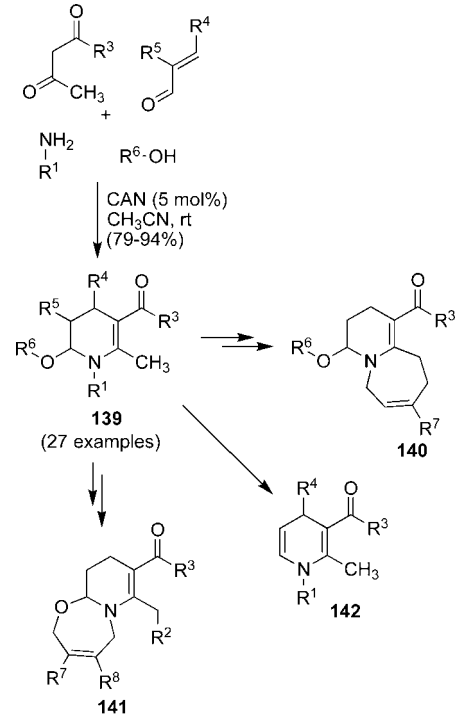
Scheme 130



Scheme 131



Scheme 132



8.4. Synthesis of Imidazoles

The reaction between benzyl or benzoin, ammonium acetate, and aromatic or heteroaromatic aldehydes in the presence of 10 mol % of CAN in 1:1 ethanol−water at 65 °C gave 2,4,5-triarylimidazoles in excellent yields. The use of terephthalaldehyde under similar conditions allowed the preparation of bis(2-imidazolyl)benzenes (Scheme 131).[156] The influence of ultrasound on this reaction has been subsequently studied, and it was shown that it allowed the reduction of the CAN loading to 5 mol % and the reaction to be carried out at room temperature.[157] A mechanism similar to the one found in Scheme 124 has been proposed to explain the oxidation of benzoin prior to condensation.[158]

8.5. Synthesis of 1,2,3,4-Tetrahydropyridines

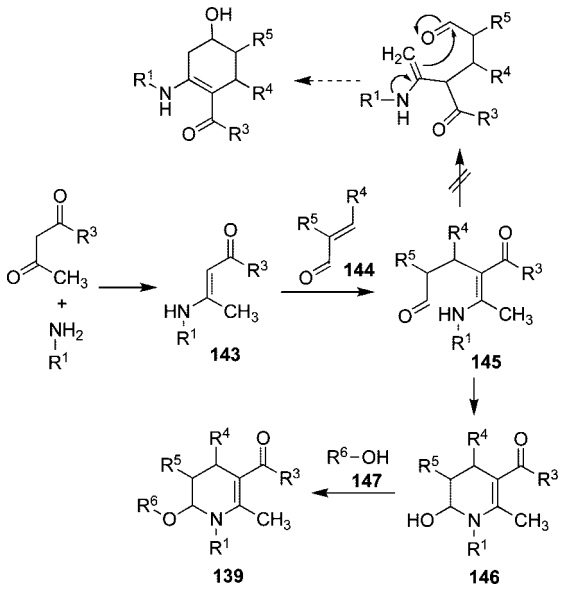
The sequential four-component reaction catalyzed by 5% CAN between primary aliphatic amines, β-ketoesters or β-ketothioesters, α,β-unsaturated aldehydes, and alcohols in acetonitrile at room temperature afforded tetrahydropyridines **139** in excellent yields (Scheme 132, Table 29).[159] This reaction allowed the very efficient synthesis of 1,2,3,4-tetrahydropyridine systems bearing up to five substituents,

Table 29. Selected Examples of the CAN-Catalyzed Synthesis of 1,2,3,4-Tetrahydropyridines by Four-Component Reaction between Primary Aliphatic Amines, β-Ketoesters or β-Ketothioesters, α,β-Unsaturated Aldehydes, and Alcohols

entry	R^1	R^3	R^4	R^5	R^6	yield of **139** (%)
1	^{n}Bu	OEt	H	H	Et	93
2[a]	^{n}Bu	OEt	H	Me	Et	86
3[a]	allyl	OMe	Me	H	Me	90
4	Bn	OEt	H	H	Et	80
5	allyl	S^{t}Bu	H	H	Et	86
6	ally	OEt	H	H	allyl	88
7	ally	OEt	H	H	2-butenyl	85
8	ally	OEt	H	H	prenyl	86
9	ally	OEt	H	H	propargyl	88
10	ally	OEt	H	H	2-hexynyl	88
11	propargyl	OEt	H	H	allyl	90
12	propargyl	OEt	H	H	2-butenyl	90

[a] As a 1:1 diastereomeric mixture.

Scheme 133



two of which were functional groups. This transformation has water as the only side product and allows the generation of four bonds in a single operation, two C−N, one C−O, and one C−C bond. The tetrahydropyridine compounds were subsequently transformed into homoquinolizines **140**[159] and fused 1,3-oxazepines (**141**) related to peptidomimetic structures using several ring-closing metathesis strategies.[160] They were also good starting materials for the synthesis of 5,6-unsubstituted 1,4-dihydropyridines **142**.[161]

A mechanistic rationale of the tetrahydropyridine synthesis is summarized in Scheme 133. The initial CAN-catalyzed reaction between amines and β-keto(thio)esters gives β-enaminones **143**. Their Michael addition to the enone system in aldehydes **144** affords intermediates **145**, followed by subsequent cyclization of the latter to 2-hydroxytetrahydropyridines **146**, which are finally transformed into the observed products **139** by nucleophilic displacement of their hydroxy group by a molecule of alcohol **147**. The main experimental observations that support this proposal can be summarized as follows: (a) Reactions starting from isolated enaminones **143** give results identical to those starting from the amines and 1,3-dicarbonyl compounds. (b) Intermediates **146**, although unstable, can be isolated by carrying out the reaction in the absence of alcohols **147** and are transformed into the final products **139** under the multicomponent reaction conditions. (c) Furthermore, it was found that the reaction between aliphatic amines, acrolein, ethyl acetoacetate, and ethanol in the presence of a large amount of a radical trap, 1,1-diphenylethylene, showed no noticeable loss in yield. This discards a radical mechanism, and hence it suggests that CAN behaves as a Lewis acid.

It is interesting to note the difference between this behavior and the one previously found in a similar reaction employing chalcones, which, as mentioned in section 8.3, afforded cyclohexene derivatives.

8.6. Synthesis of 1,4-Dihydropyridines

Besides the previously mentioned protocol based on the elimination of a molecule of alcohol from 6-alkoxy-1,2,3,4-tetrahydropyridines,[161] CAN has been shown to be a good catalyst for the Hantzsh dihydropyridine synthesis, one of the oldest and best known multicomponent reactions that is still widely used.[162] In this context, the Yao group reported the efficient, one-pot synthesis of polyhydroquinolines from cyclic 1,3-diketones, β-ketoesters, aromatic aldehydes, and ammonium acetate in the presence of 5 mol % CAN (Scheme 134 and Table 30). Interestingly, the reaction did not afford as side products dihydropyridines arising from the reaction between the ammonium salt, the aromatic aldehyde, and 2 equiv of a β-ketoester. Another interesting observation was that the use of acetylacetone instead of β-ketoesters led to decreased yields. This was attributed to the higher reactivity of acetylacetone (pK_a 9, while pK_a for methyl acetoacetate is 11), which presumably favored the formation of side products. To understand the role of CAN in the reaction, the authors assayed the use of CeF_4, another source of cerium(IV), and found that it was equivalent to CAN. Interestingly, ammonium chloride gave also very good results, and hence it was proposed that in this case both cations in CAN may act as catalysts. On the other hand, cerium(III) chloride was found to be a poor catalyst for the Hantzsch reaction.[163] Further examples of the CAN-catalyzed Hantzsch polyhydroquinoline synthesis were described subsequently by another group.[164]

Despite their widespread use, neither the Hantzsch method nor related reactions[163] can be considered as general dihydropyridine syntheses, because they do not allow the easy preparation of some important types of derivatives, including

Scheme 134

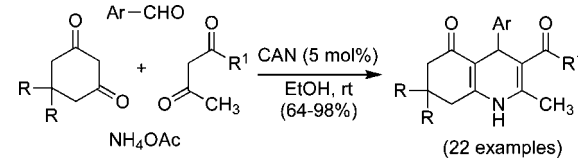


Table 30. Selected Examples of the CAN-Catalyzed Hantzsch Synthesis of Polyhydroquinolines

entry	Ar	R	R^1	reaction time	yield (%)
1	Ph	H	OEt	1.5 h	98
2	4-$CH_3OC_6H_4$	H	OEt	2.5 h	88
3	3-$NO_2C_6H_4$	H	OEt	50 min	98
4	2-furyl	H	OEt	35 min	90
5	2-thienyl	H	OEt	25 min	90
6	Ph	CH_3	OEt	1 h	92
7	4-ClC_6H_4	CH_3	OEt	35 min	88
8	Ph	H	CH_3	1 h	65
9	2-thienyl	H	$OCH_2CH_2OCH_3$	7 h	64

Scheme 135

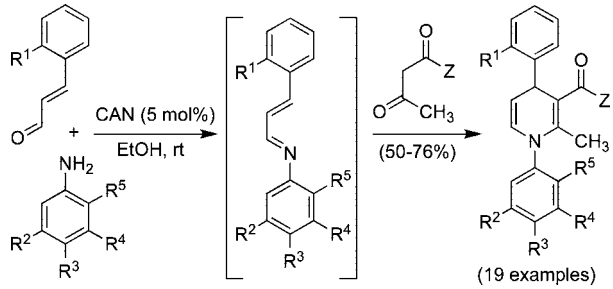


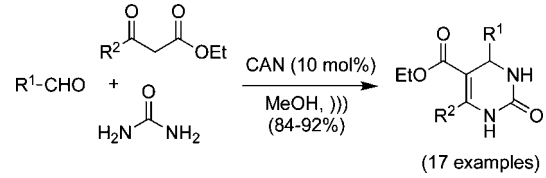
Table 31. Representative Examples of the CAN-Catalyzed, Three-Component Synthesis of 1,4-Diaryl-1,4-dihydropyridines

entry	Z	R^1	R^2	R^3	R^4	R^5	time (h)	yield (%)
1	OEt	H	H	H	H	H	1	74
2	OEt	H	H	CH_3	H	H	1	70
3	OEt	H	H	F	H	H	1	76
4	OEt	H	CH_3	H	H	H	1	71
5	OEt	H	CH_3	CH_3	H	H	1	72
6	OEt	H	H	Br	H	H	1	74
7	OEt	NO_2	H	H	H	H	1	50
8	O′Bu	H	H	H	H	H	2	52
9	O′Bu	H	H	CH_3	H	H	2	61
10	S′Bu	H	H	Cl	H	H	1	63
11	S′Bu	H	H	CH_3	H	CH_3	1	63

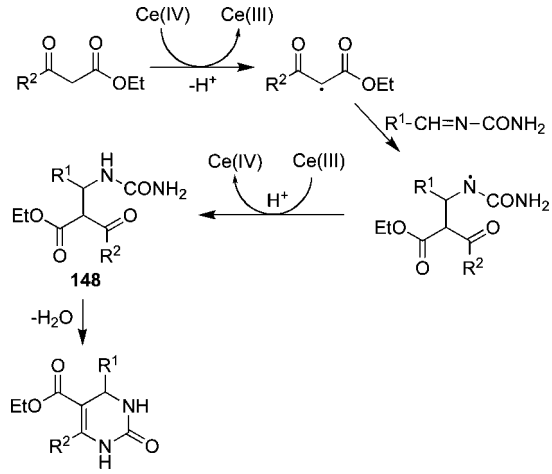
N-aryl-1,4-dihydropyridines and C_5-C_6-unsubstituted 1,4-dihydropyridines. To overcome these limitations, we developed a new CAN-catalyzed multicomponent procedure for the synthesis of dihydropyridines, based on the reaction between aromatic amines, α,β-unsaturated aldehydes, and ethyl acetoacetate in ethanol solution, as shown in Scheme 135. This reaction proceeded normally in good yields and tolerated several types of electron-releasing and electron-withdrawing groups at all positions of the nitrogen aryl substituent. The aryl group at the α,β-unsaturated aldehyde component can also bear substituents, and the reaction could also be extended to include the use of *tert*-butyl β-ketothioesters as starting materials (Table 31).[165] Both the Jørgensen[166] and the Kumar[167] groups have subsequently described organocatalyzed versions of this reaction, leading to chiral 1,4-dihydropyridines.

Mechanistically, this dihydropyridine synthesis was found to involve the domino imine formation-Michael addition−condensation sequence shown in Scheme 135, as confirmed by two additional experiments. In the first of them, the purified imine derived from aniline and cinnamaldehyde was treated at room temperature for 1 h with ethyl acetoacetate in ethanol containing 5% CAN and was found to give results identical to those of the three-component protocol. In a second experiment designed to discard an alternative Michael-initiated sequence similar to the one described by Rodriguez,[168] we found that CAN did not catalyze the Michael reaction between ethyl acetoacetate and cinnamaldehyde in ethanol under our conditions, the crude reaction product being composed of unreacted starting materials and a small amount of cinnamaldehyde diethylacetal. When the reaction between cinnamaldehyde, aniline, and ethyl acetoacetate was carried out in the presence of a large amount of 1,1-diphenylethylene, a radical trap, no noticeable loss in yield was found. This result indicates that a radical mechanism is not in operation under the reaction conditions and suggests that CAN acts as a Lewis acid.

Scheme 136



Scheme 137



8.7. Synthesis of 3,4-Dihydropyrimidines by the Biginelli Reaction

The Biginelli reaction, leading to the preparation of 3,4-dihydropyrimidine-2-ones from aldehydes, β-ketoesters, and urea, is another widely used multicomponent reaction.[169] CAN was identified as a good catalyst for the Biginelli reaction, especially under ultrasound irradiation (Scheme 136).[170]

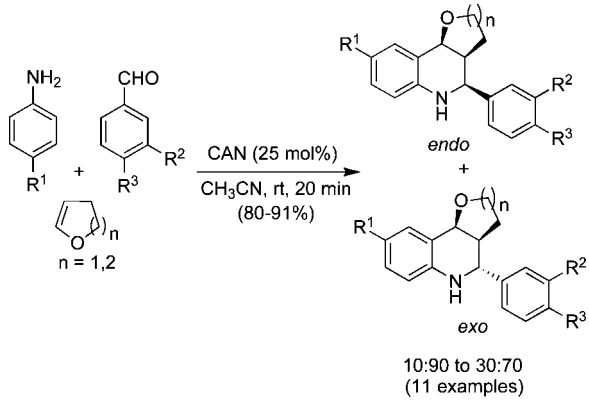
The reaction was proposed to take place by a radical mechanism that is summarized in Scheme 137. Initial formation of the β-ketoester radical would be followed by its addition to an imine generated from urea and the starting aldehyde. The transfer of one electron from Ce(III) would then regenerate Ce(IV) and lead to intermediate **148**, which would then undergo a final cyclocondensation reaction to give the final product. In support for a radical mechanism, another oxidant, manganese(III) acetate in acetic acid, was found to be also an effective promoter of the Biginelli reaction.

8.8. Synthesis of Tetrahydroquinolines via the Three-Component Povarov Reaction

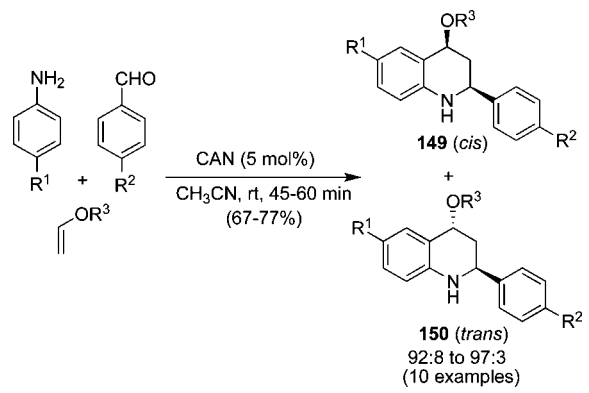
The use of CAN as a catalyst for the imino Diels−Alder reaction between aromatic imines and electron-rich olefins (Povarov reaction) has been mentioned in section 7.3.2. A three-component version of the same reaction, involving anilines, aromatic aldehydes, and 3,4-dihydro-2*H*-pyran or 2,3-dihydrofuran as olefins in the presence of 25 mol % CAN, has also been described. This reaction afforded fused pyrano and furoquinolines as mixtures of exo and endo isomers (Scheme 138).[171]

A close examination of the above quoted paper showed an intriguing discrepancy between the stereochemistry described for the major product of the Povarov reaction and the results obtained with other catalysts.[172] Besides, some key aspects regarding this transformation remained unexplored, including the possibility of employing noncyclic vinyl

Scheme 138



Scheme 139



ethers, which are less reactive than their cyclic counterparts but whose use would expand the scope of the reaction to include nonfused tetrahydroquinoline systems, which are of great chemical and biological relevance.[173] The considerations summarized above prompted us to study these aspects of the CAN-catalyzed Povarov reaction. Our first experiment consisted of the re-examination of the three-component reaction between anilines, aromatic aldehydes, and cyclic vinyl ethers in the presence of 5 mol % CAN, which in our hands gave almost equimolecular amounts of diastereoisomers, but the cis isomers were the major products, in contrast with the previous report.[172] The use of a larger amount of catalyst (25%) as previously described did not change this result.

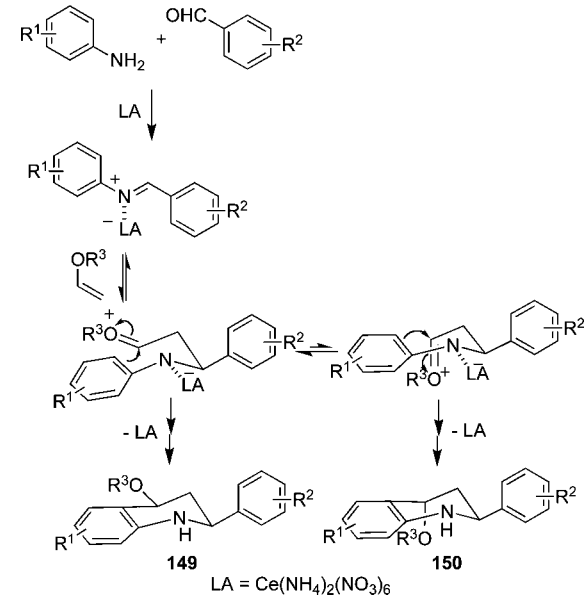
We next examined the influence of CAN on Povarov reactions involving acyclic vinyl ethers. These reactions proceeded in good yields and with almost complete diastereoselectivity, giving the *cis*-tetrahydroquinoline derivatives **149** as the only isolated products and only traces of the *trans*-compounds **150** (Scheme 139 and Table 32).[174]

The cis diastereoselectivity was explained by assuming that the reaction takes place through the three-step mechanism summarized in Scheme 140, involving the initial formation of an imine from the starting anilines and aldehydes, followed by addition of the vinyl ether to give an oxonium derivative that would finally undergo an intramolecular aromatic electrophilic substitution reaction to give the observed products. The fact that a cis arrangement between the alkoxy and aryl groups leads to minimum interactions between these bulky substituents and the axial protons in the chairlike transition state of the cyclization step leading to the tetrahydroquinoline system would explain the observed preference for the formation of the *cis*-tetrahydroquinoline derivatives **149**. The generation of the putative intermediate oxonium species postulated in the above-mentioned stepwise mechanism was confirmed by its trapping by a molecule of solvent when the reaction was carried out in ethanol.[174]

Table 32. Scope of the CAN-Catalyzed Three-Component Povarov Reaction

entry	R^1	R^2	R^3	reaction time (min)	cis:trans ratio	yield of the cis isomer **149** (%)
1	H	H	Et	45	92:8	72
2	F	H	Et	45	97:3	70
3	OCH_3	H	Et	45	95:5	67
4	CH_3	H	Et	60	95:5	70
5	H	CH_3	Et	60	97:3	74
6	H	H	Bu	45	96:4	70
7	F	H	Bu	45	96:4	76
8	CH_3	H	Bu	60	95:5	74
9	H	Cl	Bu	60	97:3	77
10	Cl	H	Bu	60	96:4	71

Scheme 140

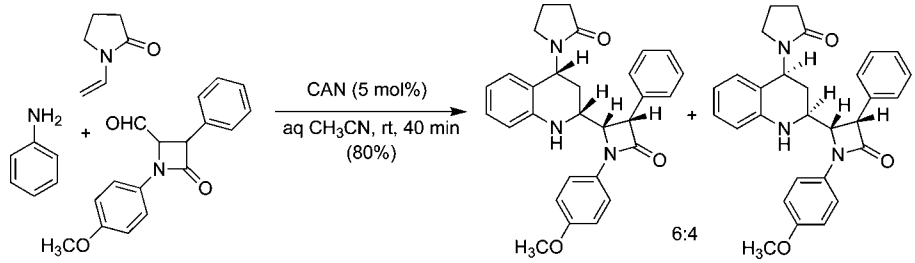


The three-component Povarov reaction was also studied using *N*-vinyl-2-pyrrolidones as the olefin component (see one example in Scheme 141). The tetrahydroquinolines could be easily oxidized to the corresponding aromatic systems by exposure to an excess of CAN.[175]

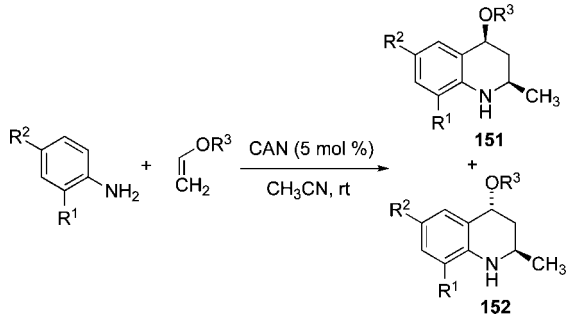
A CAN-catalyzed ABB′ three-component reaction[176] between anilines and two equivalents of vinyl ethers was found to give 2-methyl-1,2,3,4-tetrahydroquinolines in good yields and also with good diastereoselectivities, affording cis compounds **151** as the main products together with small amounts of their trans isomers **152** (Scheme 142).[177] It is interesting to mention that 2-alkyl-1,2,3,4-tetrahydroquinolines are not accessible through standard Povarov chemistry, because of the potential for imine−enamine tautomerism of the intermediate.

This reaction was proposed to proceed through a domino mechanism that comprises five individual steps and includes a Povarov-type cyclization (Scheme 143). Thus, the CAN-catalyzed condensation between the starting aniline and one molecule of the alkyl vinyl ether, which can be regarded as an enol ether derived from acetaldehyde, affords imine **153**, which then undergoes a CAN-catalyzed imino Diels−Alder

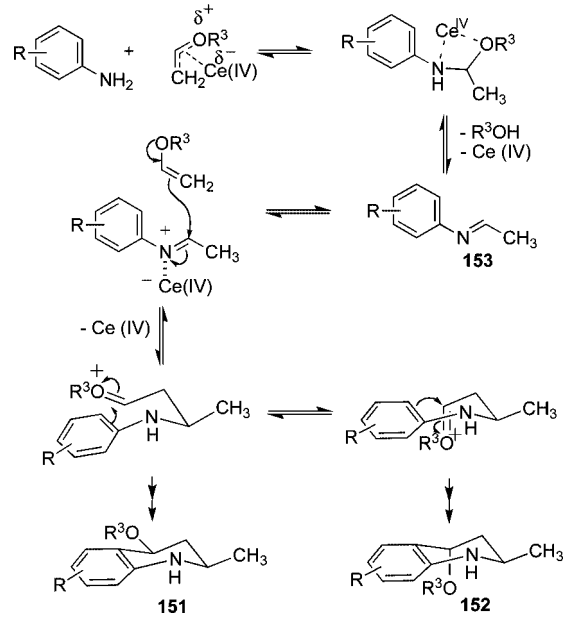
Scheme 141



Scheme 142



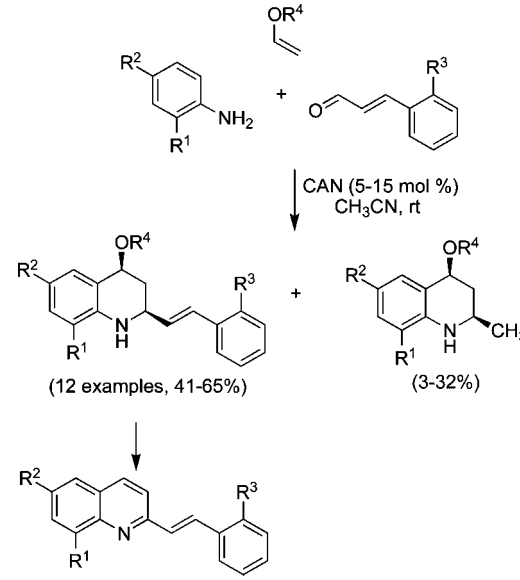
Scheme 143



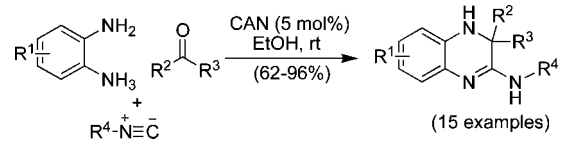
reaction with a second molecule of alkyl vinyl ether, now acting as an electron-rich dienophile, to give the observed tetrahydroisoquinolines. As in the normal Povarov reaction discussed above, the final cyclization step should take place through a chairlike transition state, explaining the preference for an equatorial arrangement of the alkoxy substituent, and hence the cis stereochemistry observed for the major products.

Because of the biological importance of styrylquinolines, especially as inhibitors of HIV integrase,[178] the study of vinylogous Povarov reactions was considered of relevance. As shown in Scheme 144, the CAN-catalyzed reaction between anilines, acyclic enol ethers, and cinnamaldehyde derivatives afforded 2-styryl-1,2,3,4-tetrahydroquinolines with complete diastereoselectivity, although the yields were only moderate because of the competing reaction between the starting aniline and two molecules of vinyl ether to give 2-methyl-1,2,3,4-tetrahydroquinolines. The aromatization of

Scheme 144



Scheme 145



the major products to 2-styrylquinolines was also studied under a variety of conditions.[179]

8.9. Three-Component Synthesis of Quinoxalines

The reaction between *o*-phenylenediamines, cyclic and acyclic ketones, and isocyanides in the presence of 5 mol % CAN in ethanol afforded 3,4-dihydroquinoxalin-2-amines. The reaction was regioselective and afforded only one of the two possible isomers, being regulated by the effect of electron-releasing or electron-withdrawing substituents on the corresponding *p*-amino group (Scheme 145 and Figure 14).[180]

The reaction was proposed to take place by the mechanism summarized in Scheme 146, which involves the CAN-catalyzed formation of iminium cation **154** from the starting diamine and carbonyl compound, followed by nucleophilic addition of isocyanide and intramolecular cylization.

8.10. Three-Component Synthesis of 1,5-Benzodiazepines

Treatment of *o*-phenylenediamines with acyclic and cyclic ketones in the presence of 10 mol % CAN afforded 1,5-benzodiazepines through a three-component reaction involving two molecules of the ketone, which probably has an

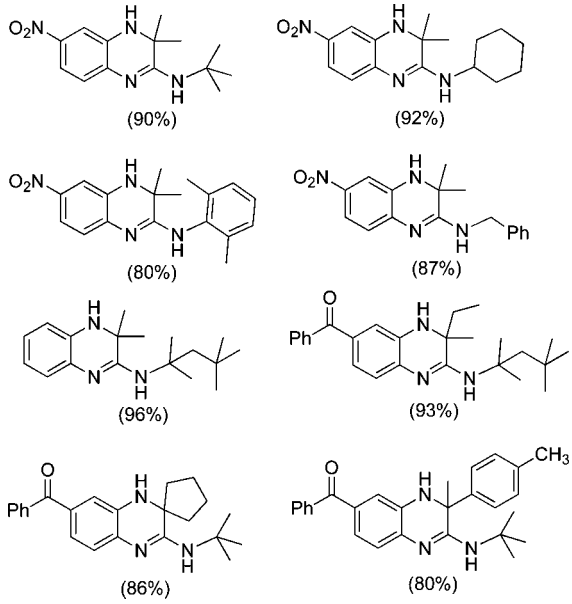
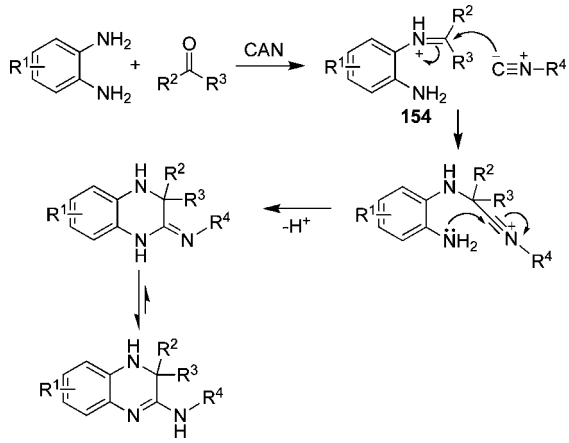
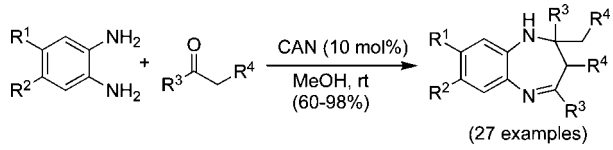


Figure 14.

Scheme 146



Scheme 147



intramolecular imine−enamine cyclization as the key step (Scheme 147 and Figure 15).[181]

8.11. Three-Component Synthesis of Benzoxanthenes and Benzochromenes

The reaction between 2-naphthol, aldehydes, and active methylene compounds such as cyclic 1,3-diketones, malononitriles, or ethyl cyanoacetate in the presence of 5 mol % CAN allowed the efficient, one-pot synthesis of libraries of benzoxanthenes and benzochromenes (Scheme 148). Solvent-free conditions were preferable for this transformation, because the reaction between 2-naphthol, benzaldehyde, and dimedone in different solvents gave also 14-phenyl-14*H*-dibenzo[*aj*]xanthene as a side product. It was subsequently established that this product came from the CAN-catalyzed reaction between 2-naphthol and benzaldehyde.[182]

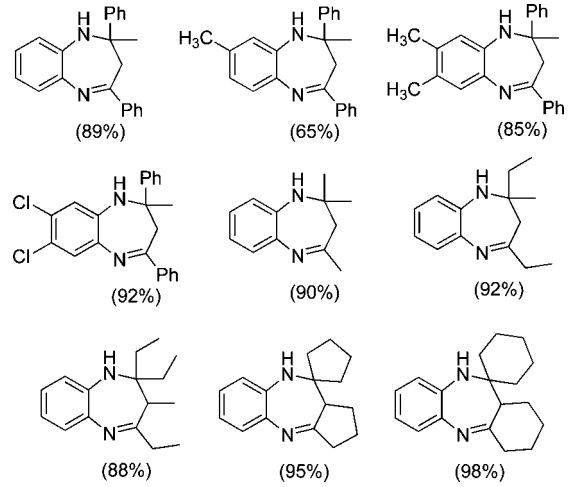
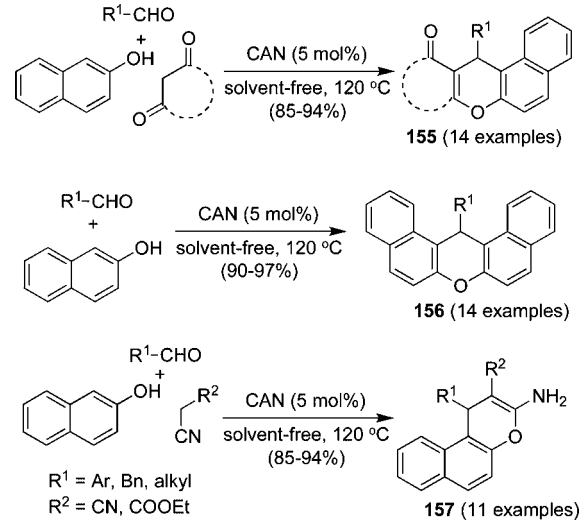


Figure 15.

Scheme 148



The reaction was proposed to be initiated by CAN-catalyzed nucleophilic addition of the β-naphthol on the aldehyde to generate the quinone methide intermediate **158**, followed by a Michael addition of the active methylene compounds and a final intramolecular dehydration (Scheme 149). In the absence of the 1,3-diketone, intermediate **158** is attacked by another molecule of β-naphthol to give the side product **156**.

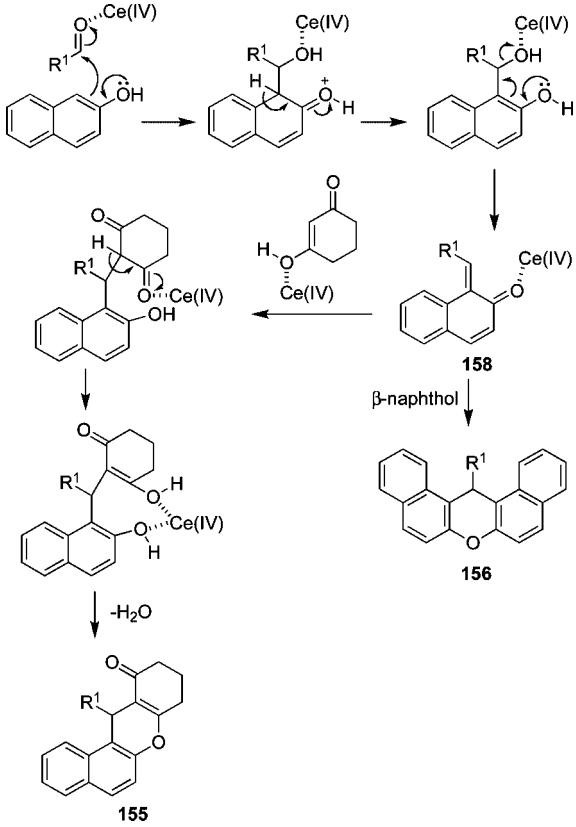
9. CAN as a Polymerization Inducer

Although it is not fully within the scope of this Review, for the sake of completeness we will make a brief commentary on the use of CAN as an initiator of radical polymerization reactions. Much of this work was devoted to the development of graft polymerization procedures onto sugar backbones, including carboxymethylcellulose,[183] starch,[184] chitosan,[185] and carboxymethylchitosan.[186] Other applications include the grafting of water-solubilizing moieties onto carbon nanotubes[187] and the electroinduced synthesis of photoconductive copolymers of *N*-vinylcarbazole and the methyl ethyl ketone-formeldehyde resin.[188]

10. Conclusion

We have shown that CAN is an excellent, multipurpose catalyst that can be used to promote a wide range of

Scheme 149



synthetically relevant reactions that go well beyond its traditional role as an oxidant. These reactions are characterized by their experimental simplicity and mild reaction conditions. From a mechanistic point of view, they may proceed via processes initiated by a one-electron oxidation, or alternatively CAN may act as a Brønsted acid catalysis, due to the generation of protons by hydrolysis of the nitrate anion, or as a Lewis acid. In this connection, the low cost and air stability of CAN may make it a useful alternative to the expensive, hygroscopic lanthanide triflates. While the results described here are a more than adequate proof of the validity of CAN as a catalyst, most of the work that we summarize here has been published in the past few years, meaning that there is still much new ground to explore. We hope that this Review will serve to stimulate research in this fascinating and very useful area of catalysis.

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