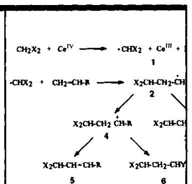
Carbon–carbon bond forming reactions mediated by cerium(IV) reagents



CHEMICAL
SOCIETY
REVIEWS

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Organic synthesis using carbon centred radicals generated by one electron oxidants is of current interest. Although $Mn(OAc)_3$ has received the most attention, it appears that cerium(IV) ammonium nitrate (CAN) would be a very useful reagent for the generation of radicals. The recent applications of CAN in the construction of C–C bonds are highlighted in this review. CAN has been shown to mediate the facile oxidative addition of 1,3-dicarbonyl compounds to activated and unactivated alkenes leading to dihydrofurans and furanones. In most cases the reactions occur under milder conditions and the yields are superior when compared to $Mn(OAc)_3$ mediated reactions. The results available thus far suggest that CAN offers vast potential in radical mediated organic synthesis.

The fundamental task in the synthesis of organic compounds, simple or complex, is the construction of carbon–carbon bonds. Among the various synthetic methods involving polar, radical or pericyclic reactions available for C–C bond formation the free radical reactions have received the least attention until recently, largely due to the erroneous notion that they lack selectivity and are uncontrollable. The past decade, however, has witnessed a dramatic resurgence of interest in the use of radical methodology[1] which is attributable in large measure to the conceptualization and demonstration by Stork[2] that the controlled formation as well as the addition of vinyl radicals to alkenes offers a unique and powerful method for complex carbocyclic constructions. The insightful investigations of Julia,[3] Beckwith,[4] Ingold[5] and others leading to a clear understanding of the structure and reactivity of carbon centred radicals and the innovative synthetic applications[1] by Giese, Curran and Pattenden[6] have contributed significantly to the acceptance of radical methodology. Today there is widespread appreciation of the potential offered by radical processes especially in the synthesis of structurally fascinating and biologically important natural products.

Various procedures involving chemical,[1] electrochemical[7] and photochemical[8] methods are known for the generation of radicals. In particular, oxidative methods[1,9,10] mediated by metal salts with adjacent stable oxidation states like those of Mn^{III}, Co^{II}, Cu^{II}, Fe^{III} and V^{V} have received considerable attention. The major difference between oxidative methods and the traditional approaches is the dual role the metal oxidants play in these reactions. *i.e.*, the initial one electron oxidation of the carbonyl compound will generate the electrophilic carbon radical which is not easily oxidised but can add efficiently to electron rich alkenes. The resulting adduct radical is more susceptible to oxidation and the products are often derived from the intermediate cation by inter- or intra-molecular capture of nucleophiles or by loss of a proton to form an alkene.

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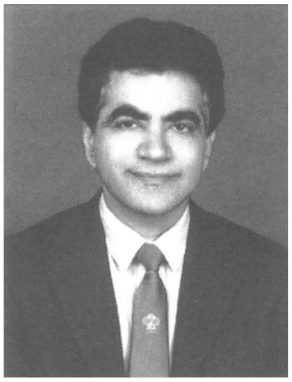

Vijay Nair

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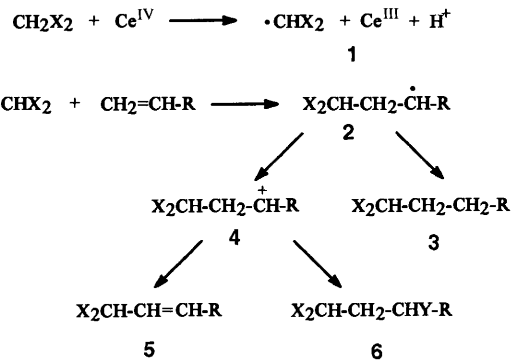
Despite the fact that $Mn(OAc)_3$ occupies a unique position among the one electron oxidants and has served as a key reagent in the synthesis of a number of important natural products,[9,10] the procedural problems associated with the use of this reagent often limit its application. Naturally, there has been considerable interest in developing newer reagents and methods for generating radicals. The pioneering work of Heiba and Dessau[11] and some subsequent investigations have shown that cerium(IV) salts can be used for the generation of radicals. This review focuses on recent advances in the application of cerium(IV) ammonium nitrate (CAN) in the construction of C–C bonds highlighting our own investigations in this area.

2 Oxidative addition of carbonyl compounds to alkenes and arenes

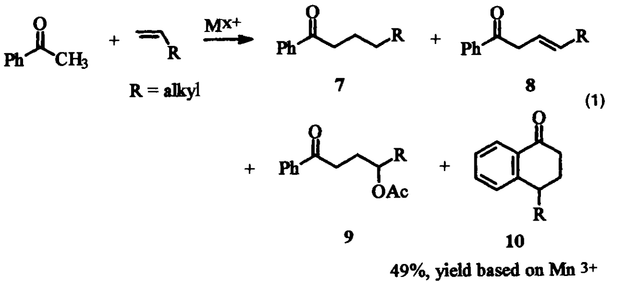
The first example of the Ce^{IV} mediated generation of carbon centred radicals involves electrophilic carbon radical[11] $\cdot CHX_2$ generated by $Ce(OAc)_4$ from CH_2X_2 and its addition to alkenes to give products **3**, **5** or **6** according to the general reaction sequence given below.



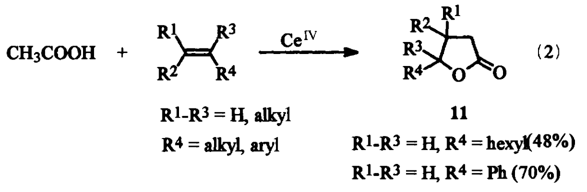
X = COOR, COR *etc.*, and Y is any nucleophilic species present in the reaction mixture

Scheme 1

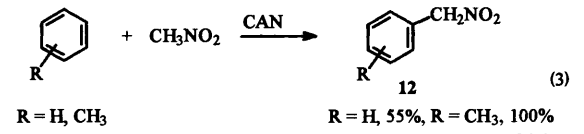
The success of the reaction rests on the selective oxidation of radical **2** by the metal ion. The initially formed α-keto radical **1** is not easily oxidised due to the electron withdrawing character of the carbonyl group whereas the secondary alkyl radical **2** undergoes rapid oxidation leading to the product **5** or **6**. When an aryl ketone such as acetophenone was used, in addition to the three expected products **7**, **8** and **9**, a new product α-tetralone **10** was obtained (total yield, 64%) presumably by the addition of the intermediate radical to the benzene ring [eqn. (1)].

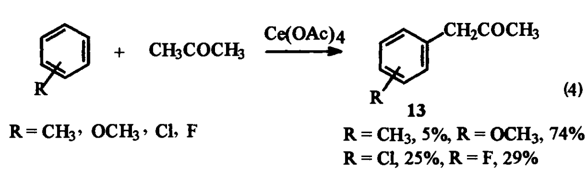


As an extension of this reaction, lactones were synthesized from alkenes and carboxylic acids[12] [eqn. (2)].

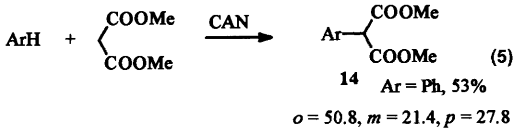


Aromatic nitromethylation[13] and acetonylation[14] have been reported to give substitution products as shown in eqns. (3) and (4).



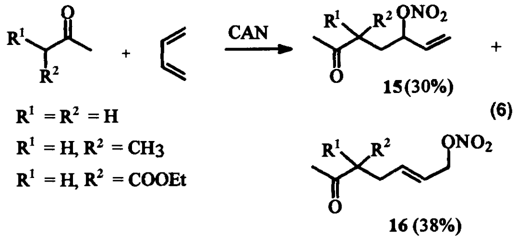


It may be pointed out that except for lactone synthesis[12] and the nitromethylation of aromatics[13] in which CAN was used as the oxidising species, all the earlier experiments involved the use of the unstable $Ce(OAc)_4$ in acetic acid medium. An important advance in this area was made by Baciocchi and Ruzziconi[15,16] who demonstrated that CAN-mediated oxidative addition reactions proceed well in solvents such as methanol and acetonitrile, thus leading to wider acceptance of CAN. The malonylation of aromatic compounds[15] mediated by CAN in methanol is an example [eqn. (5)].

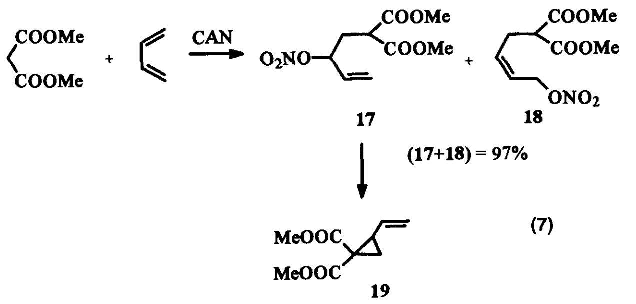


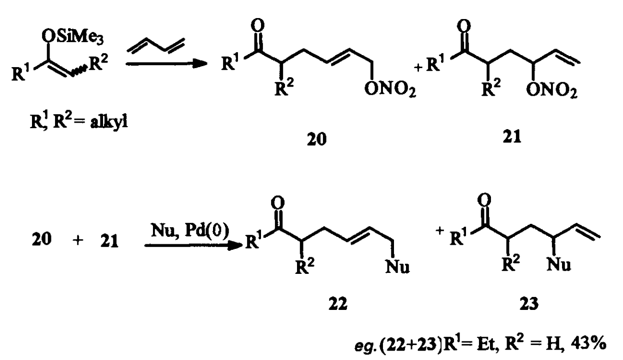
3 Oxidative additions to dienes

There are limited reports[16] on reactions in which 1,3-butadiene acts as a radical trap. The CAN mediated oxidative addition of carbonyl compounds such as acetone, butan-2-one and ethyl acetoacetate to butadiene resulted in a mixture of 1,2- and 1,4-adducts whereas the addition of dimethyl malonate furnished substituted cyclopropanes [eqns. (6) and (7)].



Recently trimethyl silyl enol ether[17] was added to 1,3-butadiene in presence of CAN and the resulting mixture of nitrates subjected to nucleophilic attack with sodium dimethyl malonate in presence of Pd^0; alkylated adducts **22** and **23** were obtained (Scheme 2).

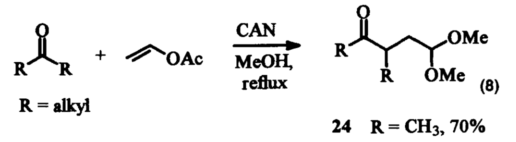


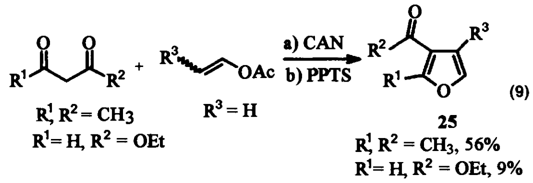


Scheme 2

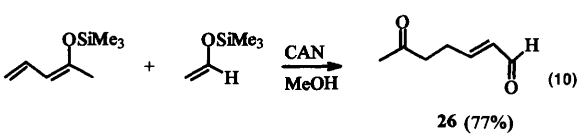
4 Oxidative additions to activated alkenes

Activated alkenes, such as enol ethers, enol acetates and enol silyl ethers take part in the oxidative addition reactions smoothly. Synthesis of 4-ketoaldehyde dimethyl acetals and 3-acyl furans by the addition of carbonyl and 1,3-dicarbonyl compounds respectively to enol acetates[18] are examples.

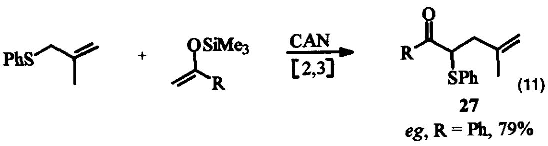


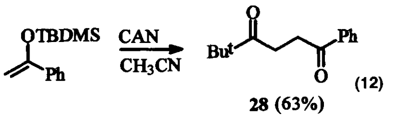


The cross coupling of 1,2-disubstituted silyl enol ethers with other enol ethers has been exploited in the synthesis of 1,4-dicarbonyl compounds.[19]



Additions of silyldienol ethers to silyl enol ethers,[20] silyloxy cyclopropanes to 1,3-butadiene[21] and 1,3-dicarbonyl compounds to allyl trimethyl silanes[22] are some other contributions in this area. The cation radicals generated from allyl phenyl sulfides and enamines undergo addition to silyl enol ethers[23] leading ultimately to the unsaturated ketone **27** and the 1,4-dicarbonyl compound **28** [eqns. (11) and (12)]. Similarly, the reaction of α-nitroalkyl radicals,[24] generated by the oxidation of nitronate anions, to silyl enol ethers proceeds well to afford β-nitroketones.





5 Oxidative additions to cyclic and acyclic unactivated alkenes

It is evident from the foregoing discussion that most of the CAN mediated oxidative additions of carbonyl compounds reported earlier involved activated alkenes. There has been no systematic investigation of Ce^{IV} mediated generation of radicals and their additions to cyclic and acyclic alkenes particularly unactivated ones. We have therefore undertaken a detailed study of Ce^{IV} mediated oxidative addition of active methylene compounds to such systems.[25] The dicarbonyl compounds chosen for the study include dimedone, acetylacetone, ethyl acetoacetate and dimethyl malonate (Fig. 1); the alkenes used are shown in Fig. 2.

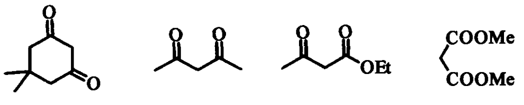


Fig. 1

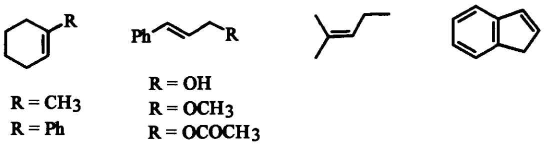
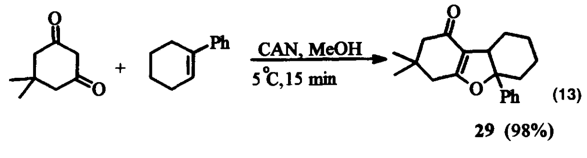


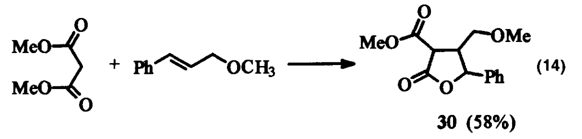
Fig. 2

CAN mediated addition of all the dicarbonyl compounds except dimethyl malonate occurred smoothly and rapidly furnishing dihydrofurans in good yields.[25] A typical example is shown in eqn. (13). Similar reaction of 1,3-dicarbonyl compounds with alkenes in the presence of cobalt(II) acetate and oxygen[26] has been reported to yield dihydrofurans in moderate to good yields.

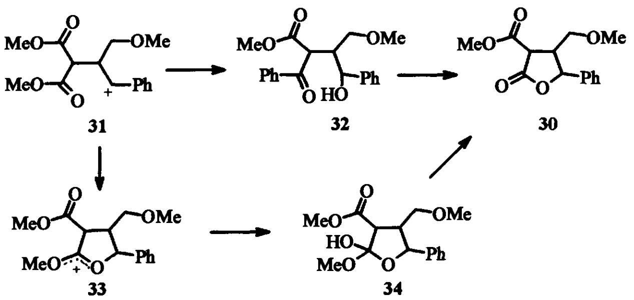


A comparative study of these reactions[25,27] *vs.* those mediated by $Mn(OAc)_3$ has revealed that CAN is a superior reagent in terms of the mildness of the procedure, experimental simplicity and higher yields of products. As an illustration, the formation of **29** in 98% yield by CAN mediated reaction in methanol at 5 °C may be contrasted with its formation in 41% yield by the $Mn(OAc)_3$ mediated procedure at the reflux temperature of acetic acid.

Unlike dimedone and acetylacetone, dimethyl malonate adds to most of the alkenes to provide lactones.[27] For example the reaction of dimethyl malonate with cinnamyl methyl ether in aqueous methanol furnished **30** [eqn. (14)].



The formation of lactone **30** may be explained as follows. The addition of dimethyl malonyl radical to cinnamyl methyl ether followed by oxidation of the resulting radical with CAN would produce the cation **31**. Since the reaction is done in aqueous methanol, **31** would be easily converted to **32** which would undergo lactonization to render **30**. Alternatively, **34** formed from **31** *via* the stabilized cation **33** can lose methanol to afford **30** (Scheme 3).



Scheme 3

As expected, extension of these reactions to exocyclic alkenes (Fig. 3) provided spirodihydrofurans[28] [eqn. (15)].

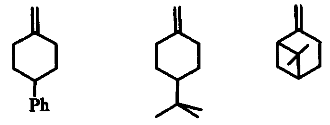
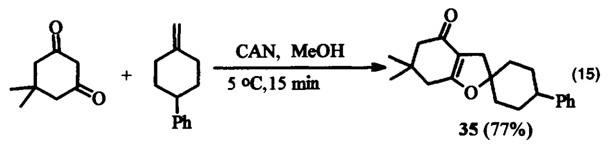
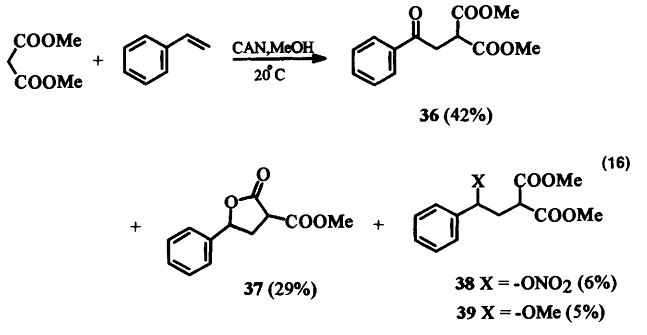


Fig. 3

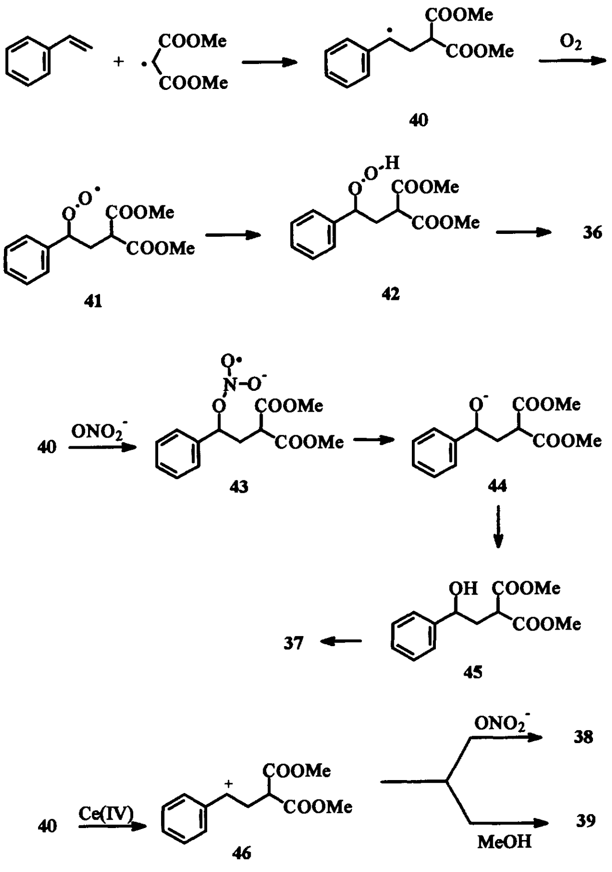


6 Oxidative additions to styrenes

An unprecedented and mechanistically fascinating reaction was encountered between dimethyl malonate and styrene.[29] When dimethyl malonate was reacted with styrene in presence of CAN, we obtained the ketone **36** and the lactone **37** as the major products [eqn. (16)]. Small amounts of **38** and **39** were also isolated. Interestingly, this contrasts with an earlier report[30] on the exclusive formation of **38** and **39** in this reaction.

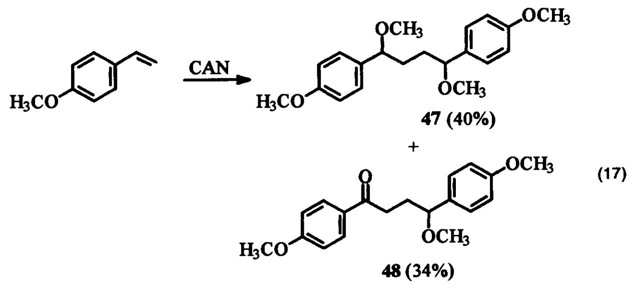


A tentative mechanism along the following lines may be suggested for the formation of these products. The benzylic radical **40** formed by the addition of malonyl radical to styrene gets quenched by molecular oxygen to furnish the peroxyl radical **41** which will be easily converted to the hydroperoxide **42**. The oxidative cleavage of **42** would lead to the ketone **36**. Support for this rationale is obtained from the fact that when the experiment was carried out under argon atmosphere only products **37**, **38** and **39** were isolated. The fragmentation of the radical anion **43**, derived from **40** by ligand transfer or reaction with nitrate, followed by protonation of the resulting alkoxide to the carbinol and lactonization of the latter would furnish **37**. The mechanism for the formation of nitrate **38** can involve either the oxidation of **43** or the trapping of the benzylic cation **46** by NO_3^-. Similarly **46** can be trapped by methanol to afford **39** (Scheme 4). An analogous reaction was observed with dimethyl malonate and a variety of ring substituted styrenes.

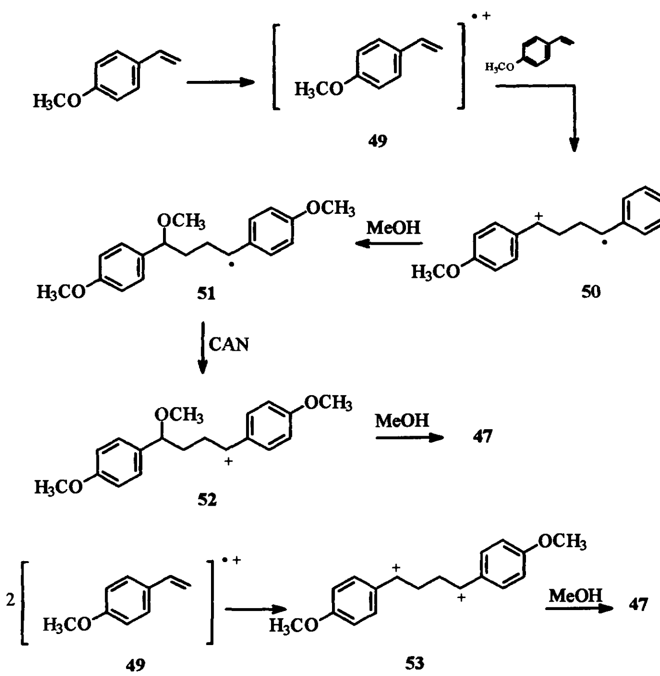


Scheme 4

While attempting to add dimethyl malonate to 4-methoxy styrene, we observed the exclusive formation[31] of dimeric products **47** and **48**.



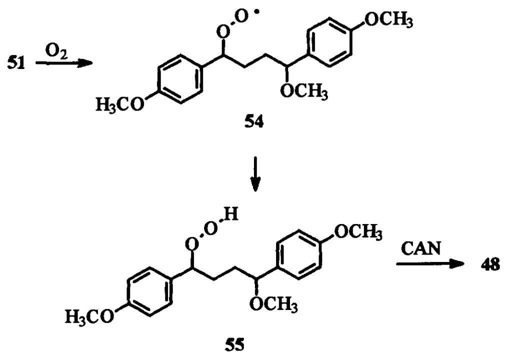
The formation of **47** and **48** may be explained as follows. Methoxy styrene gets oxidised by CAN to the radical cation **49** which then adds to another molecule of methoxy styrene leading to the intermediate **50**. Methanol addition to **50**, oxidation of the resulting radical **51** to the cation **52** and



Scheme 5

subsequent trapping of the latter by methanol would furnish **47**. Dimerization of radical cation **49** followed by the trapping of the dication by methanol **53** is also a valid possibility (Scheme 5).

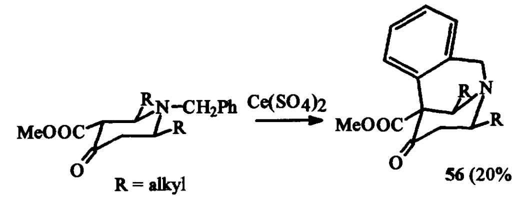
Alternatively, radical **51** may be trapped by molecular oxygen to give the peroxyl radical **54** which will be easily converted to the hydroperoxide **55**. The latter on oxidative fragmentation would provide the ketone **48** (Scheme 6).



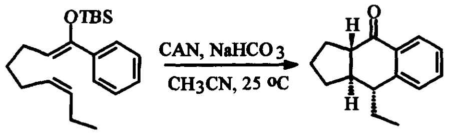
Scheme 6

7 Intramolecular and tandem cyclizations

Intramolecular cyclization of radicals generated by Ce^{IV} reagents has received only limited attention *vs.* $Mn(OAc)_3$. The cyclization of 1-benzyl-2,6-disubstituted-4-piperidone-3-carboxylic acid methyl ester with $Ce(SO_4)_2$ to **56** in low yields is an example.[32]

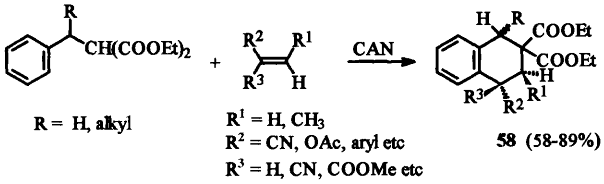
 (18)

The oxidative cyclization of silyl enol ethers of aryl ketones has been reported to provide tricyclic ketones.[33]

 (19)

57 (70%)

A report on the oxidative cyclization of dimethyl-4-pentenyl malonate has also appeared.[34] The oxidation of substituted diethyl α-benzyl malonate in the presence of alkenes produced highly functionalized naphthalenes.[35]

 (20)

8 C–C bond forming reactions mediated by Ce^{IV} *vs.* other reagents

It can be discerned from the foregoing discussion that Ce^{IV} reagents will prove to be of great value in organic synthesis. Comparative studies of Ce^{IV} with other species, especially, Mn^{III} would be particularly worthwhile. With few exceptions,[1,26] no systematic investigations involving such comparisons have been carried out. It has been reported that the order of relative reactivity of the oxidation of secondary alkyl radicals by Mn^{III}, Ce^{IV} and Cu^{II} is of the order of 1 : 12 : 350.[11] In the nitromethylation of aromatic compounds with nitromethane, Ce^{IV} salts were found to be the most promising. In the synthesis of isomeric α-nitroxylenes from xylenes and α-nitrotoluene from toluene, Ce^{IV} gave nearly 100% yield. Lower yields are observed when Ce^{IV} salts are used together with Cu^{II},[13] and only with Co^{III} acetate was any nitromethylated product observed. It is also known that Ce^{IV} reagents gave higher yields and are superior in their control of regiochemistry in alkan-2-one coupling. They can be applied efficiently in intermolecular reactions, which is not the case with Mn^{III} promoted coupling.[1] The available data clearly indicate that in intermolecular C–C bond forming reactions Ce^{IV} mediated processes are more efficient than those mediated by Mn^{III}

9 Conclusion

The credentials of CAN as a useful reagent for C–C bond formation have been recognized Most of the work using CAN has involved intermolecular reactions, it however is reasonable to assume that CAN will prove its usefulness in the intramolecular situation as well There are indications that investigations in this direction will be rewarding From a future perspective, investigations aimed at unravelling the mechanistic details of Ce^{IV} mediated reactions and efforts to make them catalytic will be very worthwhile The solubility of CAN in solvents such as methanol and acetonitrile, the mild reaction conditions and the relatively low toxicity of cerium *vis* transition metals are all factors that will help CAN find a prominent place in the repertory of synthetic organic chemistry

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