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# *meta*-Chloroperbenzoic acid (*m*-CPBA): A Versatile Reagent in Organic Synthesis

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## Contents

**Abstract**: Synthetic uses of different peroxides for organic synthesis have been studied widely. Among these peroxides *meta*-chloroperbenzoic acid (*m*CPBA) is an efficient oxidizing reagent and used for many oxidative transformations. *m*CPBA widely used in for chemical transformations such as oxidation of carbonyl compounds, iminoindolines, olefins, imines, alkanes, silyl enol ethers, *N*- and *S*-heterocycles, active methylene

groups, fluoromethylated allylic bromides, cyclic acetals, N-substituted phthalimidines, selenides, furans and phosphates. The purpose of this review is to collect and discuss the synthetic application of *meta*-chloroperbenzoic acid (*m*CPBA) over the few decades.

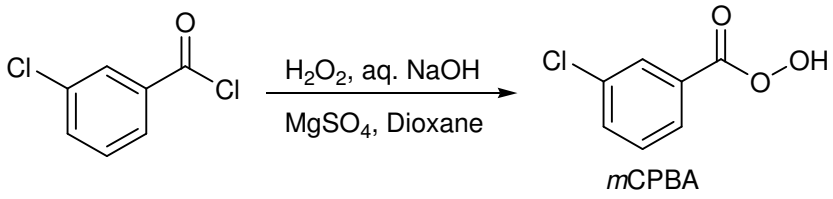
## 1. Introduction

Oxidation reactions in synthetic organic chemistry constitute one of the more important transformations employed on a regular basis and are widely used in the production of pharmaceuticals, agrochemicals and their intermediates.[1-6] However, and on the other hand, oxidations are among the most problematic processes in term of safety, environmental friendliness and operational simplicity. Often severe reaction conditions as well as the highly reactive nature of oxidants restrict their application to large scale synthetic protocols which is most likely a reason why so many basic research papers and new patents dealing with such fundamental transformations have appeared over the recent past.[6]

Organic peroxides, because of their exceptional reactivity and oxidative potential are widely used in research laboratories. Organic peracids are versatile reagents capable of oxidizing a variety of functional groups under generally mild conditions. Among organic peroxides, *meta*-chloroperbenzoic acid (*m*CPBA) is a peroxycarboxylic acid used widely as an oxidant in organic synthesis due to its versatile oxidizing power and relative ease of handling.[7] Its unique reactivity is characterized by a weak O-O bond and a nucleophilic OH group. The O-O bond of *m*CPBA transfers an oxygen atom to electron-rich substrates, while the nucleophilic attack of *m*CPBA on ketones and aldehydes results in insertion of an oxygen atom.[8]

Intially *m*CPBA was has been used extensively for the determination of the total unjaturation in various types of organic compounds.[9] In recent decades *m*CPBA has been used oxidation of carbonyl compounds, alcohols, iminoindolines, olefins, alkynes, carboxylic acids, amines, imines, alkanes, silyl enol ethers, *N*- and *S*-heterocycles, active methylene groups, fluoromethylated allylic bromides, cyclic acetals, ketals, diazoketones, *N*-substituted phthalimidines, selenides, furans, phosphates, and *N*-oxidation.[10] *m*CPBA can be prepared by the reaction of *m*-chlorobenzoyl chloride with $H_2O_2$ in presence of $MgSO_4.7H_2O$, aqueous NaOH and dioxane (Scheme 1).[11]

**Scheme 1. Preparation of *m*CPBA.**




**Scheme 1**

*m*CPBA is a white powder (mp 90 °C), easy to handle, flammable, and hygroscopic. It is soluble in $CH_2Cl_2$, $CHCl_3$, 11,2-dichloroethane, EtOAc, EtOH, *t*-BuOH, $Et_2O$, benzene and also it is slightly soluble in hexane, $CCl_4$ and insoluble in $H_2O$. However pure *m*CPBA is shock-sensitive and can deflagrate. Moreover it is potentially explosive beyond 85% purity and shows 1% degradation per year at room temperature.[10] It is interesting to note that 85% *m*CPBA is not shock-sensitive and it should be stroed in a refrigerator in tightly closed containers. *m*CPBA irritates the mucous membranes, respiratory tract, eyes and skin and moreover skin contact with *m*CPBA cause in burns

and blisters. Therefore it is recommended that *m*CPBA should be used only in a chemical fume hood.

*m*CPBA has been frequently employed over the years with many examples of its use on pilot scale and pharmaceutical manufacturing.[12] However, the safety concerns with its use on scale-up are also well-known, with the pure solid being shock-sensitive and potentially explosive in the condensed phase.[12] The commercial grade (70-77 wt %) although somewhat stabilised with chlorobenzoic acid and water still represents a significant concern when used on scale.[12] It has been reported that $CH_2Cl_2$ could be a safer solvent for preparation of *m*CPBA solution, but recently it has been reported that that that $CH_2Cl_2$ cannot be viewed as an inherently safer solvent for preparation of *m*CPBA solutions at high concentration (large scale). However on implementation of some safety measures *m*CPBA/DMF solutions could successfully applied at large. *m*-CPBA is a white powder and soluble in $CH_2Cl_2$, $CHCl_3$, 1,2-dichloroethane, ethylacetate, benzene, and ether. However *m*-CPBA is slightly soluble in hexane and insoluble in water.[13]

In this review, we summarise the most important accomplishments in the chemistry of *m*CPBA-mediated oxidative tranformations, with a hope to encourage the development of novel, more prospective synthetic applications in the near future. The review will abbreviate *meta*-chloroperbenzoic acid as *m*CPBA in the subsequent sections.

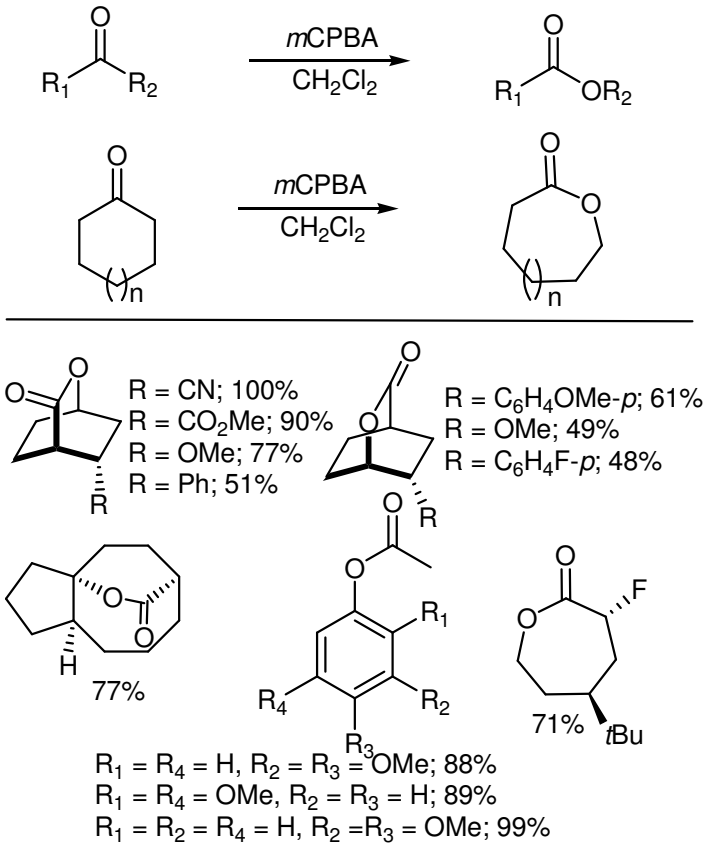
## 2. Named reactions

### 2.1. Baeyer–Villiger oxidation

The Baeyer–Villiger oxidation represents an important process for the synthesis of lactones and esters from ketones.[14-21] The reaction is of great importance for the

manufacture of lactones (Scheme 2). The regiospecificity of the reaction depends on the relative migratory ability of the substituents attached to either side of the carbonyl group. In general it has been found that substituents which are able to stabilize a positive charge migrate more readily, which has lead to the establishment of an order of preference viz., tert-alkyl > cyclohexyl > sec-alkyl > phenyl > primary-alkyl > $CH_3$. In some cases, stereoelectronic or ring strain factors also affect the regiochemical outcome. The reaction of aldehydes preferably gives formates, but sometimes only the liberated alcohol may be isolated due to the solvolytic instability of the product formate under the reaction conditions.[15,22,23] The Baeyer–Villiger oxidation by the peroxyacid consists of the nucleophilic addition of the peroxide reagent to the carbonyl carbon of the substrate to afford the tetrahedral Criegee intermediate.[24] The intermediate undergoes intramolecular rearrangement of an alkyl or aryl substituent from the central carbon to the adjacent oxygen and this migration is accompanied by cleavage of the weaker O-O bond and simultaneous formation of the ester (or lactone) and a carboxylic acid[22] (Scheme 2).

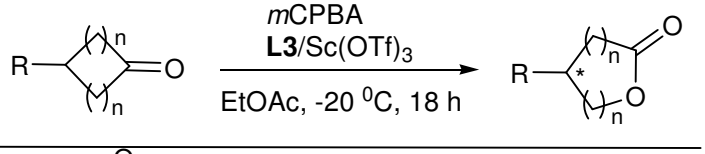
**Scheme 2. Examples of the Baeyer–Villiger oxidation of ketones using *m*-CPBA**



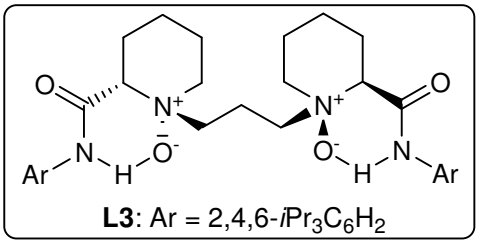

Feng et al.[25] reported the catalytic enantioselective Baeyer–Villiger oxidations of racemic and meso cyclic ketones in the presence of chiral *N*,*N*′-dioxide–$Sc^{III}$ complex catalysts. Asymmetric Baeyer–Villiger oxidation of racemic or prochiral cyclic ketones provides a simple and attractive route for the synthesis of optically active lactones.[26-28] Various *meso*-cyclohexanones provided the corresponding ε–lactones with excellent enantioselectivities (Scheme 3). The enantiocontrol of the reaction was sensitive to neither the electronic properties nor the steric hindrance of substituents on the phenyl ring of 4-aryl-substituted cyclohexanones. Generally, the desired chiral 5-aryl-substituted ε-lactones were isolated with excellent enantioselectivities (up to 95% ee) and in good yields (up to 90%). Moreover, fused-ring-substituted cyclohexanones were also tolerated, giving the desired products with excellent ee values. Catalytic systems for

Baeyer–Villiger oxidations of a variety of *meso*-cyclobutanones were explored, and the desired γ-lactones were obtained in good yields (up to 99%) with good enantioselectivities (up to 91% ee) (Scheme 3). It is interesting to note that the electronic nature of substituents in cyclobutanone starting materials had nearly no effect on the efficiency and enantioselectivity of the reaction.[25]

**Scheme 3. Substrate scope for the desymmeterization of *meso*-cyclohexanones**



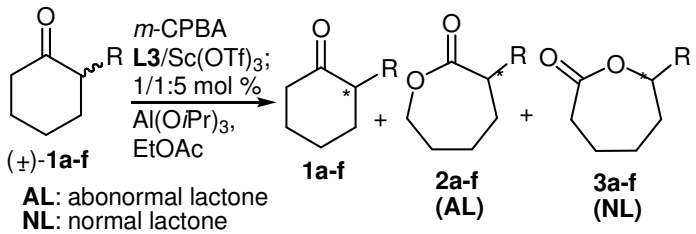

R = Ph; n = 2; Yield: 86%; ee: 95%
R = 4-MeC$_6$H$_4$, n = 2; Yield: 90%; ee: 95%
R = 3-MeC$_6$H$_4$, n = 2; Yield: 84%; ee: 94%
R = 4-F-C$_6$H$_4$, n = 2; Yield: 84%; ee: 94%
R = 4-Cl-C$_6$H$_4$, n = 2; Yield: 82%; ee: 94%
R = 3-Cl-C$_6$H$_4$, n = 2; Yield: 81%; ee: 94%
R = 1-naphthyl, n = 2; Yield: 84%; ee: 95%
R = Ph; n = 1; Yield: 82%; ee: 91%
R = 4-MeC$_6$H$_4$, n = 1; Yield: 84%; ee: 90%
R = 3-MeC$_6$H$_4$, n = 1; Yield: 80%; ee: 91%
R = 4-F-C$_6$H$_4$, n = 1; Yield: 71%; ee: 87%
R = 4-Cl-C$_6$H$_4$, n = 1; Yield: 83%; ee: 87%
R = 3-OMe-Bn, n = 1; Yield: 99%; ee: 80%




In regard to the kinetic resolution of racemic cyclic ketones through Baeyer–Villiger oxidation, the stereochemistry is affected not only by stereoelectronic control but also by chiral recognition. The first examples of Baeyer–Villiger oxidation of racemic cyclic ketones were independently reported by the groups of Bolm[29] and Strukul.[30] In general, the normal CHR-group-migrated product [i.e., the " normal " lactone (**NL**)] distribution, which depends on the migratory aptitude (tertiary > secondary > primary), was observed.

Feng et al.[25] reported kinetic resolution of racemic cyclic ketones through Baeyer–Villiger oxidation in the presence of a chiral *N*,*N*′ -dioxide–$Sc^{III}$ complex catalyst. A series of optically active ε- and γ-lactones were obtained with excellent outcomes. The latter reaction using the $Sc^{III}$ catalyst gave especially the "abnormal" lactone (**AL**) derived from a preferential migration of a $CH_2$ group with high enantioselectivity (Table 1). The kinetic resolution of a series of racemic 2-aryl-cyclohexanones **1** was then specifically examined. Interestingly compounds **AL-2** were obtained as the major products. Generally, lactones **AL-(*R*)-2** and unreacted ketones (*S*)-**1** were isolated with high conversion and (*S*) values and good to excellent **AL**-(*R*)-**2/NL-3** ratios (5.6/1 to >19/1). The reaction efficiency and enantiocontrol were sensitive to the electronic properties of the substituent on the phenyl nucleus of the substrate. Substrates with an electron-withdrawing substituent (Cl, Br) gave the unreacted ketone (*S*)-**1** and lactone **AL**-(*R*)-**2** with higher ee values than those with electron-donating ones (Me, OMe). Moreover, 2-fused-ring-substituted ketones **1** were also tolerated, giving the products and unreacted ketones with good ee values.[25]

**Table 1. Substrate scope for the kinetic resolution of racemic 2-aryl-substituted cyclohexanones**




| | Yield | | ee | | |
|---|---|---|---|---|---|
| $R_1$ | **1** | **2** | **1** | **2 + 3** | **2/3** |
| Ph | 94 (*S*) | 94 (*S*) | 46 | 51 | 17/1 |
| 4-$ClC_6H_4$ | 97 (*S*) | 93 (*S*) | 47 | 53 | 19/1 |
| 4-$BrC_6H_4$ | 97 (*S*) | 92 (*S*) | 47 | 53 | 19/1 |
| 4-$MeC_6H_4$ | 89 (*S*) | 91 (*S*) | 51 | 48 | 12/1 |

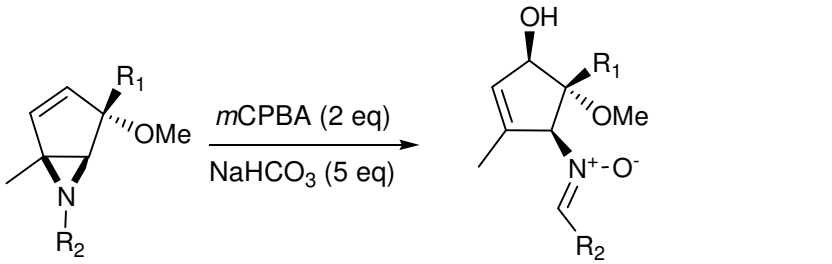
| | | | | | |
|---|---|---|---|---|---|
| 4-$MeOC_6H_4$ | 82 (*S*) | 90 (*S*) | 44 | 56 | 6/1 |
| 1-naphthyl | 99 | 98 | 49 | 51 | 19/1 |

## 2.2. Meisenheimer rearrangement

The Meisenheimer rearrangement is perhaps of more interest from a synthetic point of view, as it allows the transfer of both functionality and stereochemical information.[31] Penkett and Simpson[31] reported the oxidation of a range of aziridines with *m*CPBA which gave products arising from a [2,3] Meisenheimer rearrangement of the initial *N*-oxide, followed by further oxidation to give nitrones. It was found that two equivalents of *m*CPBA were required. It was further found that the reaction gave low yields of product in $CH_2Cl_2$ and that the yield improved considerably when the reaction was carried out in methanol or acetonitrile.

For good selectivity to be observed, it is necessary for oxidation of the aziridines to be faster than the oxidation of the nitrones. The initial oxidation step is likely to involve a larger increase in dipole moment than the second and thus a polar solvent such as acetonitrile would be expected to improve the selectivity for the nitrones. Methanol is also a very polar solvent. However the aziridinyl nitrogen lone pair of aziridines would to an extent be deactivated towards oxidation by hydrogen bonding to the solvent. This would reduce the rate of the initial oxidation and perhaps account for the reversal of selectivity. It seems likely that the reaction proceeds via the oxidation of the aziridines give the *N*-oxide, which undergoes rapid Meisenheimer rearrangement followed by further oxidation of the nucleophilic nitrogen, and then base catalysed N-O bond cleavage gives the nitrones (Scheme 4).[31]

**Scheme 4. Oxidation of aziridines**



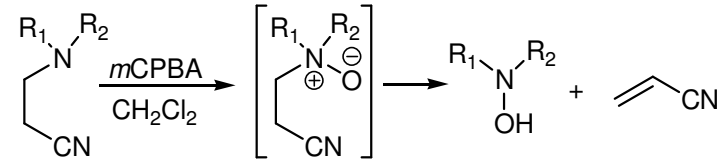

$R_1$ = OMe, $R_2$ = Et
$R_1$ = OEt, $R_2$ = Et
$R_1$ = O$^i$Pr, $R_2$ = Et
$R_1$ = OEt, $R_2$ = Me
$R_1$ = OMe, $R_2$ = Me
$R_1$ = OMe, $R_2$ = Bn

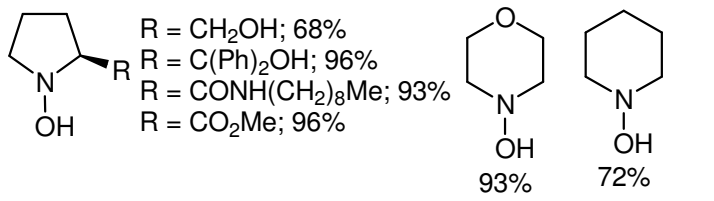
$R_1$ = OMe, $R_2$ = Me; 69%
$R_1$ = OEt, $R_2$ = Me; 66%
$R_1$ = O$^i$Pr, $R_2$ = Me; 67%
$R_1$ = Et, $R_2$ = H; 38%
$R_1$ = OMe, $R_2$ = CH=CH; 58%
$R_1$ = OMe, $R_2$ = Ph; 34%

## 2.3. Cope-elimination

Initially Nagasawa et al.[32] reported that the use of an appropriately positioned β-electron withdrawing nitrile group allows the Cope-elimination to occur at significantly lower temperatures than usually required. In another study O'Neil et al.[33] reported the oxidation of a range of ┌ β-cyanoethyl tertiary amines with *m*CPBA to afford the corresponding *N*-oxides, which can either be isolated or allowed to undergo Cope-elimination to give secondary hydroxylamines (Scheme 5). The reaction works for both cyclic and acyclic systems.

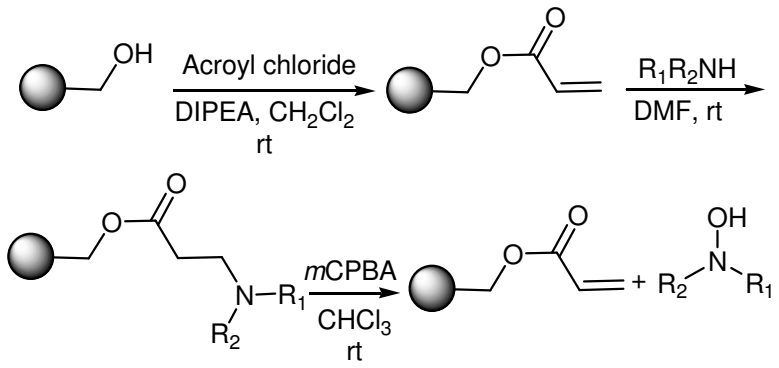
**Scheme 5. Synthesis of secondary hydroxylamines via Cope elimination of β-cyanoethylamines**



Sammelson and Kurth[34] reported the solid phase Cope oxidative elimination for the synthesis of *N*,*N*-disubstituted hydroxylamines from REM resin (polymer-bound benzyl acrylate) (Scheme 6). This solid-phase route to hydroxylamines via the Cope oxidative elimination began by attachment of acryloyl chloride to hydroxymethyl polystyrene to produce the REM resin. Michael addition of secondary amines produced the corresponding tertiary ┌ β-amino ester. After washing the resin, this tertiary amine was reacted with *m*-CPBA in chloroform for 1–2 h to form the *N*-oxides which in turn underwent the Cope oxidative elimination and to produce *N*,*N*-disubstituted hydroxylamines and regenerate the acrylate resin. Sammelson and Kurth[34] also examined other oxidation protocols viz., $H_2O_2$ in THF, peracetic acid in various solvents, and dimethyldioxirane in acetone/$CH_2Cl_2$ and came to the conclusion that these procedures were not as effective as *m*CPBA/$CHCl_3$.

**Scheme 6. Solid-phase synthesis of hydroxylamines via Cope oxidative elimination**

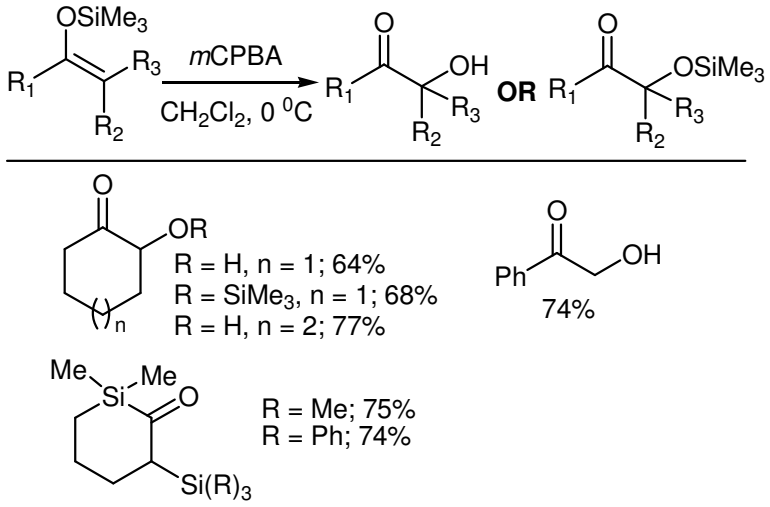



## 2.4. Rubottom oxidation

The synthesis of α-hydroxy ketones is achieved by reaction of silyl enol ethers with *m*CPBA, with subsequent rearrangement. Aqueous workup gives the desired product after desilylation.[35-38] Silyl enol ethers are readily prepared from enolizable ketones using base and chlorosilane.[39-41] The silyl enol ethers are usually treated with a slight excess of

*m*-CPBA in $CH_2Cl_2$ at 0 ºC followed by workup by addition of pentane. Perusal of Scheme 7, which summarizes several representative Rubottom oxidation products, reveals that the introduction of the hydroxy group is regiospecific and that no exchange occurs with respect to the position of the original carbony1 group in the ketonic precursor. However, nonaqueous workup of the oxidation products yielded α-trimethylsiloxy ketones.[35]

**Scheme 7. Rubottom oxidation using *m*-CPBA**

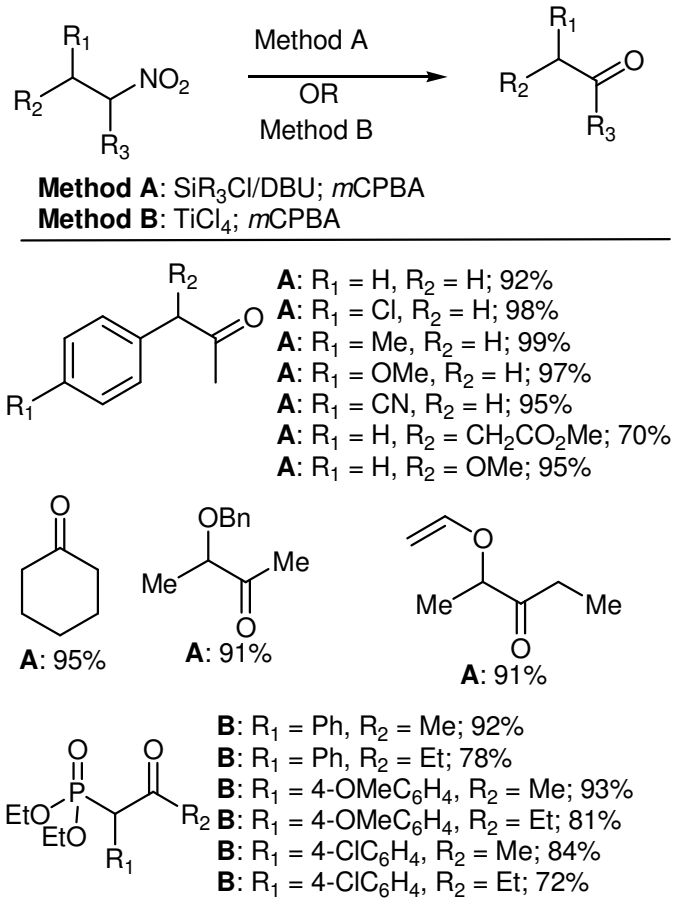



## 2.5. Nef reaction

Conversion of a nitro into a carbonyl group has been firmly established and applied since its discovery by Nef more than a century ago, and is regarded as one of the most important functional group transformations in synthetic protocols. The success of this procedure has been verified by the large bodies of different synthetic protocols that have been set up over the years in order to accomplish this transformation with an increasingly higher level of chemoselectivity.[42] Since the Nef reaction often involves either strongly acidic or strongly basic conditions[43-48] and it is well known that trialkylsilyl enol ethers (which can be generated from trialkyl chloride and DBU) readily undergo α-

hydroxyalkylation by means of *m*CPBA under extremely mild conditions.[35,37,38,49]. Therefore Aizpurua et al.[50] reacted different nitroalkanes with trialkyl chloride and DBU followed by oxidative cleavage of trialkylsilyl enol ethers with *m*CPBA in method A.[50,51] In another study Kim and Oh[52] reported the conversion of nitro compounds to carbonyl compounds (Nef reaction) using $TiCl_4$ and *m*CPBA (method B). Various structurally diverse secondary nitro compouds have thus been converted to carbonyl compounds with both methods A and B (Scheme 8).

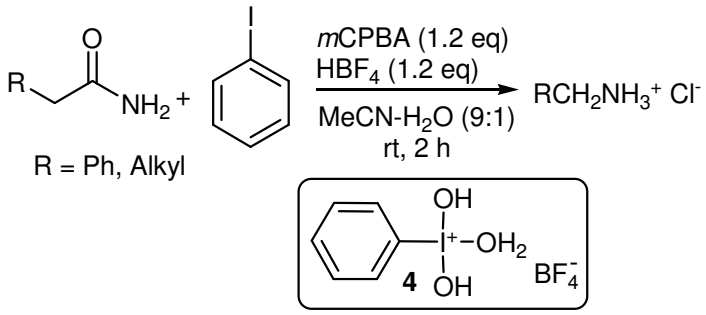
**Scheme 8. Nef reaction with *m*-CPBA**




## 2.6. Hofmann rearrangement

The classical Hofmann rearrangement using sodium hypobromite or hypochlorite under basic conditions effects conversion of primary carboxamides to primary amines possessing one less carbon atom, through the intermediacy of either *N*-bromo- or *N*-chloroamides.[53-55] Tetra-coordinated bis(aqua)(hydroxy)phenyl-$\lambda^3$-iodane complex **4**[56,57], generated from a stoichiometric amount of iodobenzene by its reaction with *m*CPBA in aqueous acetonitrile in the presence of 48% aqueous $HBF_4$, was found to initiate the Hofmann rearrangement of α-phenylacetamide (Scheme 9).[58] The reaction took place smoothly at room temperature and was finished within 2 h. Subsequent treatment with aqueous HCl solution, afforded rearranged benzylammonium chloride quantitatively. Introduction of both electron-donating (*p*-Me, 3,5-$Me_2$ and 2,4,6-$Me_3$) and electron-withdrawing groups (*p*-Cl and *p*-$CF_3$) into the iodobenzene ring decreased the yield. Aliphatic iodides such as methyl, trifluoroethyl, and 1-adamantyl iodides showed no catalytic efficiency. The new catalytic method has found a general use in the Hofmann rearrangement of primary carboxamides and all of the unfunctionalized simple linear, branched, and cyclic aliphatic carboxamides examined, afforded the corresponding alkylammonium chlorides with one less carbon atom at room temperature and in high yields. The catalytic conditions are compatible with the presence of various kinds of functionalities such as halogens (F, Cl, Br), sulfonamides, amines, methoxy and nitro groups.[58]

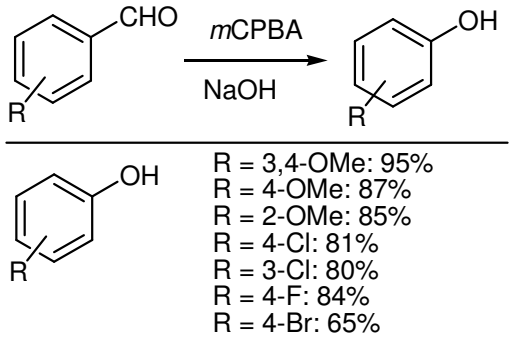
**Scheme 9. Hofmann rearrangement of α-phenacylacetamides with *m*-CPBA**




## 2.7. Dakin oxidation

The Dakin reaction formally consists of conversion of hydroxybenzaldehydes into phenols using alkaline hydrogen peroxide.[59] Phenols are suitable intermediates for many purposes and have proved to be useful in the synthesis of several biologically active compounds.[60] Although there are several different methodologies focusing on the preparation of phenols from benzaldehydes,[61-67] Fraga et al.[68] reported the *m*CPBA mediated Dakin reaction that had the advantage of requiring shorter reaction times and easier workup. Fraga et al.[68] described a solid-state Dakin oxidation using *m*-CPBA and various nonactivated benzaldehydes which could all be converted into their corresponding phenols with a remarkable reduction of reaction time and high yield, in comparison with other previously reported standard type methodologies.[61-67] Simple very careful mixing together of the aromatic aldehyde and *m*CPBA by using a pestle in a mortar results in a pasty mass and after a few minutes yields of the desired phenol derivative, easily isolated after a sequence of alkaline hydrolysis, were obtained[69,70] (Scheme 10).

**Scheme 10. Dakin oxidation of aromatic aldehydes using *m*-CPBA**

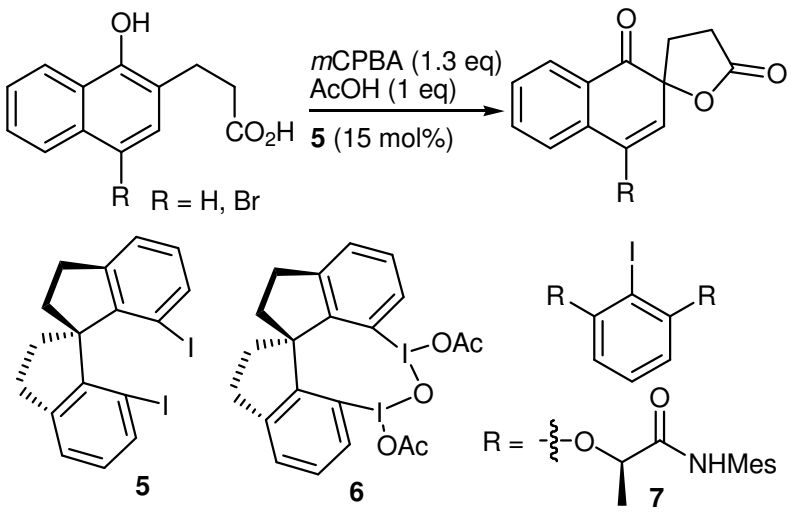



## 2.8. Kita lactonization

A variety of natural products bearing spirocyclic systems exist, and many of them are biosynthetically formed by an oxidative spiroannulation processes.[6,71,72] Hypervalent iodine(III) reagents are generally considered to be one of the most effective oxidants to effect the oxidation processes. In evaluating their low toxicity, the method has been widely used for the total synthesis of natural products having important biological properties such as antitumor, antibacterial, antifungal, and antiprotozoan activities.[73-75] *m*CPBA is one of a few chemical oxidants which can convert iodine compounds to the corresponding iodine(III) forms selectively in organic solvents at room temperature.[76-83] Kita and co-workers reported on the enantioselective oxidative dearomatization of 1-naphthol derivatives to spirolactones with high enantioselectivities (up to 69% ee) using stoichiometric amounts of chiral iodine(III) reagent **6**, which was generated in situ from **5** and *m*-CPBA in the presence of acetic acid (Scheme 11).[84,85] In another study Ishihara et al.[86] reported conformationally flexible $C_2$-symmetric chiral iodoarenes **7** as highly effective precatalysts in the presence of *m*-CPBA as terminal oxidant for the enantioselective Kita oxidative spirolactonization (Scheme 11).[86] In this report, they described a detailed investigation of enantioselective oxidative spirolactonization. A

broad range of substrates and products have also been described with higher enantioselectivities of up to 92% ee using **7** and *m*CPBA.[87]

**Scheme 11. Enantioselective Kita oxidative spirolactonization of 1-naphthols**



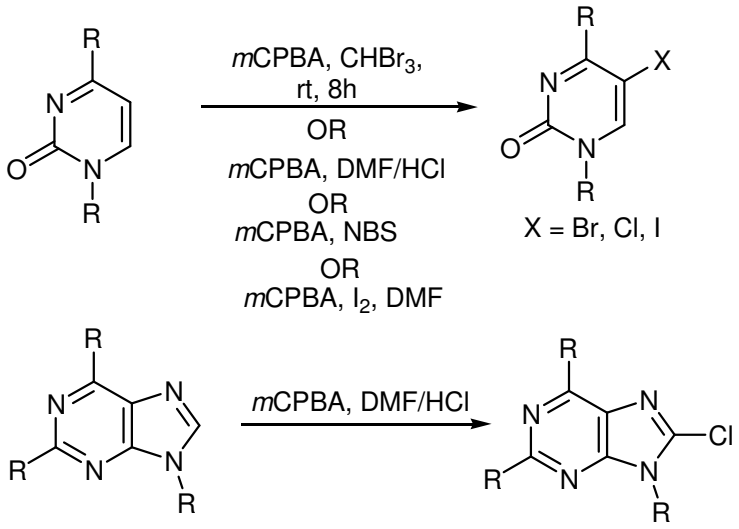

## 3. Halogenation

### *3.1. Halogenation of pyrimidine and purine derivatives*

Selective oxidative halogenation of organic compounds in a simplified manner has received considerable interest in recent years.[88] Numerous methods have been reported[89-95] for halogenation of uracil because it is a fundamental building block in the nucleic acids[96] as well as having an important position in halogenated uracils in medicinal chemistry.[97] Molte-Leth and Jorgenson[88] reported the oxidative bromination of uracil by using *m*CPBA and $CHBr_3$. In another study Ryu and MacCoss[98] reported the synthesis of 5-chloro-substituted pyrimidine nucleosides and 8-chloro-substituted purine nucleosides using *m*CPBA in in an aprotic solvent such as dimethylformamide (DMF). Chlorination of different pyrimidine and purine derivatives were achieved after reaction with *m*CPBA in dipolar aprotic solvents containing HCl. In the pyrimidine series, both uracil and

cytosine derivatives gave the corresponding 5-chloro derivatives in high yields. Application of the same reaction conditions to the purine derivatives adenosine and guanosine, afforded the 8-chloro nucleosides in good yield.[98] Similarly Zanatta et al.[99] reported the preparation of 5-bromo-substituted pyrimidine nucleosides by using *m*CPBA and NBS while Ryu et al.[100] reported on the preparation of 5-iodo-substituted pyrimidine nucleosides by using *m*CPBA, $I_2$, and DMF (Scheme 12).

**Scheme 12. Halogenation of pyrimidine and purine derivatives**




## *3.2. Halogenation of organic compounds with the mCPBA/HCl/DMF system*

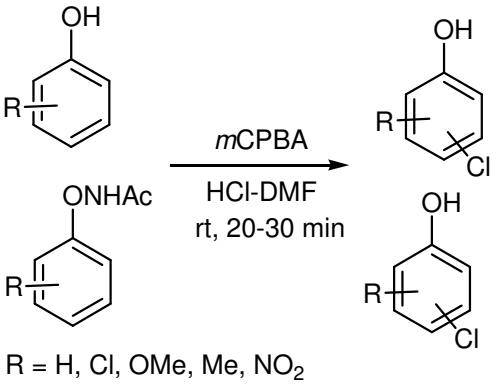
### *3.2.1. Halogenation of aromatic compounds*

Since the middle of 19th centuary, chlorination of phenols has been extensively described using an extensive array of different reagents.[101-111] Ryu et al.[112] reported on the chlorination of phenols under mild condition using a *m*CPBA/HCl/DMF system (Scheme 13). Reaction of 2-naphthol, 2-chlorophenol, 4-chlorophenol with an equimolar amount

of HC1 and *m*-CPBA in DMF gave the corresponding monochloro-substituted phenols in good yields with high regioselectivity. Monochlorination of phenol ether, such as anisole, also proved to be equally effective. Accordingly, mono-chlorination of chlorophenols, such as 2- and 4-chlorophenols, afforded excellent yields of the dichloro-substituted compounds. Dichloro or trichloro-compounds were also obtained by the reaction of phenol, o-cresol, 1-naphthol as well as ethyl salicylate with two or three-fold excess of HC1 and *m*-CPBA, in high yields with high regioselectivity respectively.[112]

Despite the numerous methods for chlorination of acetanilides,[113-119] Ryu et al.[120] used the *m*CPBA/HCl/DMF system under mild conditions (Scheme 13) to effect monochlorination of acetanilides, such as acetanilide, 2-methylacetanilide, 3,5-dimethylacetanilide, and 2-chloroacetanilide, which gave the corresponding monochloro-acetanilides in good yields with high regioselectivity and dichloroacetanilide. In the case of 4-methylacetanilide and nitroacetanilides, the corresponding mono-chloroacetanilides were obtained in moderate yields. It is noteworthy that in the case of 2,4-disubstituted acetanilides, the desired chloro compounds were obtained in poor yields. Dichlorination of acetanilides was also effected with a two-fold excess of HC1 and *m*CPBA producing the corresponding dichlorinated compounds in good yields and high regioselectivity.[120]

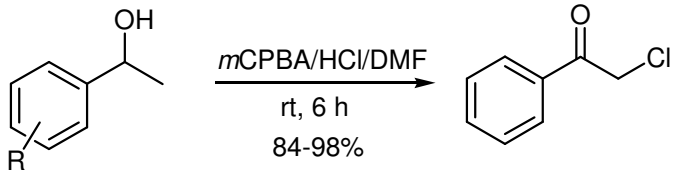
**Scheme 13. Chlorination of aromatic compounds with the *m*CPBA/HCl/DMF system**




### *3.2.2. α-Halogenations*

A wide variety of synthetic reagents and methods are currently available for the synthesis of α-chloroketones[121] and the large majority of these chlorination methods involve α-chlorination of ketones, whereas only a few examples for the direct conversion of secondary alcohols into α-chloroketones have been reported.[122-125] Ryu et al.[126] found that secondary benzylic alcohols were easily oxidized concomitantly to in situ using the *m*CPBA/HCl/DMF system to yield α-chloroketones in good yields (Scheme 14). It was found that the reaction initially involved rapid transformation of the alcohols into ketones followed by α-chlorination. In the cases of electron-donating groups (hydroxy and alkoxy groups), a mixture of several compounds were obtained due to chlorination of the aromatic ring. It is interesting to note that the molar ratio of *m*-CPBA to HC1 was (3:3.3) and by adding one additional equivalent of *m*-CPBA, higher yields with minimizing the side products could be attained.[126]

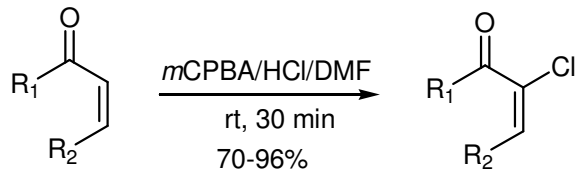
**Scheme 14. α-Chloroketones from secondary benzylic alcohols by the *m*CPBA/HCl/DMF system.**




R = Me, Cl, Br

In another study, Ryu et al.[127] used the *m*CPBA/HCl/DMF system for the chlorination of α,β-unsaturated enones to synthesise α-chloro α,β-unsaturated enones in good yields and with highly regioselectivity (Scheme 15). Different oxidizing agents such as Oxone and ammonium cerium nitrate have also been tried but these reagents gave unsatisfactory results.

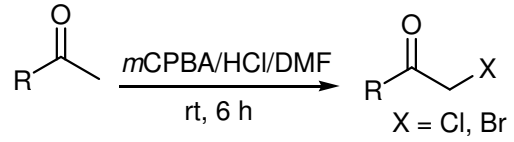
**Scheme 15. Chlorination of α,β-unsaturated enones with *m*CPBA/HCl/DMF**



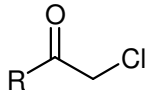

$R_1 = R_2 = -(CH_2)_2-$
$R_1 = R_2 =$ Me, Ph

Similarly Ryu et al.[128] used *m*CPBA/HCl/DMF (method A) for the chlorination of ketones and Inukai et al.[129] used *m*CPBA/$MgBr_2$ (method B) for the corresponding bromination of ketones. It is interesting to note that when the reaction temperature or the molar ratio of HCl-DMF to the substrate was raised, formation of the side products increased and subsequently the yield of α-haloketones was decreased in method A (Scheme 16).

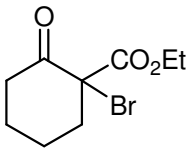
**Scheme 16. α-Halogenations of ketones**




**Method A**: *m*CPBA/HCl/DMF
**Method A**: *m*CPBA/$MgBr_2$



**A**: R = Ph; 96%
**A**: R = 4F-$C_6H_4$; 80%
**A**: R = 4Cl-$C_6H_4$; 85%
**A**: R = 4Br-$C_6H_4$; 84%
**A**: R = 4Me-$C_6H_4$; 86%
**A**: R = 3$NO_2$-$C_6H_4$; 85%

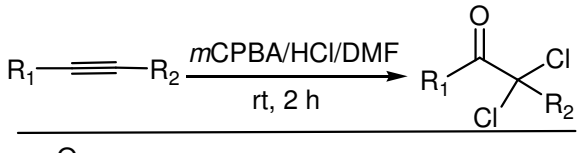


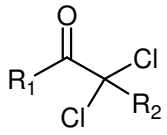
**B**: 100%

### *3.2.3. Chlorination of alkynes*

Ryu et al.[130] further reported on reaction of alkynes with *m*-CPBA/HCl/DMF that provided the corresponding α,α-dichloroketones in moderate yields (Scheme 17). Ryu et a.[130] also attempted the same reaction using other oxidants such as hydrogen peroxide and Oxone. The group found that Oxone gave the best results. However by using *m*CPBA formation of α-monochloroketones were increased.

**Scheme 17. Oxidative chlorination of alkynes with *m*CPBA/HCl/DMF.**



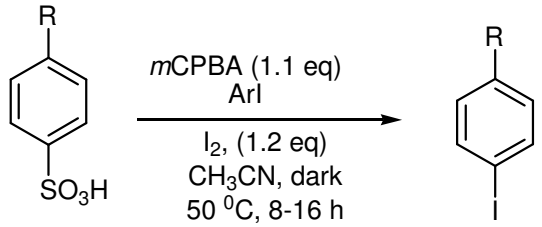
$R_1$ = Ph, $R_2$ = H; 40%
$R_1$ = Ph, $R_2$ = Me; 35%
$R_1$ = Propyl, $R_2$ = H; 41%
$R_1$ = $(CH_2)_2$Ph, $R_2$ = H; 60%

## *3.2. Miscellaneous halogenations*

Treatment of *p*-alkylbenzenesulfonic acids with *m*CPBA and molecular iodine gave *p*-alkyliodobenzenes in good to moderate yields via an electrophilic *ipso*-substitution by the iodonium species ($I^+$) formed (Scheme 18). This desulfonyloxyiodination was promoted

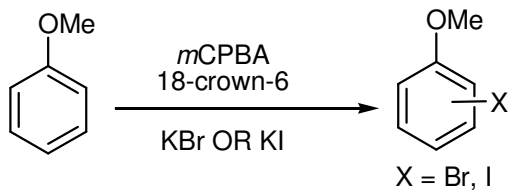
by the addition of a catalytic amount of, interestingly enough, iodoarenes, such as *o*-iodobenzoic acid.[131] Similar treatment of dimethylbenzenesulfonic acids and trimethylbenzenesulfonic acids with *m*CPBA and molecular iodine proceeded smoothly both in the absence and in the presence of *o*-iodobenzoic acid to provide the corresponding monoiodo-dimethylbenzene and diiodo-dimethylbenzene, and monoiodo-trimethylbenzene and diiodo-trimethylbenzene, in good to moderate yields, respectively. On the other hand, the same desulfonyloxyiodination of benzenesulfonic acid and *p*-chlorobenzenesulfonic acid with *m*CPBA and molecular iodine proceeded only in the presence of o-iodobenzoic acid to generate iodobenzene and *p*-chloroiodobenzene, respectively, in moderate yields.[131]

**Scheme 18. Desulfonyloxyiodination and iodination with *m*CPBA/ArI/$I_2$**




In another study it has been reported that several types of phenyl ethers could be monobrominated in the aryl ring in good yields with potassium bromide in the presence of 18-crown-6 on oxidation with *m*CPBA (Scheme 19).[107] Similarly monoiodination was also possible with both phenyl ethers and free phenols by using potassium iodide in the presence of 18-crown-6 on oxidation with *m*CPBA.

**Scheme 19. Halogenation of phenyl ethers**

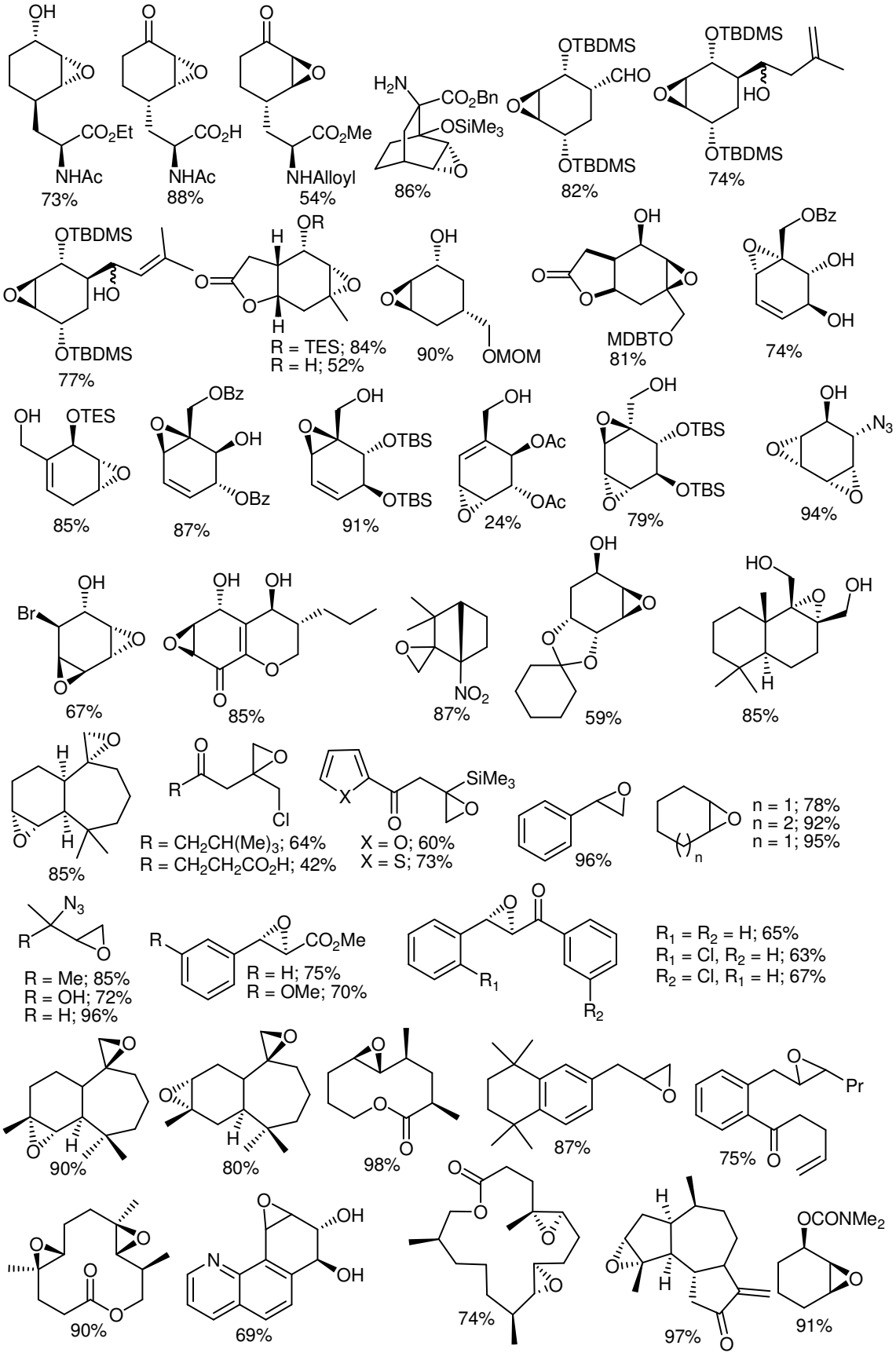


# 4. Olefin functionalization

## *4.1. Epoxidation of olefins*

Despite the development of many new oxidation procedures, the use of peroxy acids such as *m*CPBA still constitutes one of the most useful synthetic procedures for the epoxidation of alkenes on a laboratory scale[132,133] Oxygen atom transfer from *m*CPBA to an alkene is facilitated by electron-donating substituents on the carbon-carbon double bond and electron-withdrawing groups on the peroxy acid.[134-143] High yields were obtained for a variety of substituted olefins (Figure 1)[144-198] and there are numerous reports[199-305] in which *m*CPBA is used for epoxidations of different substrates.

**Figure 1. *m*CPBA epoxidation products of different alkene substrates**

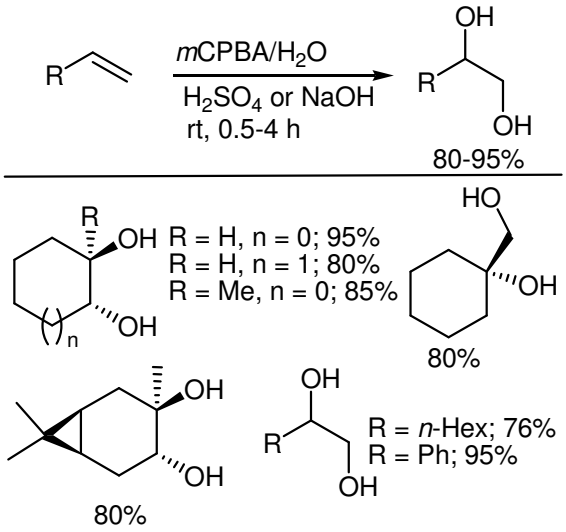


## *4.2. 1,2-Dioxygenation of olefins*

### *4.2.1. Dihydroxylation*

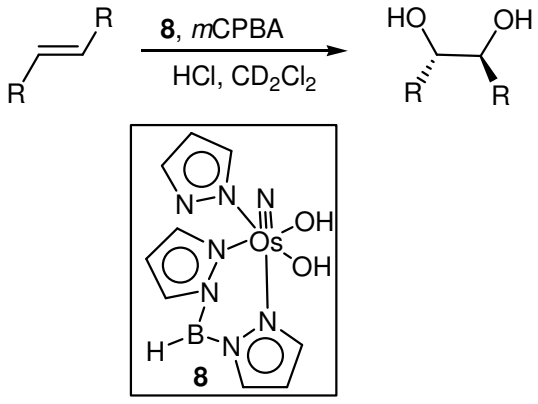
Perhydroxylation of carbon-carbon double bonds is a process of most vital synthetic and theoretical interest and therefore many reagents and procedures have been investigated to obtain highly stereoselective reactions with high yields.[306] The anti 1,2-dihydroxylation process is achieved by a vast number of different methods[307-312] but sometimes these methods give mixtures of the diol and its corresponding esters and thus it is necessary that further hydrolysis is necessary to obtain the pure diol. This additional inconvenience reduces the overall yield and increases the time of the reaction. To overcome these problems, Fringuelli et al.[313] reported a very simple procedure which allows one to prepare anti 1,2-diols in excellent yield in a one-pot-two step synthesis which does not require organic solvents (Scheme 20). In this protocol the alkene is firstly epoxidized by *m*CPBA in deionized water followed by ring opening of the epoxide by acid or basic hydrolysis. High yields were always observed (80-95%) and the diol was the only reaction product isolated (Scheme 20). The epoxidation stage occurs in water under very mild conditions and therefore this one-pot process is suitable for acid sensitive alkenes.[313] In another study Davies et al.[314] reported the 1,2-dihydroxylation of *N*,*N*-dibenzylcyclohex-2-enamine with $Cl_3CCO_2H$ and *m*CPBA.

**Scheme 20. Synthesis of anti 1,2-diols in water by epoxidation-hydration reactions**




In another study Mayer et al.[315] reported the *cis*-dihydroxylation of olefins using Tp–osmium complex (**8**), *m*CPBA, and HCl (Scheme 21). Different alkenes were subjected to dihydroxylation under the same condition and interestingly for all of the alkenes, dihydroxylation occurs in a *cis* fashion. Styrene, *trans*-4-dimethylamino-4′-nitrostilbene, cyclohexene, trans-dimethyl fumarate and *trans*-methyl cinnamate were all converted to their respective *cis*-diols. It is interesting to note that the reaction proceeds well with hydrocarbons, electron-deficient alkenes, and an alkene with an electron-donating dimethylaniline substituent.

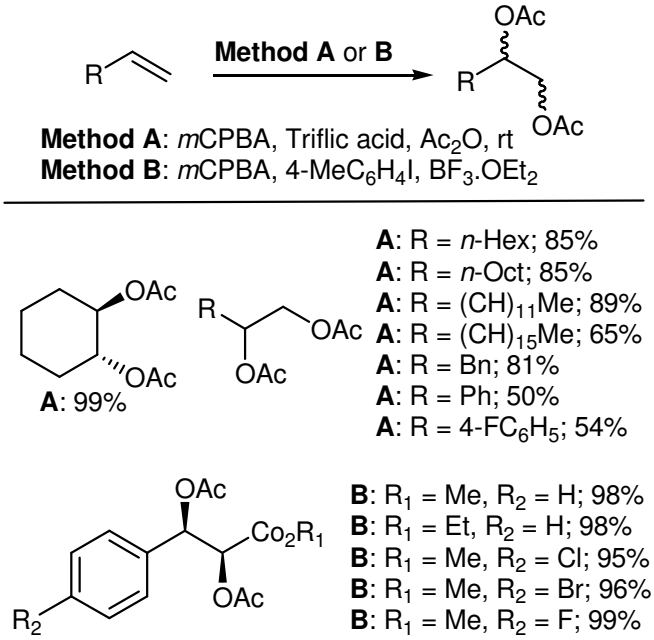
**Scheme 21. *Cis*-dihydroxylation of olefins by 8 and *m*CPBA**



### *4.2.2 Diacetoxylation and lactonization of olefins*

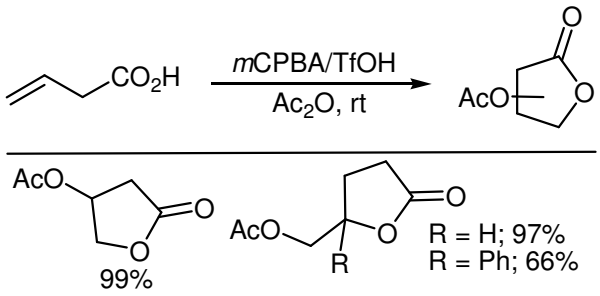
Gade et al.[316] reported clean and efficient *trans*-diacetoxylation reaction of alkenes catalyzed by triflic acid using *m*CPBA as the oxidant (method A) (Scheme 22). Under these conditions, both linear and cyclic aliphatic alkenes were converted to their corresponding diacetoxylation products in good to excellent isolated yields: Terminal alkenes and cyclic alkenes in general gave the corresponding diacetoxylation products in good to high yields. On the other hand, when the double bond was not terminal, a relative decrease in yield was observed as also found for aromatic alkenes such styrenes. Recently a novel method for the organocatalytic syn diacetoxylation of alkenes has been developed by Li et a.[317] using 4-$MeC_6H_4I$ as an efficient catalysts and *m*CPBA as oxidant (method B). A broad range of substrates, including electron-rich as well as electron-deficient alkenes, were smoothly transformed and furnishing the desired products in good to excellent yields with high diastereoselectivity (up to >19:1 dr).

**Scheme 22. Diacetoxylation of alkenes using *m*-CPBA as oxidant**



Method A was also very efficient in the oxidative lactonization of ω-unsaturated carboxylic acids to afford five-membered lactones (Scheme 23). Notably, 4-phenylpentenoic acid gave the corresponding lactone in moderate yield, whereas only a rearrangement product due to 1,2-phenyl migration was isolated in the TfOH-catalyzed lactonizations using $PhI(OAc)_2$ as the oxidant.[318] 5-Hexenoic acid and 6-heptenoic acid failed to afford the corresponding lactones but yielded the linear diacetoxylation products instead.

**Scheme 23. Lactonization of alkenes using *m*CPBA as oxidant.**

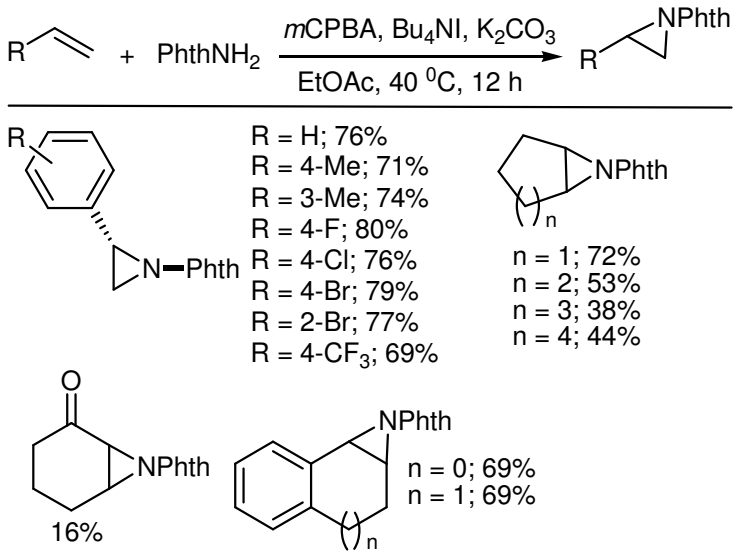



## *4.3. Aziridination of olefins*

Aziridination of alkenes is an important chemical transformation and is a convenient method for accessing various biologically active nitrogen-containing products and synthetic intermediates.[319-322] Zhdankin et al.[323] reported the metal-free catalytic aziridination using catalytic amounts of tetrabutylammonium iodide (TBAI), *m*CPBA as the terminal oxidant, and $PhthNH_2$ as the nitrenium precursor (Scheme 24). Various substituted alkenes were transformed into their respective aziridines with good to excellent yield. In general, all styrenes with either electron-donating or electron-with-drawing substituents afforded products in good yields. This reaction also gave good yields for α- or β-substituted styrenes. In the reactions of nonhindered cycloalkenes, the products were obtained in moderate yields, although a substituted cycloalkene, 1-

methylcyclohexene and seven- or eight-membered cycloalkenes gave lower yields of aziridines. Reactions of 1-decene and α,β-unsaturated cyclic ketones under these conditions afforded the corresponding aziridines in low yield. Unfortunately yields were not improved upon using stoichiometric amounts of TBAI.

**Scheme 24. Aziridination of alkenes**



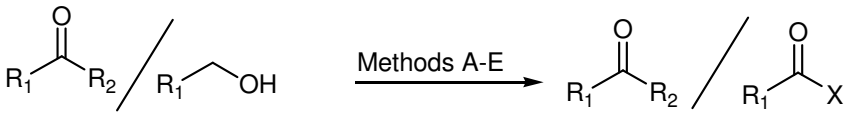

## 5. Oxidation of functional groups

### *5.1. Oxidation of alcohols*

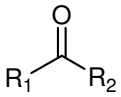
Oxidation of alcohols is probably one of the most important protocols in organic synthesis and since carbonyl compounds are widely used as intermediates both in manufacturing and laboratory,[324] development of new oxidative protocols continues to receive renewed attention in spite of the availability of several methods to achieve such objectives. Interestingly, methods A (*m*CPBA, HCl, and DMF),[325] method B (*m*CPBA, TEMPO, $CH_2Cl_2$),[326] method C (*m*CPBA, tetramethylpiperidine, $CH_2Cl_2$),[327,328] method D (*m*CPBA, PhI, *N*-hydroxyphthalimide [NHPI]),[329] and method E (*mC*PBA, HCl, THF)[330] can selectively oxidize primary alcohols to their corresponding aldehydes and

carboxylic acids and secondary alcohols (benzylic, aliphatic, alicyclic, and heterocyclic alcohols) to their corresponding ketones in excellent yield (Scheme 25). It is noteworthy that except for the case of cyclohexanol, no Baeyer-Villiger oxidation of the ketonic products was encountered under method C. This is not surprising, since the Baeyer-Villiger oxidation generally requires longer reaction times or higher temperatures and employs stronger peracids than are necessary for the alcohol oxidation. Cyclohexanol (a notable exception) is considerably more reactive than its cyclic congeners in the Baeyer-Villiger oxidation. With cyclohexanone, it was possible to suppress or enhance the Baeyer-Villiger oxidation by proper choice of reaction conditions. In general, Baeyer-Villiger oxidation of the ketonic products can be avoided by conducting the reaction under mild conditions. In particular, method D was effective for the chemoselective oxidation of the primary alcoholic functionality in the presence of a secondary alcoholic functionality. In methods C and D the primary alcohols were oxidized to carboxylic acids. A limitation of method E is that the reaction conditions are unsuitable for the oxidation of acid sensitive compounds.

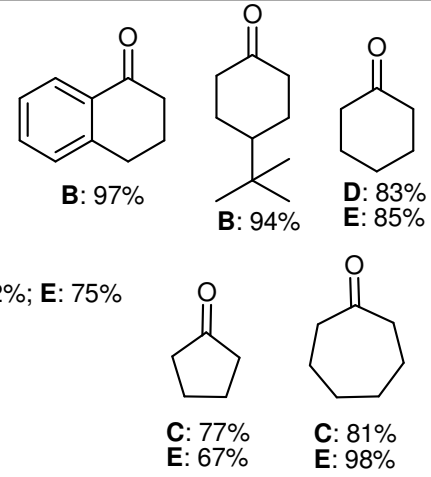
**Scheme 25. Selective oxidation of primary and secondary alcohols to their corresponding aldehydes or carboxylic acids and ketones**




**Method A**: *m*CPBA, HCl, DMF, rt, 5 min
**Method B**: *m*CPBA, TEMPO, $CH_2Cl_2$, rt
**Method C**: *m*CPBA, Tetramethylpiperidine, $CH_2Cl_2$, rt
**Method D**: mCPBA, PhI, NHPI, rt
**Method E**: *m*CPBA, HCl, THF, rt



$R_1$ = Ph, $R_2$ = H; **A**: 92%; **C**: 76%; **D**: 81%
$R_1$ = 4Cl-$C_6H_4$, $R_2$ = H; **A**: 100%
$R_1$ = 4OH-$C_6H_4$, $R_2$ = H; **A**: 100%
$R_1$ = 4$CF_3$-$C_6H_4$, $R_2$ = H; **A**: 100%
$R_1$ = Ph, $R_2$ = Me; **A**: 93%; **B**: 91%; **D**: 99%
$R_1$ = 4OMe-$C_6H_4$, $R_2$ = Me; **A**: 98%
$R_1$ = 4Cl-$C_6H_4$, $R_2$ = Me; **A**: 98%
$R_1$ = $R_2$ = Me; **A**: 99%
$R_1$ = $R_2$ = Ph; **D**: 95%
$R_1$ = *n*-Hex, $R_2$ = Me; **B**: 92%; **C**: 94%; **D**: 92%; **E**: 75%
$R_1$ = Ph, $R_2$ = Et; **B**: 98%
$R_1$ = Bn, $R_2$ = Me; **C**: 87%; **E**: 50%
$R_1$ = Cyclopropyl, $R_2$ = Me; **C**: 81%; **E**: 98%
$R_1$ = *n*-Bu, $R_2$ = OH; **C**: 90%
$R_1$ = *n*-Hex, $R_2$ = H; **C**: 40%
$R_1$ = Ph, $R_2$ = OH; **D**: 99%
$R_1$ = Bn, $R_2$ = OH; **D**: 88%
$R_1$ = 4$NO_2$-$C_6H_4$, $R_2$ = OH; **D**: 93%



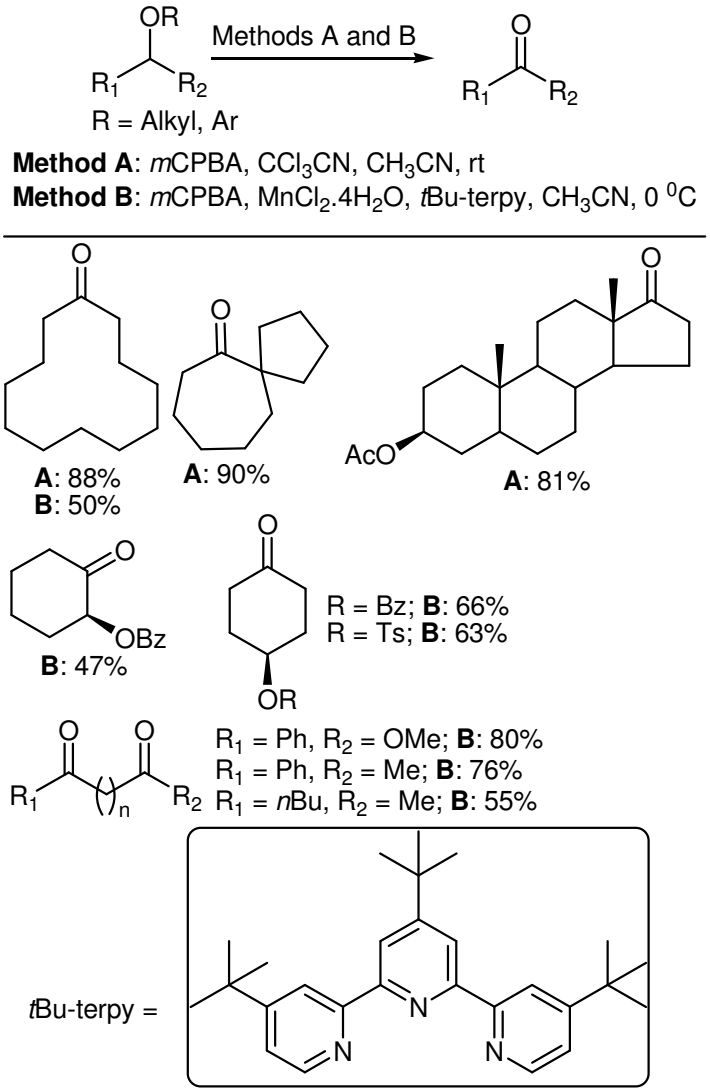

## *5.2. Oxidation of ethers*

Oxidation of organic compounds is of general fundamental importance in chemistry.[331] Inoue et al. reported two methods for the direct oxidation of ethers to ketones. Method A (*m*CPBA, $CCl_3CN$, MeCN)[8] and method B (*m*CPBA, $MnCl_2.4H_2O$, *t*-Bu-terpy, $CH_3CN$)[332] chemoselectively converted alkyl ethers to ketones under mild conditions (Scheme 26). To explore the substrate scope and chemoselectivity of method A, variously substituted ethers were treated under the optimized reaction conditions. Initially, oxidation of cyclododecyl ethers was investigated and similar to the case of methyl ether, oxidations of the octyl, isopropyl, and benzyl ethers all produced ketones. The sterically more demanding *t*-butyl group, on the other hand, impeded the oxidation. However, 4-pentenyl ether and the cyclohexanone analogue were both converted into their respective

ketones. Similarly methyl ether substituted carboskeletons were subjected to the reaction and oxidation of the seven-membered methoxy ring gave the ketone in high yield. Importantly, only the methyl ethers of the differentially protected cyclohexane diols were oxidized to the carbonyl groups.. The electron-withdrawing acetyl and mesyl groups and the sterically bulky TBDPS and trityl as ether groups effectively protected the hydroxy functionalities, demonstrating the high chemoselectivity of the reaction.

Similarly variations of cyclododecanol derivatives were prepared and subjected oxidation using method B. It was found that oxidation of cyclododecyl octyl ether proceeded in a similar way to that of methyl ether, and formation of the ketone and octanoic acid was confirmed by analysis of the crude reaction mixture. The observation of formation of octanoic acid indicated that the octan-1-ol that was eliminated from cyclododecanol was further oxidized to give octanoic acid under the reaction conditions. The oxidation of benzyl ethers gave the ketone as the major product in 46–55% yield. In addition oxidation of electron-rich 4-methoxybenzyl ether was completed in a shorter reaction time (1 h at 0 °C) than that of the other benzyl ethers, although similar yields of ketone were obtained irrespective of the electronic properties of the aromatic ring.

**Scheme 26. Oxidation of ethers**



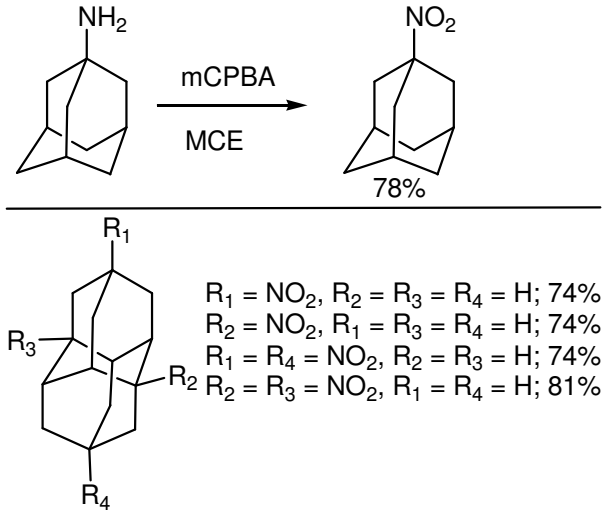

## 5.3. *Oxidation of amines*

### 5.3.1. *Oxidation of amines to nitro compounds*

Nitroalkanes are a versatile class of materials that can be used as intermediates in chemical transformations (e.g., Nef and Henry reaction). They are also frequently used for the preparation of pharmaceuticals, dyes and agrochemicals. The nitro derivatives of aliphatic caged compounds, such as cubane or adamantane, have been explored as highly energetic materials.[333] Although the synthesis of primary and secondary nitroalkanes from amines using *m*CPBA and 1,2-dichloroethane (DCE) has been reported by Gilbert

and Borden,[334] Schreiner[333] found that this procedure was also applicable for the preparation of nitro diamondoids (Scheme 27). During their synthesis of unequally disubstituted diamantane derivatives they utilized *m*CPBA to oxidize the amino function in order to prepare the corresponding nitro compounds. Diamondoid amines can be fairly easily be prepared either by chloroacetamidation of alcohols followed by acidic cleavage using thiourea or by treatment of a carboxylic acid with diphenylphosphoryl azide followed by hydrolysis.[335] This has thus made it possible for various diamondoid nitro derivatives to be synthesized by the *m*CPBA oxidation of the corresponding amines.

**Scheme 27. Synthesis of diamondoid nitro compounds from amines with *m*CPBA**



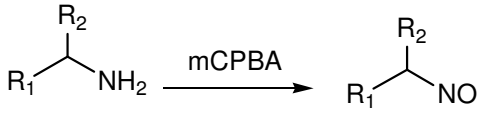

## *5.3.2. Oxidation of amines to nitroso compounds*

From the late 1960s onward, there have been many reports of the use of *m*-CPBA for the synthesis of nitroso compounds (Scheme 28). A particular example of such a transformation is the oxidation of 3-aminobenzamide by *m*CPBA in DMF at 0-5 °C to give 3-nitrosobenzamide.[336,337] Preparation of 6-nitroso-1,2-benzopyrone, 5- nitroso-1(2*H*)-isoquinolinone, 7-nitroso-1(2*H*)-isoquinolinone, and 8-nitroso-1(2*H*)-isoquinolinone have also been reported. These aryl nitroso compounds were prepared in

order to test their suitability as specific inactivators of retroviral zinc fingers and as antitumor agents.[336] Preparation of 2,6-dimethyl-, 2,6-diethylnitrosobenzene and 2-ethyl-6-methylnitrosobenzene using dichloromethane as solvent has also been reported[338] and this reaction has been extended using acetonitrile-$d_3$ as solvent to prepare the same products and 2-methyl-6-tert-butylnitrosobenzene. It was also found that very low yields of < 5% of the corresponding nitroso products were obtained upon oxidation of the 2-chloro-4-methylaniline and 2,4-dimethylaniline precursors.[339]

Reaction of *m*-CPBA with aliphatic primary amines (viz., 2-butylamine, 1-hexylamine, 1-propylamine, 2-phenylethylamine and cyclohexylamine in dichloromethane at room temperature has been shown to give excellent yields of the dimeric nitroso compounds.[334] Baer and Chiu[340] prepared a number of dimeric nitroso sugars from the chloroform or chloroform-methanol solution of the amino sugar being added dropwise to a refluxing solution of *m*-CPBA in chloroform. Furthermore, *trans*-dimeric 2-nitrosocyclohexanol was also prepared by the same method. Several C-nitroso compounds such as nitrosomesitylene, 2-nitrosotoluene, nitrosocyclohexane, 1-alkyl-1-nitrosocyclohexane (alkyl = Me, Et, cyclohexyl), 1-ethyl-1-nitrosocyclopentane, nitroso-*tert*-butane, 2-nitrosoisocamphane, and 2,2,4-trimethyl-4-nitrosopentane have been prepared using *m*-CPBA as the oxidant.[337,341]

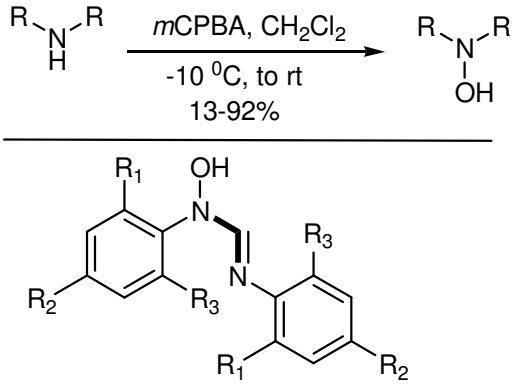
**Scheme 28. Conversion of amines to nitroso compounds with *m*CPBA**




## *5.3.3. Oxidation of amines to hydroxylamines*

*N*,*N*′-Disubstituted hydroxyamidines/amidoximes have been studied for their biological activity (antituberculars and hypotensives) and their pharmacological properties (bactericidal, fungicidal, local anaesthetics) to mention just a few.[342] They have also found good use as precursors in the synthesis of cyclic compounds.[343,344] The *N*-oxidation of *N*,*N*′-disubstituted amidines with *m*CPBA afforded a mild, rapid, and efficient route to the corresponding hydroxyamidines (Scheme 29). The efficiency of the *N*-oxidation reaction is influenced by the substitution on the *N*,*N*′-aryl rings. The substrates with electron-donating bis-ortho substituents give in general good yields (88–92%), while moderate yields (41–59%) were obtained for the compounds bearing electron-donating mono-ortho substituents. Absence of ortho substitution results in rather poor yields (13–22%), as the compounds also decompose during purification. The effect of ortho substitution on the efficiency of the reaction could be explained by the higher stability of the *o*-substituted compounds, as the central carbon is best protected on steric grounds. Electron-donating ortho substituents also increase the basicity of the imido-nitrogen, which has the determining role in driving the *N*-oxidation reaction by electronic considerations. For the very bulky ortho-substituted substrates, steric hindrance starts to have a product reduction of the *N*-oxidation reaction as well.[342]

**Scheme 29. Synthesis of hydroxyformamidines by the *N*-oxidation of their corresponding formamidines**




$R_1 = R_2 = R_3 = H$; 20%
$R_1 = R_3 = H$, $R_2 = Br$; 13%
$R_1 = R_3 = H$, $R_2 = OMe$; 15%
$R_1 = R_3 = H$, $R_2 = Me$; 22%
$R_2 = R_3 = H$, H, $R_1 = Me$; 41%
$R_2 = R_3 = H$, H, $R_1 = i$Pr; 58%
$R_2 = R_3 = H$, H, $R_1 = Ph$; 59%
$R_2 = H$, H, $R_1 = R_3 = Me$; 92%

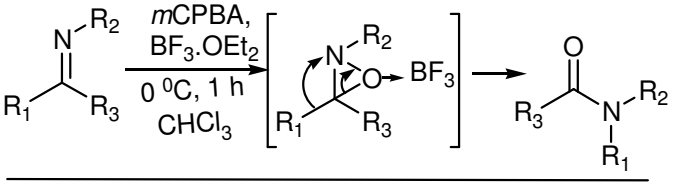
## 6. Unnamed rearrangements

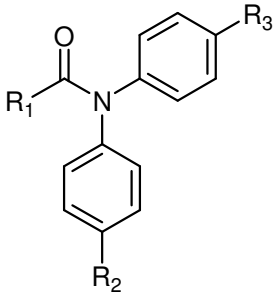
### *6.1. Oxidative rearrangement of ketimines to amides*

The amide moiety is one of the most popular and important functional groups used in many research groups. The amide unit is frequently found in various bioactive natural compounds and it can be a valuable intermediate for the preparation of many other functional groups, such as amines, aldehydes and acids to name but a few.[345] Conversion of ketones to amides has been extensively reported by using a wide range of different methods and reagents.[346-372] Rhee and coworkers[373] reported an oxidative rearrangement of alkyl aryl ketimines to amides by *m*CPBA and $BF_3.OEt_2$ (Scheme 30). It was found that in the protocol aryl groups migrated from carbon to the nitrogen atom in every reaction and that the reaction product was strongly influenced by the migratory aptitude between aryl and alkyl group that conforms to the results of the Baeyer–Villiger oxidation. The alkyl group migration of ketimines was not observed at all. Interestingly in the presence of *p*-toluidine the yield of the oxidative rearrangement dropped due to

more decomposition of ketimines with *m*CPBA. The electronic effect of the *para* substituent on the aryl group of ketimines did not affect the reaction yield all that much. However, an electron withdrawing substituent on the aryl ring was inclined to lower the yield of product compared to H and electron-donating groups.

**Scheme 30. Oxidative rearrangement of ketimines to amides by *m*CPBA and $BF_3.OEt_2$**



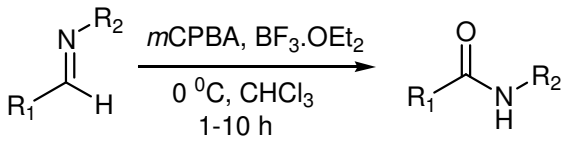

$R_1$ = Me, $R_2$ = $R_3$ = H; 91%
$R_1$ = $R_2$ = Me, $R_3$ = H; 86%
$R_1$ = Me, $R_2$ = OMe, $R_3$ = H; 82%
$R_1$ = Me, $R_2$ = Br, $R_3$ = H; 87%
$R_1$ = Me, $R_2$ = $NO_2$, $R_3$ = H; 78%
$R_1$ = Et, $R_2$ = $R_3$ = H; 87%
$R_1$ = *n*Pr, $R_2$ = $R_3$ = H; 85%
$R_1$ = $R_3$ = Me, $R_2$ = H; 73%
$R_1$ = $R_2$ = $R_3$ = Me; 69
$R_1$ = $R_3$ = OMe, $R_2$ = Me; 70%
$R_1$ = $R_3$ = Me, $R_2$ = Br; 50%
$R_1$ = Et, $R_2$ = H, $R_3$ = Me; 67%
$R_1$ = *n*Pr, $R_2$ = H, $R_3$ = Me; 64%
$R_1$ = Me, $R_2$ = H, $R_3$ = Cl; 91%
$R_1$ = $R_2$ = Me, $R_3$ = Cl; 89%
$R_1$ = Me, $R_2$ = OMe, $R_3$ = Cl; 88%
$R_1$ = Me, $R_2$ = Br, $R_3$ = Cl; 89%
$R_1$ = Me, $R_2$ = $NO_2$, $R_3$ = Cl; 72%
$R_1$ = Et, $R_2$ = H, $R_3$ = Cl; 90%
$R_1$ = *n*Pr, $R_2$ = OMe, $R_3$ = Cl; 89%

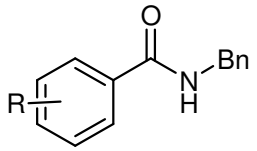
## *6.2. Oxidative rearrangement of aldimines to amides*

Rhee and coworkers reported on the oxidative rearrangement of *N*-benzylaldimines to *N*-benzylamides using a combination of *m*CPBA and $BF_3.OEt_2$ (Scheme 31). *N*-Benzylamide was obtained in every reaction along with some recovered arylaldehyde.[374]

The electronic effect of substituenst on the aryl group of the benzaldimines did not affect the reaction yields to any great extent.[374]

**Scheme 31. Oxidation of N-benzylaldimines to N-benzylamides by *m*CPBA and $BF_3.OEt_2$**



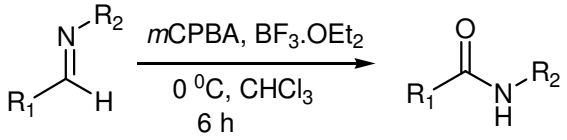

R = H; 80%
R = 4-Me; 80%
R = 4-*i*Pr; 83%
R = 2,5-dMe; 83%
R = 4-Ph; 76%
R = 4-OMe; 67%
R = 4-OEt; 68%
R = 4-F; 80%
R = 4-Cl; 72%
R = 4-Br; 65%
R = 2,4-Cl; 64%
R = 4-CN; 82%
R = 4-$NO_2$; 62%
R = 3-$NO_2$; 68%

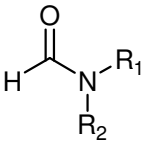
In another study Rhee et al.[375] reported on the oxidation of a different group of aldimines to afford amides by using a similar combination of *m*CPBA and $BF_3.OEt_2$ (Scheme 32). This study indicated that the reaction product was strongly influenced by the electron releasing capacity of the aromatic substituent. In the case of electron-releasing substituents on the aryl group, oxidation of imines afforded formamides in which the aryl group migration occurred. However, in the cases of an electron-withdrawing substituent being on the aryl group the reaction provided the amide formed from the alternative hydride migration. In the case of the chloro substituent, the formamide was obtained as the major product (83% yield) along with 5.6% of the amide. Some authors suggested[376-

[378] that oxaziridine ring formation to be involved in but the actual mechanism has not been defined.

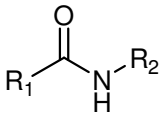
In contrast to this, when *p*-anisidine is used for the oxidation of aldimine, the oxidation affords only the *N*-(*p*-methoxyphenyl)-*p*-substituted-benzamide along with a considerable amount of the recovered arylaldehyde. It was presumed that the reaction follows an internal hydrogen abstraction and decomposition to the corresponding aldehyde. The electron releasing group, i.e. the methoxy group of *p*-anisidine, increases the electron density on the nitrogen atom and helps the coordination of the Lewis acid on the lone pair of the nitrogen atom. After the formation of the peroxy intermediate by the attack of *m*CPBA on the iminium carbon, rapid fragmentation of the peroxy intermediate presumably occurs to provide the amide.[375]

**Scheme 32. Oxidation of aldimines to amides by *m*CPBA and $BF_3.OEt_2$**




$R_1 = R_2 = Ph$; 82%
$R_1 = Ph$, $R_2 = 4Me\text{-}C_6H_4$; 90%
$R_1 = Ph$, $R_2 = 4OMe\text{-}C_6H_4$; 91%
$R_1 = Ph$, $R_2 = 4Cl\text{-}C_6H_4$; 89%
$R_1 = 4Cl\text{-}C_6H_4$, $R_2 = 4Me\text{-}C_6H_4$; 84%
$R_1 = 4Cl\text{-}C_6H_4$, $R_2 = 4OMe\text{-}C_6H_4$; 86%
$R_1 = R_2 = 4Cl\text{-}C_6H_4$; 82%

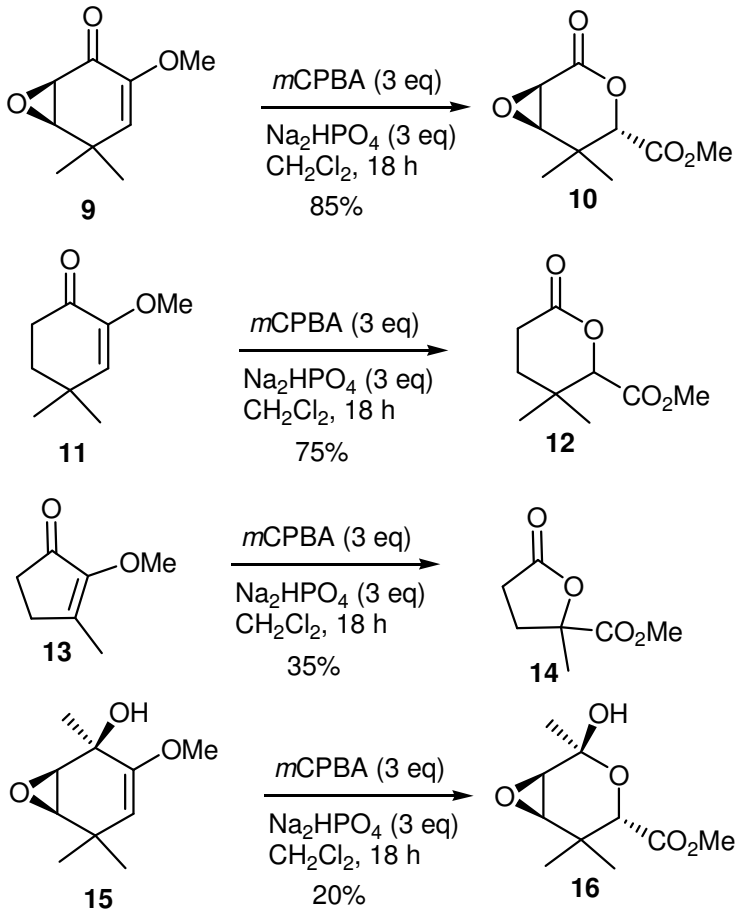



$R_1 = Ph$, $R_2 = 4OMe\text{-}C_6H_4$; 42%
$R_1 = 4Me\text{-}C_6H_4$, $R_2 = 4OMe\text{-}C_6H_4$; 52%
$R_1 = 4Cl\text{-}C_6H_4$, $R_2 = 4OMe\text{-}C_6H_4$; 39%
$R_1 = Ph$, $R_2 = 4NO_2\text{-}C_6H_4$; 71%
$R_1 = Ph$, $R_2 = 4CB_2\text{-}C_6H_4$; 79%
$R_1 = Ph$, $R_2 = 4CF_3\text{-}C_6H_4$; 75%
$R_1 = R_2 = Ph$; 75%

## *6.3. Oxidative rearrangement of cyclic enol ethers to α-alkoxyesters*

Wipf and coworkers[379] treated epoxide **9** with 3 equivalents of *m*CPBA buffered with $Na_2HPO_4$ for a possible Barton cascade reaction. It was interesting to note that they isolated only racemic epoxylactone **10** in 80% yield but as a single diastereomer. Wipf and coworkers[379] examined additional substrates, including five-and six-membered diosphenol ethers (**11**[380,381] **13**[382]), and the highly functionalized hydroxy enol ether **15**. An epoxide (as in **9**) was clearly not necessary since enone **11** underwent an oxidative rearrangement to afford lactone **12** in 75% yield (Scheme **33**). In contrast, the yield for the conversion of the five-membered enone **13** to lactone **14** was only 35%. A carbonyl functionality was also not necessary to facilitate the rearrangement because the epoxy alcohol **15**, prepared by the addition of MeLi to ketone **9**, succumbed to the oxidative rearrangement to give hemiacetal **16** albeit in a rather low 20% yield as a racemic single diastereomer.

**Scheme 33. Oxidative rearrangement of cyclic enol ethers to α-alkoxyesters with *m*CPBA**

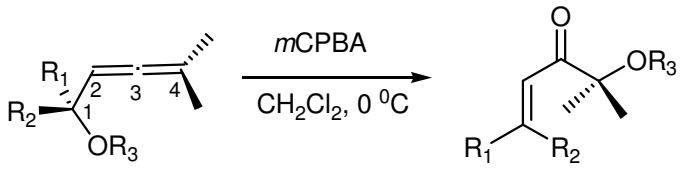



## *6.4. Oxidative rearrangement of α-alkoxy allenes to α′-alkoxy enones*

Lacote and coworkers[383] developed an original and rapid access route towards α′-alkoxy enone derivatives by selective oxidation of α-alkoxy allenes with *m*CPBA (Scheme 34). Both alkyl and silyl ethers of the allene systems underwent efficient migration to from C1 to C4 as illustrated. However, the sterically demanding triisopropylsilyloxy group proved to be too large and this resulted in no rearranged ketone being produced under these conditions. In addition, various combinations of alkyl and aryl groups at C1 viz., $R_1$ and $R_2$ were used in the work (only achiral or racemic allenes were available). This demonstrated that firstly, the prototropy is the one major limitation to the migration in α-

alkoxy allenes, and the second factor steering the reactivity away from oxacyclization is the steric hindrance at C1. Notably, when several oxidizable groups were present on the molecules, oxidation occurred exclusively at the allene framework, and not on the allyl, styryl, or propargyl moieties. Lastly, the facile transformational migration of substrates containing protecting groups, such as benzyl, and, above all, trimethylsilyl, provided access to synthetically useful α′-hydroxy enones after deprotection.[383]

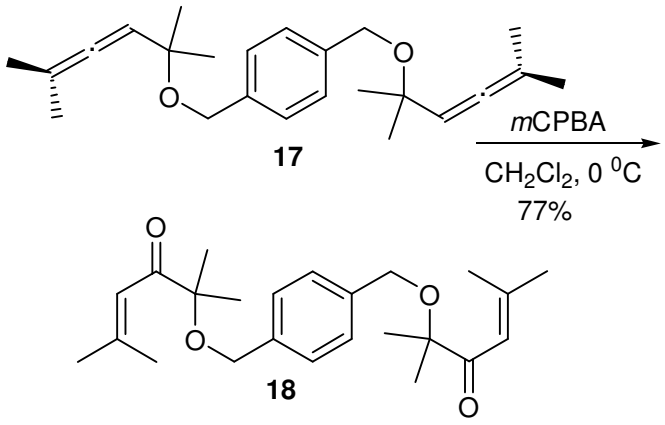
**Scheme 34. Oxidation of tertiary α-alkoxy allenes to α′-alkoxy enones**




$R_1 = R_2 = Ph$, $R_3 = Bn$; 93%
$R_1 = R_2 = Ph$, $R_3 = allyl$; 78%
$R_1 = R_2 = Ph$, $R_3 = proparagyl$; 68%
$R_1 = R_2 = Ph$, $R_3 = CH_2CH(OCH2)_2$; 86%
$R_1 = R_2 = Ph$, $R_3 = SiMe_3$; 94%
$R_1 = R_2 = Ph$, $R_3 = Si(iPr)_3$; 0%
$R_1 = R_2 = Me$, $R_3 = Bn$; 87%
$R_1 = Me$, $R_2 = iPr$, $R_3 = Bn$; 89%
$R_1 = (E)$-styryl, $R_2 = Ph$, $R_3 = Bn$; 76%

In a most intreging case, smooth double migration was achieved from oxidation of the bis-allene **17** (Scheme 35) using 2 equiv of *m*-CPBA in which reaction proceeded within 2 h at 0 ºC to deliver diketone **18** in 77% yield. No traces of any over oxidation product were detected in the product.

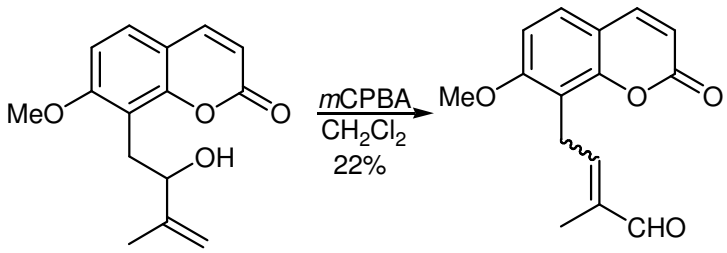
**Scheme 35. Oxidation of a bis-allene derivative**




## 6.5. *Miscellaneous rearrangements*

An oxidative rearrangement took place during *m*CPBA epoxidation of the secondary allylic alcohol, auraptenol, leading to the enal shown in Scheme 36. This reaction has been used in an approach case for the synthesis of gravol and arnottinin.[384-386] The precise reason why the initially formed intermediate epoxide undergoes further rearrangement in this case is not known other than the possibility of the *m*CPBA by-product being able to act as an acidic catalyst to initiate protonation of the epoxide oxygen.

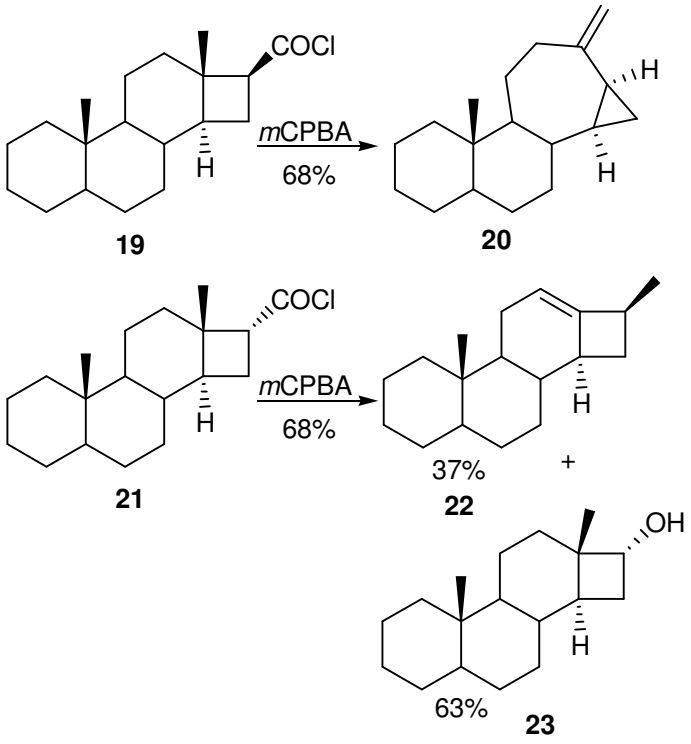
**Scheme 36. *m*CPBA mediated rearrangement of auraptenol**




Ring D in norsteroidal carboxylic acid chloride (**23**) did not follow the normal carboxy inversion reaction expected on treatment with *m*CPBA (Scheme 37).[387,388] Very interestingly it was found that β-acid chloride **19** undergoes an unexpected rearrangement to the allylic cyclopropane **20** in good yield, whilethe corresponding α-acid chloride **21** gave the expected alcohol **23** in 63% together with the product of

elimination with methyl migration **22** in 37% yield. Conformational analysis of these substrates suggested that the stereochemistry of the acid chloride group dictated the course of rearrangement, since the bond *trans* to the migrating group must be suitably disposed to participate in a decarboxylation.

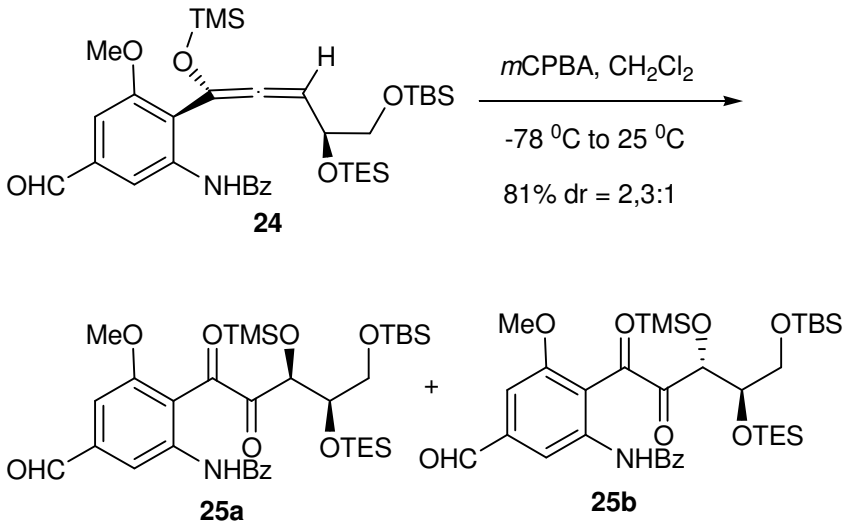
**Scheme 37. Rearrangement of D norsteroidal carboxylic acid chlorides with *m*CPBA**




Williams and coworkers showed that epoxidation of a highly functionalized aryl allene with *m*CPBA gave a rearranged enone.[389] Exposure of **24** to *m*-CPBA effected allene oxidation and rearrangement to enones **25** (dr = 2.3:1, Scheme 38).[390] Importantly, there was no evidence of any arene oxidation. Although the precise stereochemical assignment of the major product has not been unequivocally established, the modest apparent selectivity suggested that epoxidation of the disubstituted terminus double bond occurs

first, an event which would be expected to take place with high facial selectivity and lead to the predominance of a single allene oxide intermediate (not shown). This stereocenter would be destroyed upon eventual enone formation. The expected high reactivity of the allene oxide toward epoxidation would lead to the rapid formation of spirodiepoxide. The second epoxidation would be expected to be less selective; and this stereocenter would be retained in the final enone product.

**Scheme 38. Oxidative Rearrangement of aryl allene with *m*CPBA**



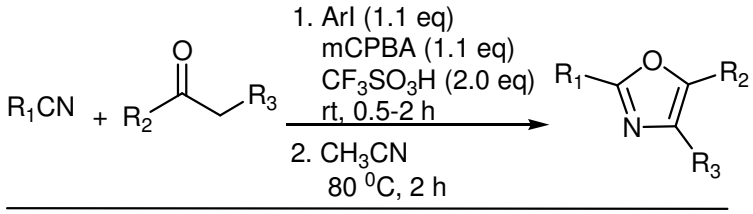

## 7. Cyclization reactions

### *7.1. One-pot preparation of oxazoles*

The oxazole group is one of the key units present in many biologically active natural products, including diazonamides, inthomycins, calyculins and phorboxazoles, and has been extensively used in medicinal chemistry.[391-396] Kawano and Togo reported the PhI-catalyzed direct preparation of 2,5-disubstituted and 2,4,5-tri-substituted oxazoles from reaction between alkyl aryl ketones and nitriles with TfOH and *m*CPBA (Scheme 39).[397]

Different iodoarenes such as iodobenzene, 4-iodotoluene, 4-chloroiodobenzene, 4-iodoanisole, 1-iodonaphthalene, 4,4′-diiodobiphenyl, 1,4-bis(4′-iodophenyl)benzene, and poly(4-iodostyrene) were used as catalyst with *m*CPBA and TfOH. However, in the absence of iodoarene, for example, 2-methyl-5-phenyloxazole was not formed at all. However, in the presence of iodoarene, 2-methyl-5-phenyloxazole was formed in moderate yields (54–60%) in a one-pot manner, especially with iodobenzene, 4-iodotoluene, and 4-chloro-iodobenzene. The same reaction was carried out with butyronitrile and isobutyronitrile instead of acetonitrile using iodobenzene and *m*CPBA. IL-supported PhI could also be used in the same preparation of oxazoles from ketones and nitriles and could be reused in the same reaction to obtain moderate yields of oxazoles.[397]

**Scheme 39. Preparation of oxazoles with *m*CPBA**




$R_1$ = Me, $R_2$ = Ph, $R_3$ = H; 60%
$R_1$ = Me, $R_2$ = 4Me-$C_6H_4$, $R_3$ = H; 64%
$R_1$ = Me, $R_2$ = 4Cl-$C_6H_4$, $R_3$ = H; 61%
$R_1$ = Me, $R_2$ = 4$NO_2$-$C_6H_4$, $R_3$ = H; 77%
$R_1$ = $R_3$ = Me, $R_2$ = Ph; 66%
$R_1$ = Me, $R_2$ = Ph, $R_3$ = $C_7H_{15}$; 50%
$R_1$ = Et, $R_2$ = Ph, $R_3$ = H; 68%
$R_1$ = Et, $R_2$ = 4Me-$C_6H_4$, $R_3$ = H; 45%
$R_1$ = Et, $R_2$ = 4Cl-$C_6H_4$, $R_3$ = H; 48%
$R_1$ = Et, $R_2$ = 4$NO_2$-$C_6H_4$, $R_3$ = H; 78%
$R_1$ = Et, $R_3$ = Me, $R_2$ = Ph; 50%
$R_1$ = Et, $R_2$ = Ph, $R_3$ = $C_7H_{15}$; 36%

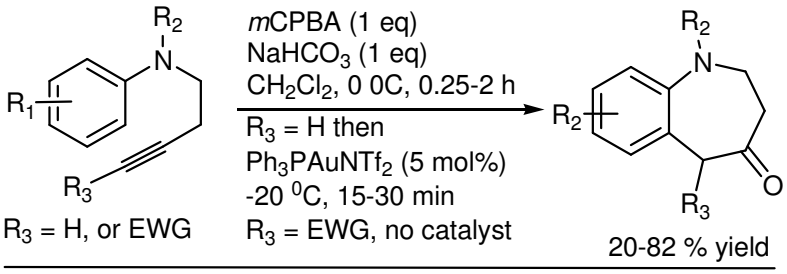
## *7.2. One-pot Synthesis of tetrahydrobenz[b]azepin-4-ones*

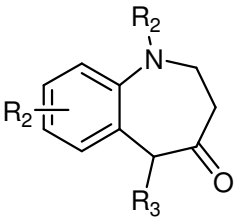
Tetrahydrobenz[*b*]azepin-4-one represents a biologically significant class of benzene-fused heterocycles and has been studied as a mitochondrial benzodiazepine receptor (MBR) antagonist,[398] as an AMPA receptor antagonist,[399] and as oxytocin and vasopressin antagonists.[400] Zhang et al.[401] reported on a one-pot synthesis of tetrahydrobenz[*b*]azepin-4-ones from tertiary *N*-( but-3-ynyl)anilines by using *m*CPBA (Scheme 40). The aniline nitrogen in *N*-(but-3-ynyl)anilines plays an interesting role of relaying "O" from *m*CPBA to the gold-activated C-C triple bond, which is particularly noteworthy considering that alkynes are generally inert towards *m*CPBA oxidation under the reaction conditions (i.e., 0 °C in $CH_2Cl_2$).

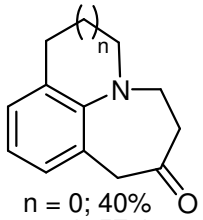
Interestingly substituents with different electronic characters were tolerated in the *meta* and *para* positions, and electron-donating groups such as MeO and Me as well as weakly electron-withdrawing groups such as halides led to better yields than those of strongly electron-withdrawing groups. In most cases, acceptable to good yields were obtained in this two-step, one-pot transformation. In the case of substrates with *meta* substituents, the regioselectivity was low. Moreover, in the case of *m*-$NO_2$, the major product was surprisingly the more hindered ortho-substitution isomer. Noticeably, functional groups such as halides and $NO_2$ on the benzene ring allow easy derivatization of these bicyclic heterocycles when these products are used further. In addition, a benzyl group was suitable as the aniline nitrogen substituent, and its ready removal would open a good route to functionalize the azepinone nitrogen.[401] While longer alkyne chains such as pent-4-ynyl did not present any problems in the transformation other groups such as *i*-Pr or phenyl when attached at the but-3-ynyl group adversely affected the N-oxide formation. Substitutions at the butyne terminus were then studied. A phenyl group did not lead to

any desired product, but a more electron-deficient *p*-$NO_2$Ph group underwent the reaction in a fair yield.[401]

**Scheme 40. One-pot synthesis of tetrahydrobenz[*b*]azepin-4-ones**




n = 0; 40%
n = 1; 57%

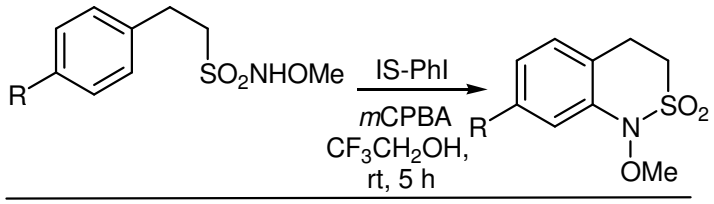
$R_1$ = 2-Me, $R_2$ = Me, $R_3$ = H; 20%
$R_1$ = H, $R_2$ = Me, $R_3$ = 4$NO_2$-$C_6$H; 44%
$R_1$ = H, $R_2$ = Me, $R_3$ = $CO_2$Me; 73%
$R_1$ = H, $R_2$ = Me, $R_3$ = Ac; 76%
$R_1$ = H, $R_2$ = Me, $R_3$ = Bz; 82%
$R_1$ = H, $R_2$ = Me, $R_3$ = Ms; 63%
$R_1$ = 4-Br, $R_2$ = Me, $R_3$ = H; 73%
$R_1$ = 4-I, $R_2$ = Me, $R_3$ = H; 78%
$R_1$ = 4-OMe, $R_2$ = Me, $R_3$ = H; 73%
$R_1$ = 3-$NO_2$, $R_2$ = Me, $R_3$ = H; 58%
$R_1$ = 3-Me, $R_2$ = Me, $R_3$ = H; 70%
$R_1$ = 4-$EtO_2C$, $R_2$ = Me, $R_3$ = H; 40%
$R_1$ = 4-Me, $R_2$ = Me, $R_3$ = H; 70%

## *7.3 Cyclization of N-methoxy-2-arylethanesulfonamides*

It is well known that sulfonamides possess very usefull biological activities.[402-409] Cyclic sulfonamides (sultams), in particular, are important as therapeutic compounds[410,411] and chiral auxiliaries.[412-416] Among them, 3,4-dihydro-2,1-benzothiazine-2,2-dioxides (benzosultams) have proven potent biological activities, viz., lipoxygenase inhibitory activity and are used as drugs for treating heart diseases.[417] Hideo and Togo[417] reported the ion-supported PhI-catalyzed cyclization of *N*-methoxy-2-arylethanesulfonamides with

*m*CPBA to form the corresponding *N*-methoxy-3,4-dihydro-2,1-benzothiazine-2,2-dioxides in moderate to good yields in the solvent 2,2,2-trifluoroethanol (Scheme 41). In the absence of ion-supported PhI, the product *N*-methoxy-3,4-dihydro-2,1-benzothiazine-2,2-dioxide was not formed at all. The reactive and essential hypervalent iodine intermediate compounds, viz., the ion-supported [(hydroxy)(tosyloxy)iodo]benzenes, were formed in situ and reacted with *N*-methoxy-2-arylethanesulfonamides in the presence of *m*CPBA to afford the corresponding *N*-methoxy-3,4-dihydro-2,1-benzothiazine-2,2-dioxides in an electrophilic manner on the aromatic ring. Moreover, ion-supported PhI could be efficiently reused to provide the same products in good yields. The same ion-supported PhI-catalyzed cyclization of *N*-methoxy-3-phenylpropionamide and *N*-methoxy-4-phenylbutyramide with *m*-CPBA was carried out to form the corresponding N-methoxy benzo-lactams in moderate yields in 2,2,2-trifluoroethanol.[417]

**Scheme 41. Cyclization of *N*-methoxy-2-phenylethanesulfonamide with *m*CPBA**




R = H; 93%
R = Me; 58%
R = F; 35%
R = Cl; 62%
R = Br; 85%
R = $CH_2Cl$; 89%
R = OMe; 71%

## *7.4. Stereoselective synthesis of 2,5-disubstituted tetrahydrofurans*

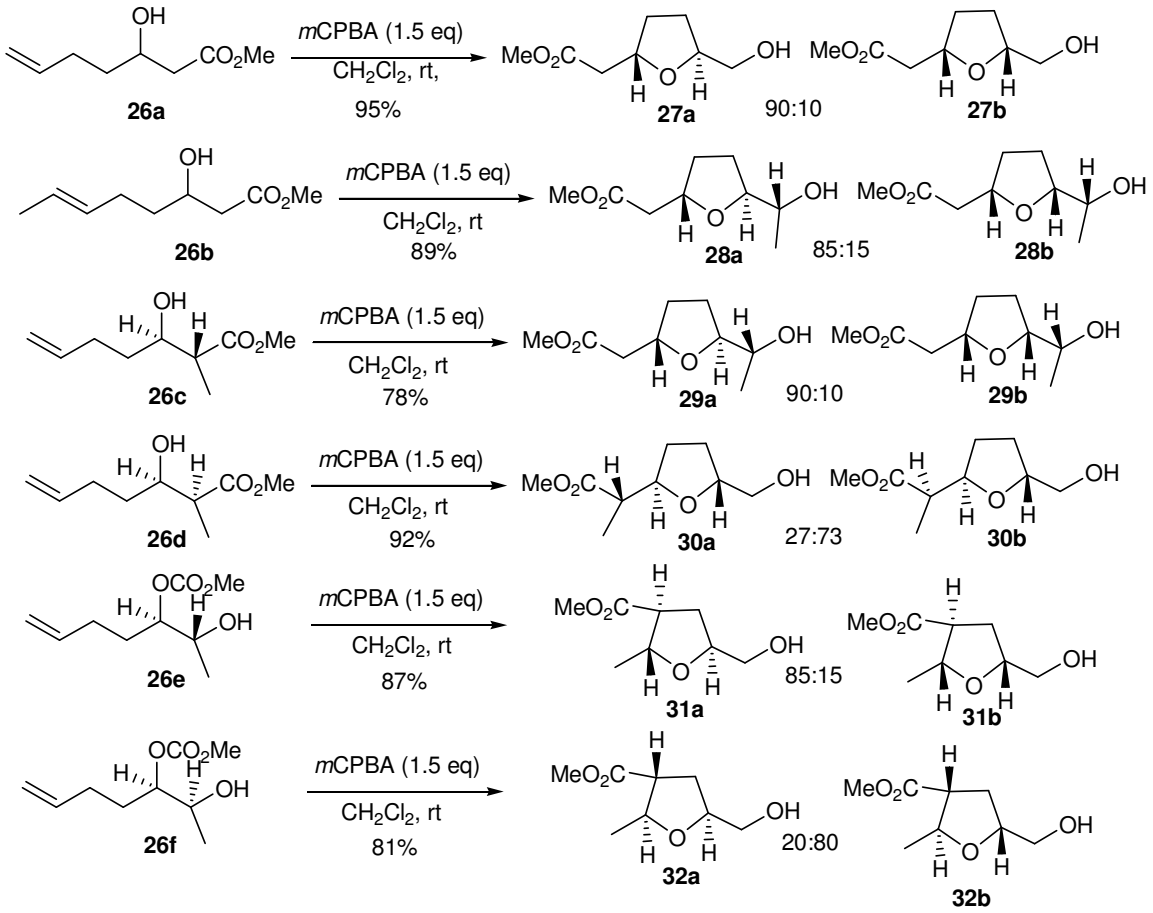
Stereoselective synthesis of 2,5-disubstituted tetrahydrofurans have received considerable attention from organic chemists during the last three decades.[418] Iqbal and coworkers[418] reported on a one pot stereoselective synthesis of *cis* or *trans* 2,5-di-substituted

tetrahydrofurans in high yields via electrophilic cyclisation of the corresponding *cis* or *trans* α- or γ-allyl-β-hydroxyesters mediated by *m*CPBA (Scheme 42). The ally1 β-hydroxyesters **26a-f** were subjected to treatment with *m*CPBA (1.5 equivalent) in dichloromethane for 4-6 hours and demonstrated the presence of one diastereomer of 2,5-disubstituted tetrahydrofuran as the major product. The β-hydroxy ester **26a** provided **27a** predominantly whereas **26b** undergoes a smooth cyclisation to yield **28a** as the major product. Similarly *trans* β-hydroxyester **26c** provided the *trans-cis* isomer **29a** as the major product in excellent yields. On the other hand the corresponding *cis* diastereomer **26d** provided the *cis-trans* isomer **30b** as the major product and the *trans* diastereomer of α-allyl-β-hydroxy ester **26e** was smoothly cyclised and gave the *trans-trans* tetrahydrofuran **31a** as the major product. In contrast the corresponding *cis* diastereomer **26f** cyclised very slowly and provided the *cis-trans* diastereomer **32b** as the major product.[418]

The high *cis*-stereoselectivity during formation of the tetrahydrofurans **27a-29a** can be explained by invoking the involvement of the methoxycarbonyl group during the 5-*exo-trig* cyclisation process. This assumption was based on the fact that usually electrophilic cyclisation of γ,δ-unsaturated alcohols resulted in the *trans* stereochemistry at the ring junction. In this case the alcohols **26a-c** mainly gave rise to the *cis* stereochemistry at the ring junction indicating that the methoxycarbonyl group may be responsible for this specific stereoselectivity. On the other hand the *cis* stereochemistry during the electrophilic cyclisation of alcohols **26a-c** can be explained by the stabilising interactions, between the developing positive charge on the protonated oxirane and the

oxygen lone pair of the ester carbonyl via hydrogen bonding could most likely be responsible for the high stereoselectivity.[418]

**Scheme 42. Synthesis of tetrahydrofurans with *m*-CPBA**



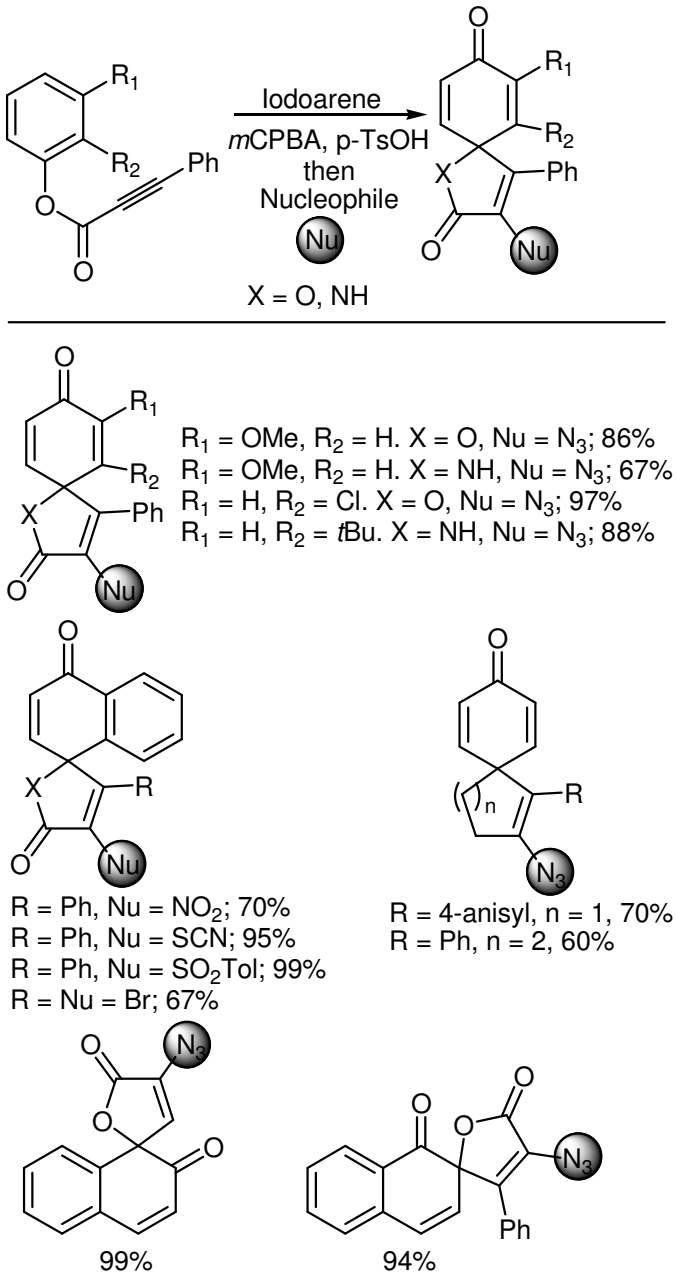

## *7.5. Spirocyclization*

A great variety of spirocyclic compounds are known to exist in nature, and these molecules consist of classes that have received significant interest in recent years as being the privileged structures of some pharmaceuticals, organic materials for optoelectronics and other applications, chiral ligands and catalysts for synthetic uses to mention but a few.[419-424] Kita and coworkers[425] developed a very effective one pot spirocyclization

procedure for installing nucleophiles (Nu = $N_3$, $NO_2$, SCN, $SO_2Tol$, and halogens) via iodonium(III) salts using a combination of iodoarene and *m*-CPBA (Scheme 43). This procedure involves three key steps: firstly, in situ generation of the cationic hypervalent iodine species from iodoarenes using *m*-CPBA; secondly, alkyne activation by the electrophilic iodine for inducing *ipso*-cyclization of aryl alkynes directed by their methoxy group at the aryl ring, forming the spirocyclized iodonium(III) salts; and thirdly, installation of the nucleophiles by reductive coupling between the formed salts to produce the functionalized spirocyclic compounds.[425]

Regarding the iodoarene, the ortho-diiodinated biaryl structure should be essential for developing the transformations with good performance. The minor manipulations of the substituents in the bis(iodoarene)s would contribute to not only the *ipso*-cyclization and the formation of the spirocyclized iodonium salts, but also to the final substitution event by the nucleophiles at the alkenyl moieties. In addition to the construction of five- and six-membered *para*-spirocyclized cyclohexadienones, application of this protocol to formation of the valuable ortho-spirolactone structures that are frequently seen in some natural products[426-429] was also successful based on the demonstrations of the aryl alkynes. In addition to the azide functionality, a series of nitrogen, sulfur, and halogen nucleophiles participated effectively in the spirocyclization in which the starting material had different alkynes.

**Scheme 43. Spirocyclization with *m*-CPBA**

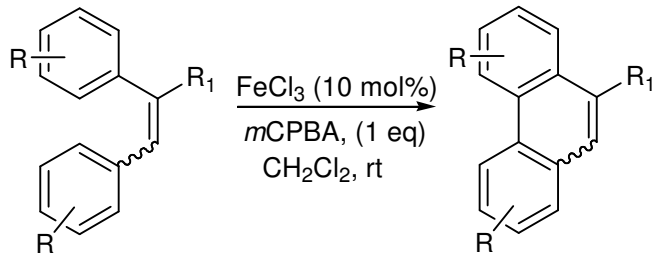


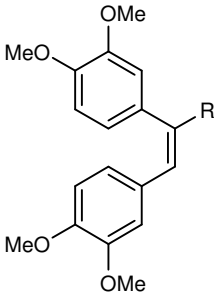
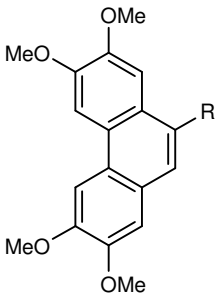
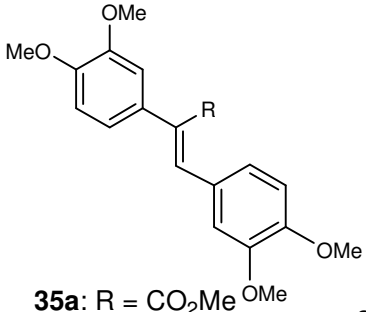
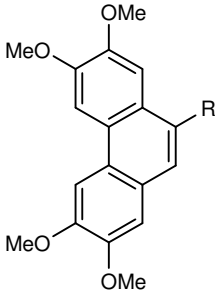

## *7.6. Oxidative cyclization of aromatic nuclei*

The phenanthrene ring and biaryl linkages are found extensively in natural products, pharmaceuticals and many other important organic molecules,[430-432] especially in the phenanthroindolizidine and phenanthroquinolizidine alkaloids and 1,1′-binaphthalene derivatives. Phenanthroindolizidine and phenanthroquinolizidine alkaloids exhibit

interesting pharmacological properties, among which antitumor activity is the most notable.[432-434] Wang and coworker[435] reported that the easily available and nontoxic $FeCl_3$ is able to catalyze an intramolecular oxidative coupling for the direct construction of the phenanthrene ring using *m*CPBA as sole oxidant at room temperature and in excellent yields (Scheme 44). Intially (*E*)-methyl-2,3-bis(3,4-dimethoxyphenyl)acrylate (**33a**) was investigated for the intramolecular oxidative coupling (cyclization) reaction. The desired coupling product **33b** was obtained in 99% yield with $FeCl_3$ as the catalyst and *m*CPBA as oxidant. Compared with di-*tert*-butylperoxide (DTBP), *m*CPBA demonstrates a higher oxidative ability. Further investigations showed that *m*CPBA alone was not effective for the oxidative coupling of **33a**. Similarly substrate (*E*)-**34a**, which also has an electron-withdrawing group (-$CO_2H$) on the double bond, was found to react smoothly under these conditions and gave the desired product **34b** in 96% yield. Intramolecular oxidative coupling of (*Z*)-**35a** and (*Z*)-**36a** with $FeCl_3$ (10 mol %) and *m*CPBA also gave the corresponding coupling products **33b** and **36b** in almost quantitative yield, respectively, suggesting that the configuration of the double bond has no effect on the outcome of the oxidative reaction.

**Scheme 44. Intramolecular oxidative cyclization of diphenyacrylates**




| Sunbstrate | Product (yield) |
|---|---|
|  |  |
| **33a**: R = $CO_2Me$<br>**34a**: R = $CO_2H$ | **33b**: R = $CO_2Me$; 99%<br>**34b**: R = $CO_2H$; 96% |
|  |  |
| **35a**: R = $CO_2Me$<br>**36a**: R = CN | **33b**: R = $CO_2Me$; 98%<br>**36b**: R = CN; 99% |

## 8. Miscellaneous

### *8.1. α-Functionalization*

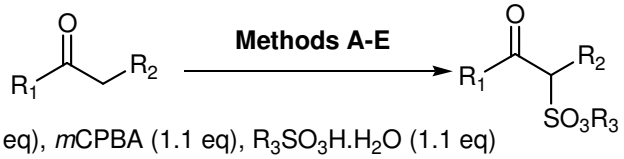
#### *8.1.1. Non-asymmetric (racemic) α-oxytosylation of ketones*

α-Tosyloxy ketones are very important strategic precursors for the construction of various heteroaromatics, such as thiazoles, imidazoles, imidazo[1,2-*a*]pyridines, oxazoles, selenazoles, pyrazoles, and benzofurans.[436-453] Interestingly, method A [PhI (0.1 eq), *m*CPBA (1.1 eq), $RSO_3H.H_2O$ (1.1 eq)],[454,455] method B [polymer-supported-PhI (0.1 eq), *m*CPBA (2.1 eq), TEMPO (cat), *p*-$TsOH.H_2O$ (1.1 eq)],[456] method C [$I_2$ (0.1 eq),

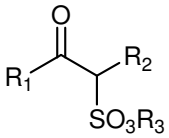
*m*CPBA (2.2 eq), *p*-TsOH.$H_2O$ (2.1 eq)],[457] method D [$I_2$ (0.1 eq), *m*CPBA (2.2 eq), *t*-BuPh (0.2 eq), *p*-TsOH.$H_2O$ (1.5 eq)][457] and method E [IL-Supported-PhI (0.1 eq), *m*CPBA (1.3 eq), IL (0.1 eq), *p*-TsOH.$H_2O$ (1.1 eq)][458] could selectively converted ketones to their corresponding α-tosyloxyketones (Scheme 45).

Various ketones viz., alkyl aryl ketones, dialkyl ketones and cyclic ketone were converted to the corresponding α-tosyloxyketones under methods A-E. Aldehydes were also reacted under the conditions of method A. However, the corresponding α-tosyloxyaldehydes were not obtained at all due to the instability of the products under the reaction conditions. In unsymmetrical methyl ketones, α-tosyloxylation at the alkyl group was favored over that of the methyl group in method A. On the other hand, the yields of α-tosyloxy ketones with alkyl aryl ketones bearing an electron-donating group on the aromatic ring were low in method C, and those of dialkyl ketones were likewise low. Overall, the yields with method D were higher than those with method C. However, α-tosyloxyketones were not obtained at all in the absence of iodine in methods C and D. Moreover, the ionic-liquid reaction media containing a catalytic amount of IL-supported PhI in method E could be reused for the α-tosyloxylation of ketones.

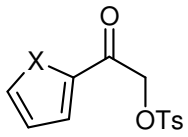
**Scheme 45. α-Tosyloxylation of ketones**




**Method A**: PhI (0.1 eq), *m*CPBA (1.1 eq), $R_3SO_3H.H_2O$ (1.1 eq)
**Method B**: polymer-supported-PhI (0.1 eq), *m*CPBA (2.1 eq), TEMPO (cat), *p*-TsOH.$H_2O$ (1.1 eq)
**Method C**: $I_2$ (0.1 eq), *m*CPBA (2.2 eq), *p*-TsOH.$H_2O$ (2.1 eq)
**Method D**: $I_2$ (0.1 eq), *m*CPBA (2.2 eq), *t*-BuPh (0.2 eq), *p*-TsOH.$H_2O$ (1.5 eq)
**Method E**: IL-Supported-PhI (0.1 eq), *m*CPBA (1.3 eq), IL (0.1 eq), p-TsOH.$H_2O$ (1.1 eq)




$R_1$ = $C_6H_5$, $R_2$ = H, $R_3$ = 4Me-$C_6H_4$; **A**: 85%; **B**: 64%; **C**: 71%; **D**: 70%; **E**: 83%
$R_1$ = 2,4,6Me-$C_6H_2$, $R_2$ = H, $R_3$ = 4Me-$C_6H_4$; **C**: 20%; **D**: 58%
$R_1$ = $C_6H_5$, $R_2$ = $CO_2Et$, $R_3$ = 4Me-$C_6H_4$; **C**: 43%; **D**: 63%
$R_1$ = COMe, $R_2$ = $CO_2Me$, $R_3$ = 4Me-$C_6H_4$; **C**: 41%; **D**: 60%
$R_1$ = 4Me-$C_6H_4$, $R_2$ = H, $R_3$ = 4Me-$C_6H_4$; **A**: 75%; **B**: 65%; **C**: 43%; **D**: 66%; **E**: 60%
$R_1$ = 4Cl-$C_6H_4$, $R_2$ = H, $R_3$ = 4Me-$C_6H_4$; **A**: 88%; **B**: 60%; **C**: 71%; **D**: 75%; **E**: 77%
$R_1$ = $C_6H_5$, $R_2$ = H, $R_3$ = 4Me-$C_6H_4$; **A**: 88%
$R_1$ = $C_6H_5$, $R_2$ = H, $R_3$ = Me; **A**: 78%
$R_1$ = 4$NO_2$-$C_6H_4$, $R_2$ = H, $R_3$ = 4Cl-$C_6H_4$; **A**: 78%
$R_1$ = 4$NO_2$-$C_6H_4$, $R_2$ = H, $R_3$ = 4Me-$C_6H_4$; **B**: 65%; **C**: 90%; **D**: 96%; **E**: 71%
$R_1$ = 3$NO_2$-$C_6H_4$, $R_2$ = H, $R_3$ = 4Me-$C_6H_4$; **C**: 85%; **D**: 95%
$R_1$ = $C_6H_5$, $R_2$ = Me;, $R_3$ = 4Me-$C_6H_4$; **A**: 74%; **E**: 83%
$R_1$ = $C_6H_5$, $R_2$ = $C_7H_{15}$, $R_3$ = 4Me-$C_6H_4$; **A**: 74%; **B**: 75%; **C**: 65%; **D**: 80%; **E**: 81%
$R_1$ = $C_6H_5$, $R_2$ = Me, $R_3$ = 4Me-$C_6H_4$; **A**: 63%; **B**: 80%; **C**: 69%; **D**: 71%
$R_1$ = Naphthyl, $R_2$ = H, $R_3$ = 4Me-$C_6H_4$; **C**: 72%; **D**: 72%
$R_1$ = $C_2H_5$, $R_2$ = Me, $R_3$ = 4Me-$C_6H_4$; **A**: 76%; **C**: 31%; **D**: 62%; **E**: 69%
$R_1$ = $C_5H_{11}$, $R_2$ = $C_4H_9$, $R_3$ = 4Me-$C_6H_4$; **A**: 67%; B: 60%; **C**: 14%; **D**: 57%; **E:** 66%




X = O; **C**: 30%; **D**: 47%
X = S; **C**: 24%; **D**: 49%

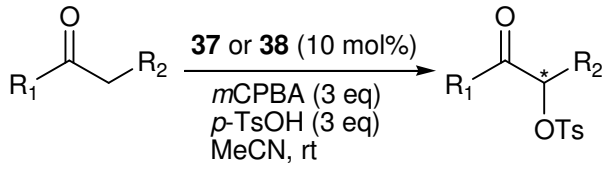
## *8.1.2. Asymmetric α-oxytosylation of ketones*

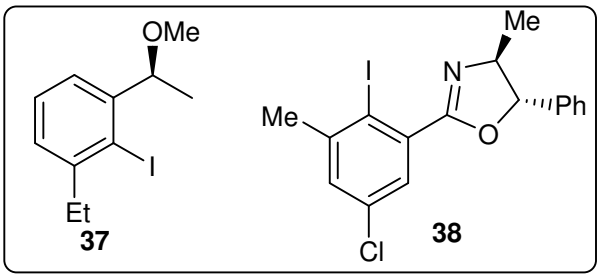
Wirth and coworkers[459,460] reported on the next obvious development viz., the enantioselective α-oxytosylation of ketones using *m*CPBA as the stoichiometric oxidant and *p*-toluenesulfonic acid monohydrate (TsOH.$H_2O$) as the source of the tosylate nucleophile (Scheme 46). The reactions using stoichiometric (10 mol%) quantities of iodoarene **37** were performed and simple propiophenone derivatives generally gave good yields and reliable enantioselectivities. Electron-rich propiophenones underwent side reactions, possibly as a result of the anisole function,[461] and could not be purified. Increasing the steric congestion on the prochiral methylene group led to a slower

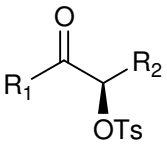
reaction. Indanone gave a high yield and an enantioselectivity consistent with the acyclic propiophenone derivatives but tetralone underwent a very slow reaction giving an almost racemic product. However, cyclopentanone and cyclohexanone underwent Baeyer–Villiger oxidation under these conditions.

In another study Legault and coworkers[462] explored the reaction scope with catalyst **38** and treated a variety of ketones under the described conditions. Variation of the alkyl chain of propiophenone did not result in any significant differences in terms of yields or enantioselectivities. Use of a cyclic ketone such as indanone gave a decrease in selectivity. Surprisingly, tetralone is unreactive under the reaction conditions. The method tolerates electron-withdrawing groups on the aryl ring of propiophenone fairly well but electron-donating groups result in a drastic decrease in reactivity, with the *p*-methoxy derivative being almost unreactive. Introduction of ortho substitution on the aryl ring of propiophenone also has a detrimental effect on both the yield and selectivity. Lastly, aliphatic ketones were tested and found to be unreactive under the reaction conditions.

**Scheme 46. Asymmetric α-oxytosylation of ketones**




$R_1$ = Ph, $R_2$ = Me;
**37**: Yield: 78%; ee: 27%
**38**: Yield: 80%; ee: 48%
$R_1$ = Ph, $R_2$ = Et;
**37**: Yield: 66%; ee: 24%
**38**: Yield: 70%; ee: 48%
$R_1$ = Ph, $R_2$ = *n*-Hex;
**37**: Yield: 86%; ee: 27%
**38**: Yield: 73%; ee: 49%
$R_1$ = 4Me-$C_6H_4$, $R_2$ = Me;
**37**: Yield: 48%; ee: 45%
$R_1$ = 4F-$C_6H_4$, $R_2$ = Me;
**38**: Yield: 77%; ee: 46%
$R_1$ = 3F-$C_6H_4$, $R_2$ = Me;
**37**: Yield: 70%; ee: 28%
**38**: Yield: 65%; ee: 47%
$R_1$ = 2F-$C_6H_4$, $R_2$ = Me;
**38**: Yield: 53%; ee: 20%

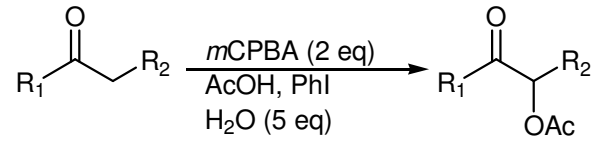
### *8.1.3. α-Acetoxylation of ketones*

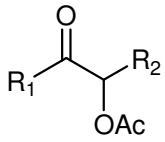
Ochiai and coworkers[463] showed that exposure of acetophenone to dried *m*CPBA (1.4 equiv) in acetic acid in the presence of a catalytic amount (10 mol %) of iodobenzene, $BF_3.Et_2O$ (3 equiv), and water (5 equiv) at room temperature provided α-acetoxyacetophenone in 84% yield (Scheme 47). It is important to note that addition of water is crucial to the success of α-acetoxylation of acetophenone since in the absence of water, α-oxidation was almost inhibited with 95% recovery of the ketone. Formation of α-acetoxyacetophenone was not observed when reaction was carried out in the absence of

iodobenzene as well. Similarly, $BF_3.Et_2O$ was also an essential contributer for this direct α-oxidation of acetophenone and α-acetoxylation of acetophenone did not take place at all in the absence of $BF_3.Et_2O$. Use of other Lewis acids instead of $BF_3.Et_2O$ such as $Yb(OTf)_3$, $CF_3SO_3H$, and $HBF_4.Me_2O$ afforded a moderate yield of α-acetoxyacetophenone.[463]

A variety of dialkyl and alkyl aryl ketones are also smoothly oxidized at the α-positions under these catalytic conditions and afforded α-acetoxy ketones in good yields. Substituted acetophenones with halogens (F, Cl, Br, and I) at the para position gave comparable results, indicating the high selectivity for oxidation of iodobenzene by *m*CPBA over *p*-iodoacetophenone. In the case of unsymmetrical ketones, oxidation of a methylene group of linear long chain alkyl groups was favored over that of a methyl group indicated that the reactivity of α-methylene groups toward acetoxylation decreases in the order ethyl > pentyl > nonyl.[463]

**Scheme 47. α-Acetoxylation of ketones**



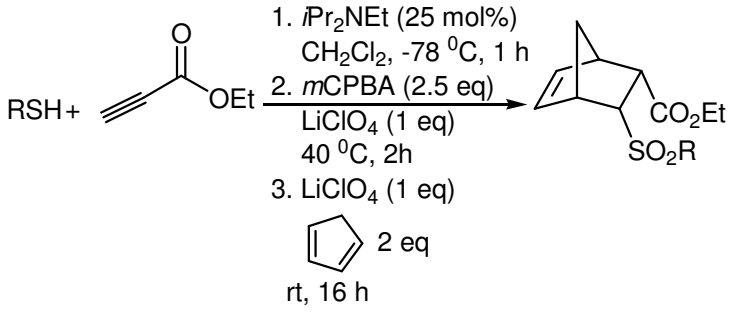



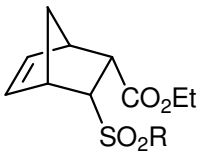

$R_1$ = Et, $R_2$ = *n*Pr; 79%
$R_1$ = *n*Pr, $R_2$ = *n*Bu; 73%
$R_1$ = *n*Bu, $R_2$ = *n*Pent; 65%
$R_1$ = 4F-$C_6H_4$, $R_2$ = H; 76%
$R_1$ = 4Cl-$C_6H_4$, $R_2$ = H; 72%
$R_1$ = 4Br-$C_6H_4$, $R_2$ = H; 76%
$R_1$ = 4I-$C_6H_4$, $R_2$ = H; 67%
$R_1$ = $C_6H_5$, $R_2$ = Me; 84%
$R_1$ = $C_6H_5$, $R_2$ = *n*Pr; 78%
$R_1$ = Cyclopropyl, $R_2$ = H; 71%
$R_1$ = $C_6H_5$, $R_2$ = $CO_2Et$; 49%

## *8.2. Diel Alder reaction*

Ethyl propiolate undergoes a one-pot three-step thioconjugate addition-oxidation-Diels–Alder cycloaddition when treated with a variety of thiols in the presence of catalytic base, *m*CPBA, lithium perchlorate and cyclopentadiene (Scheme 48).[464] Electron-rich aryl thiols were found to be the most successful substrates. In some cases, addition of a second equivalent of $LiClO_4$ during the cycloaddition step was unnecessary to achieve both high yield and selectivity. In the case of *p*-bromothiophenol, the reaction was performed in 1,2-dichloroethane in order to achieve a higher reflux temperature during the oxidation step, ensuring full oxidation to the sulfone. In general, halogenated thiophenol derivatives appear to react some-what less selectively than their counterparts, which corresponds to lower isolated yields of the major cycloaddition adduct. Benzyl mercaptan reacted analogously to that of the S-aryl thiols, providing the major isomer in 67% yield. Diastereoselectivity varied somewhat from substrate to substrate and both the exo isomer derived from the *Z* enoate and diastereomers resulting from the cycloaddition of the *E* enoate were frequently observed as minor products, but in all cases the major endo isomer was easily purified by column chromatography.[464]

**Scheme 48. One-pot three-step reaction with aryl thiols**

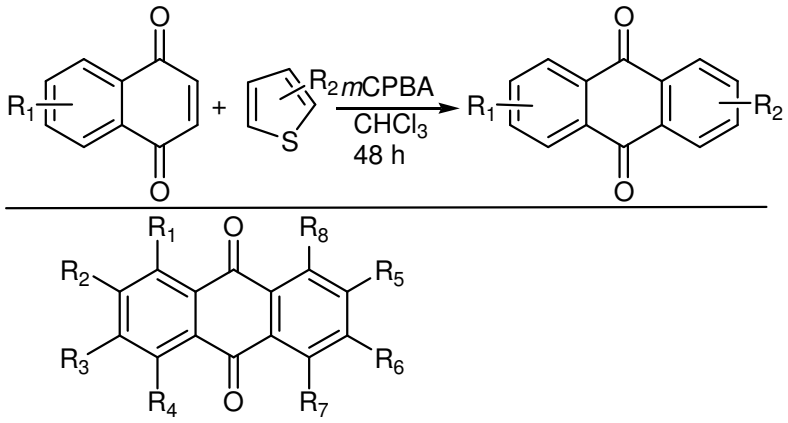



R = $C_6H_5$; dr = 70:30; Yield: 75%
R = 4Me-$C_6H_4$; dr = 76:24; Yield: 81%
R = 4OMe-$C_6H_4$; dr = 87:13; Yield: 81%
R = 4F-$C_6H_4$; dr = 76:24; Yield: 56%
R = 4Br-$C_6H_4$; dr = 71:29; Yield: 57%
R = Bn; dr = 76:24; Yield: 67%

In another study Thiemann et al.[465] reported that brominated anthraquinones can be synthesized directly from bromothiophenes via a Diels Alder reaction when these are reacted with 1,4-naphthoquinones in the presence of *m*CPBA (Scheme 49) . Under these conditions, cycloaddition between intermediately formed thiophene S-oxides and 1,4-naphthoquinones take place, where the formulated, primary sulfoxy-bridged cycloadduct loses the SO-bridge with concomitant aromatization.

**Scheme 49. Synthesis of brominated anthraquinone with *m*CPBA**



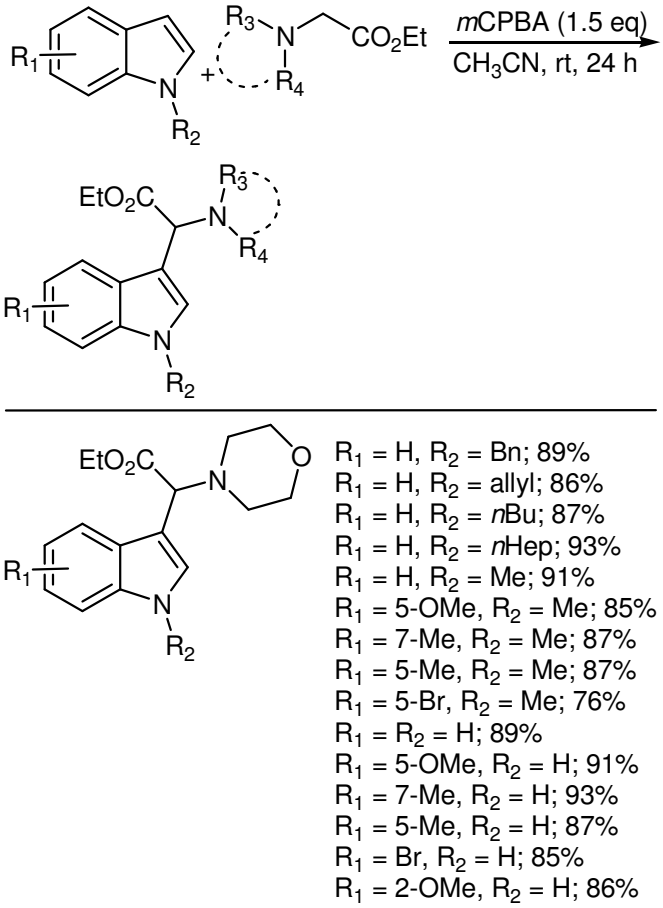

$R_1 = R_2 = R_3 = R_4 = R_5 = R_6 = H$, $R_7 = R_8 = Br$; 29%
$R_1 = R_4 = R_5 = R_6 = H$, $R_2 = R_3 = Me$, $R_7 = R_8 = Br$; 28%
$R_2 = R_3 = Cl$, $R_5 = R_6 = H$, $R_1 = R_4 = Me$, $R_7 = R_8 = Br$; 30%
$R_1 = R_2 = R_3 = R_4 = R_6 = H$, $R_5 = R_7 = Br$, $R_8 = Ph$; 26%
$R_1 = R_2 = R_3 = R_4 = R_6 = H$, $R_5 = R_7 = Br$, $R_8 = 4Me\text{-}C_6H_4$; 28%
$R_1 = R_2 = R_3 = R_4 = H$, $R_5 = R_6 = R_7 = R_8 = Br$; 35%
$R_1 = R_2 = H$, $R_3 = R_4 = Me$, $R_5 = R_6 = R_7 = R_8 = Br$; 25%
$R_1 = R_2 = R_3 = R_4 = R_5 = R_6 = H$, $R_7 = Me$, $R_8 = Br$; 24%
$R_1 = R_4 = R_5 = R_6 = H$, $R_2 = R_3 = R_7 = Me$, $R_8 = Br$; 23%

## *8.3. Oxidative coupling of indoles with ethyl 2-(disubstituted amino)acetates*

Indolylglycine derivatives are important synthetic intermediates or building blocks for drug development[466] as well as natural product synthesis.[467-472] Bao and coworkers showed that the oxidative coupling of ethyl 2-(disubstituted amino)acetates with indoles has been found to proceed in the presence of *m*CPBA under metal-free conditions to

provide indolylglycine derivatives in satisfactory to excellent yields (Scheme 50).[473] *m*-CPBA acted as an oxidant in this methodology. Different solvents were initially tested but $CH_3CN$ proved to be the best. The reactions of different indole derivatives with various *N*-protecting groups such as benzyl, allyl, *n*-butyl, *n*-heptyl, and methyl proceeded smoothly with ethyl 2-morpholinoacetate and furnished the corresponding coupling products in good to excellent yields (86-93%). This result indicated that the size of the *N*-protecting group did not influence the reactivity of the indole substrate. *N*-Me indoles bearing electron-donating groups viz., OMe and Me on the benzene rings are also able to undergo the desired oxidative coupling reaction smoothly to yield the corresponding products in good yields (85-87%). However, *N*-Me indole bearing a bromine atom, an electron-withdrawing group, on the benzene ring showed relatively low reactivity in this type of oxidative coupling reaction. These results showed that the reaction yield was indeed influenced by the electronic property of the substituent linked to the benzene ring of the indole moiety. Subsequent studies revealed that the free (*N*H)-indole substrates can also undergo this type of oxidative coupling reaction.[473]

**Scheme 50. Oxidative coupling of various indole derivatives with ethyl 2-morpholinoacetate**

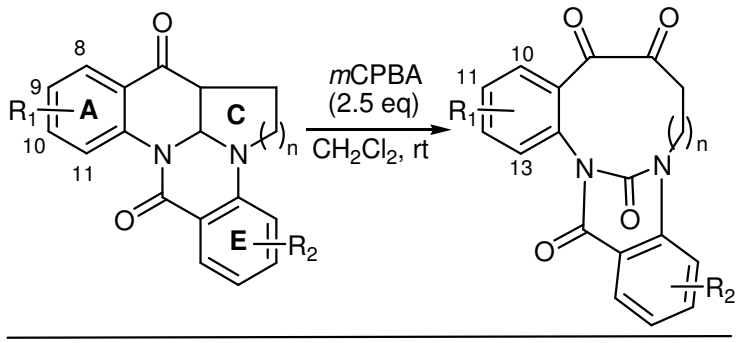



## *8.4. Oxidative cleavage of polycyclic systems*

Medium- to large-sized rings can be synthesized via oxidative cleavage of internal double bonds in polycyclic systems. Interestingly the nine- and ten-membered ring containing compounds that resulted from the *m*CPBA-mediated oxidative cleavage reaction were shown to exhibit atropisomerism.[474] The scope of the oxidative cleavage was explored as a function of the substituents in ring A of the substrate. Whereas, in general, the yield decreased slightly in the presence of substituents at the C9-, C10- and C11-positions in reactansts for the n = 1 series, the reaction proceeded in moderate to good yield. When an electron-donating $R_2$ substituent was incorporated in ring E, the reaction failed with only extensive decomposition being observed (Scheme 51). The presence of either an electron-

withdrawing or electron-donating substituent in ring A was unable to rescue the reaction outcome for an electron-donating substituent in ring E. Expansion of ring C in the reactants was well tolerated.[474]

**Scheme 51. Oxidative cleavage reaction with *m*CPBA**




$R_1 = R_2 = H$, n = 1; 70%
$R_1$ = 11-Me, $R_2 = H$, n = 1; 50%
$R_1$ = 11-Cl, $R_2 = H$, n = 1; 47%
$R_1$ = 12-Me, $R_2 = H$, n = 1; 47%
$R_1$ = 12-OMe, $R_2 = H$, n = 1; 36%
$R_1$ = 12-Cl, $R_2 = H$, n = 1; 37%
$R_1$ = 13-Me, $R_2 = H$, n = 1; 75%
$R_1$ = 13-Cl, $R_2 = H$, n = 1; 64%
$R_1 = R_2 = H$, n = 2; 79%
$R_1$ = 13-Me, $R_2 = H$, n = 2; 79%
$R_1$ = 13-Cl, $R_2 = H$, n = 2; 80%
$R_1$ = 13-Me, $R_2$ = 3-OMe, n = 2; 94%
$R_1$ = 12-Me, $R_2$ = 3-OMe, n = 2; 41%

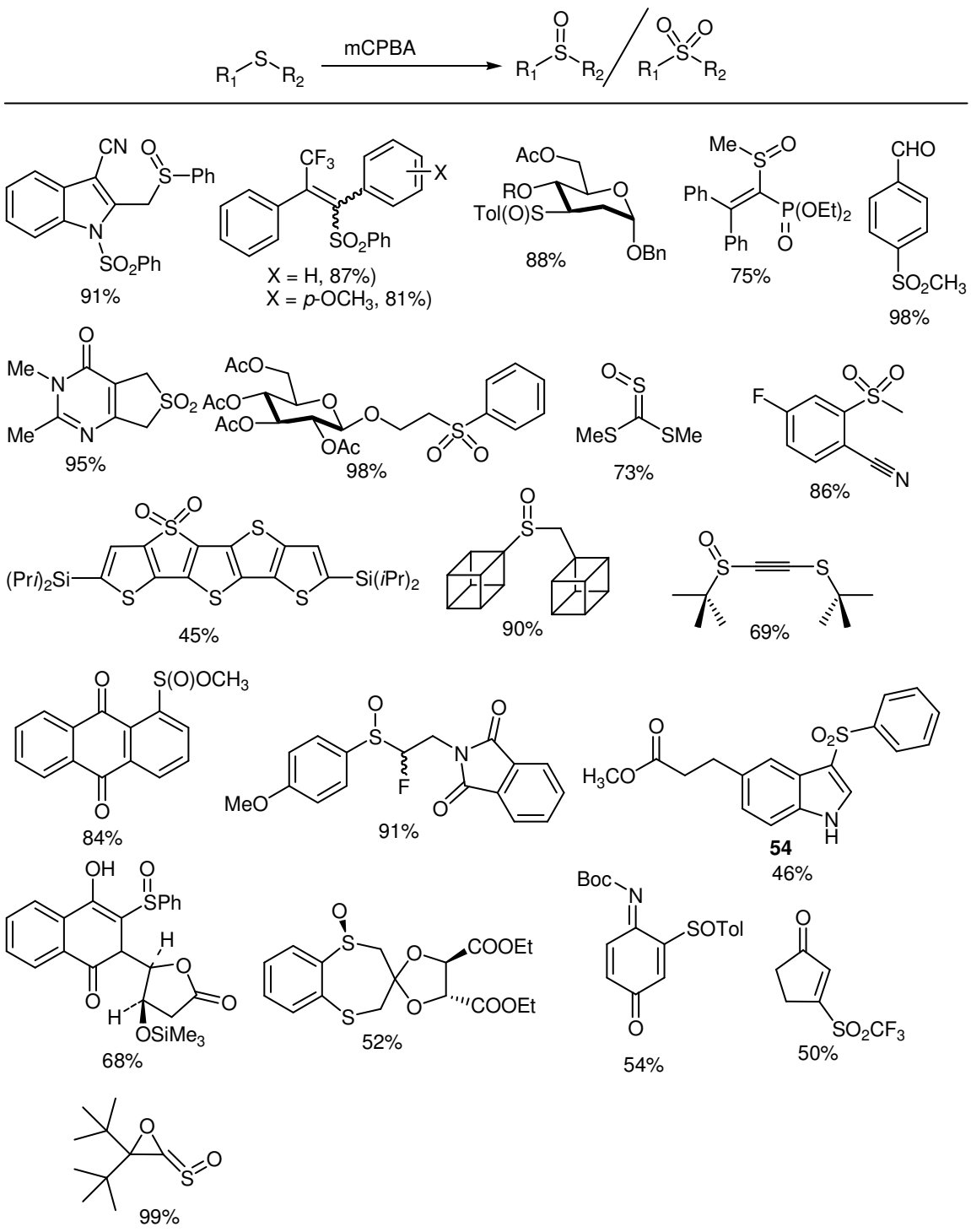
## 8.5. Heteroatom Oxidation

### *8.5.1. Oxidation of sulfides to sulfoxides and/or sulfones*

Sulfones are valuable synthetic intermediates for the construction of chemically and biologically important molecules[475-478] especially those that have demonstrated biological activities.[479-486] *n*-Butanethiol was oxidized by *m*CPBA in $CH_2Cl_2$ at -30 ºC to yield in 82% yield n-butanesulfinic acid (*n*-$BuSO_2H$) and interestingly other thiols reacted similarly.[487] Sulfides were oxidized chemoselectively to sulfoxides by *m*CPBA at -70 ºC.[488] Three reagents viz., *m*CPBA, sodium periodate and iodosylbenzene are regarded as

ideal for the oxidation of sulfides to sulfoxides.[489] *m*CPBA is the most popular and extensively reagent used for the oxidation of sulfides to their corresponding sulfoxides and sulfones and the results are summarized in Scheme 52.[490-549]

**Scheme 52. Oxidation of sulfies to sulfoxides or sulfones with *m*-CPBA**

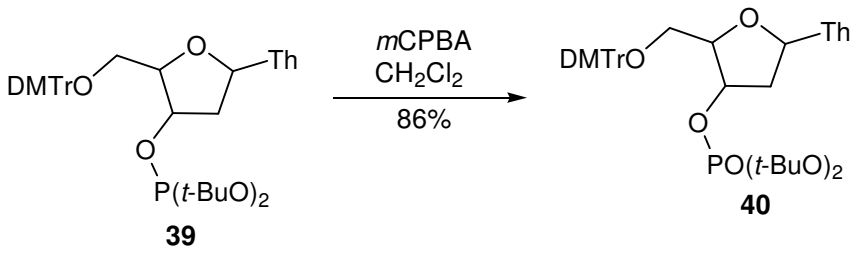



## *8.5.2. Oxidation of phosphorous*

*m*-CPBA stereospecifically oxidized phosphate **39** to afford phosphate **40** in 86% yield (Scheme 53).[550] Similarly *m*CPBA oxidation of thiophosphate triesters provided the

corresponding phosphate esters with retention of configuration.[551] In another study Chow and Berkman[552] prepared phosphate esters of *N*-phosphoryl amino acids by using *m*CPBA for the oxidation of phosphorous.

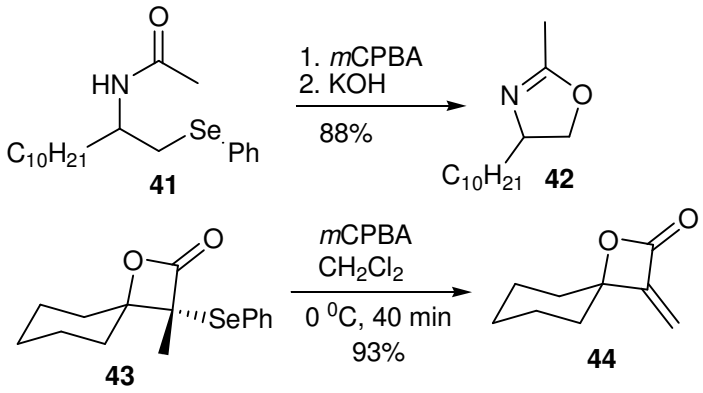
**Scheme 53. Phosphorous oxidation with *m*CPBA**




## *8.5.3. Oxidation of selelnides*

The selenoyl group has been demonstrated to be a good leaving group and therefore its generation in a compound can lead to the preparation of cyclic compounds if other functional groups are correctly predisposed. In this way oxazoline **42** has been prepared through oxidation of selenide **41** followed by treatment of the oxidized material with base.[553] Similarly oxidation of selenide **43** with *m*CPBA was very efficient to introduce exocyclic unsaturation under mild conditions for the preparation of compound **44**.[554] Similarly phenyl selenides react rapidly with *m*CPBA at -10 ºC but at higher temperatures of between 0 ºC to rt they are inclined to undergo a t cis elimination (Scheme 54).[555]

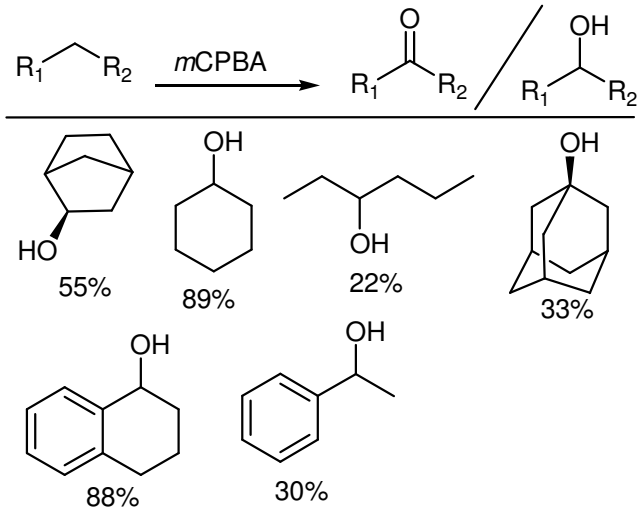
**Scheme 54. Oxidation of selenides with *m*-CPBA**




## *8.6. Oxidation of C-H bonds*

Selective functionalization of saturated hydrocarbons is of major importance in synthetic organic chemistry and considerable attention over the past decades has been given in this regard for development of efficient methods for both regio- and stereoselective C-H bond activation.[556] Kim et al.[557] reported the catalytic hydroxylation of aliphatic hydrocarbons by *m*-CPBA in the presence of electron-deficient iron(III) porphyrin complexes (Scheme 55). High yields of alcohol products were obtained together with minor amounts of ketones. The hydroxylation of *cis*- and *trans*-1,2-dimethylcyclohexane provided the corresponding tertiary alcohols with high stereoretention, indicating that these reactions are highly stereospecific. Hydroxylation of norbornane provided the *exo*-norborneol as as major product. In another study by Konoike et al.[558], they reported a novel allylic hydroxylation using the mixture: *m*CPBA-Fe(PFPP)Cl on the triterpenes oleanolic acid, ursolic acid, dihydrolanosterol and their derivatives bearing stericaily hindered olefin groups and it was apparent that these reactions were catalyzed by the Fe(PFPP)CI modality since all were converted to their corresponding allylic alcohols under the relatively mild conditions.

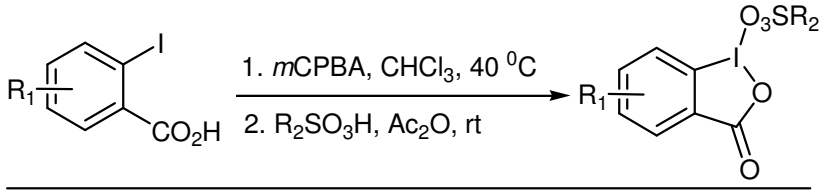
**Scheme 55. Oxidation of C-H bonds with *m*CPBA**

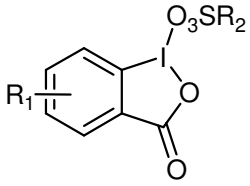



## *8.7. Generation of aryl iodide(III) from iodoarenes*

Hypervalent iodines have a long history of being widely used in organic synthesis.[559] Kita et al. demonstrated the synthesis of novel 1,3,5,7-tetrakis[4-(diacetoxy-iodo)phenyl]adamantane and tetrakis[4-(diacetoxy-iodo)phenyl]methane from 1,3,5,7-tetrakis(4-iodophenyl)adamantane and tetrakis(4-iodophenyl)methane, respectively, with *m*CPBA under diluted conditions at room temperature.[83] Generally, room temperature conditions are required for the synthesis of [hydroxy(sulfonyloxy)iodo]arenes from the reaction of (diacetoxyiodo)arenes with *p*-toluenesulfonic acid monohydrate, due to the high reactivity of [hydroxy(sulfonyloxy)iodo]arenes. Yamamoto and Togo[560] showed that various [hydroxy(sulfonyloxy)iodo]arenes could efficiently be obtained in high yields from the reaction of iodoarenes and *m*CPBA in the presence of sulfonic acids in a small amount of chloroform at room temperature, through a one-pot procedure. Variuos sulfonic acids, including *p*-toluenesulfonic acid monohydrate, were reacted to furnish the corresponding [hydroxy(sulfonyloxy)iodo]benzenes in good yields (Scheme 56). 1-(Arenesulfonyloxy)benziodoxolones could also be prepared from o-iodobenzoic acid in a one-pot procedure.

**Scheme 56. One-pot preparation of [hydroxy(sulfonyloxy)iodo]arenes from iodoarenes with *m*CPBA**

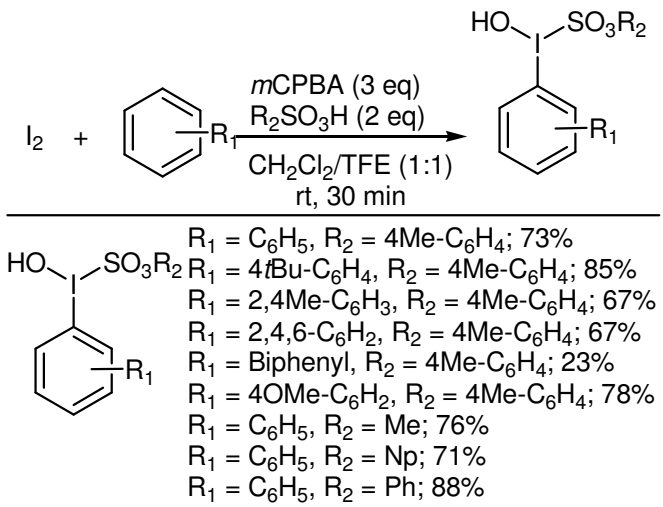



$R_1 = C_6H_5$, $R_2 = 4Me\text{-}C_6H_4$; 95%
$R_1 = C_6H_5$, $R_2 = 3NO_2\text{-}C_6H_4$; 87%
$R_1 = C_6H_5$, $R_2 = 2,4NO_2\text{-}C_6H_3$; 87%
$R_1 = C_6H_5$, $R_2 = 4Cl\text{-}C_6H_4$; 88%
$R_1 = C_6H_5$, $R_2 = 2\text{-Naphthyl}$; 76%
$R_1 = C_6H_5$, $R_2 = C_6H_5$; 98%
$R_1 = C_6H_5$, $R_2 = Me$; 97%
$R_1 = R_2 = 4Me\text{-}C_6H_4$; 100%
$R_1 = 2Me\text{-}C_6H_4$, $R_2 = 4Me\text{-}C_6H_4$; 95%
$R_1 = 3CF_3\text{-}C_6H_4$, $R_2 = 4Me\text{-}C_6H_4$; 85%
$R_1 = 4Cl\text{-}C_6H_4$, $R_2 = 4Me\text{-}C_6H_4$; 96%

In another study Olofsson et al.[561] reported on a one-pot synthesis of neutral and electron-rich [hydroxy(tosyloxy)iodo]arenes from iodine and arenes, thereby avoiding the need for expensive iodine(III) precursors (Scheme 57). *tert*-Butylbenzene, *p*-xylene and mesitylene proved to be excellent substrates, delivering the corresponding products in good yields. On the other hand biphenyl was surprisingly unreactive, and prolonged reaction time failed to improve the yield. The acid was subsequently varied using benzene as the arene. Methanesulfonic acid, 2-naphthalenesulfonic acid, and benzenesulfonic acid all delivered the corresponding [hydroxy(tosyloxy)iodo]arenes in good yields, whereas camphorsulfonic acid did not work.

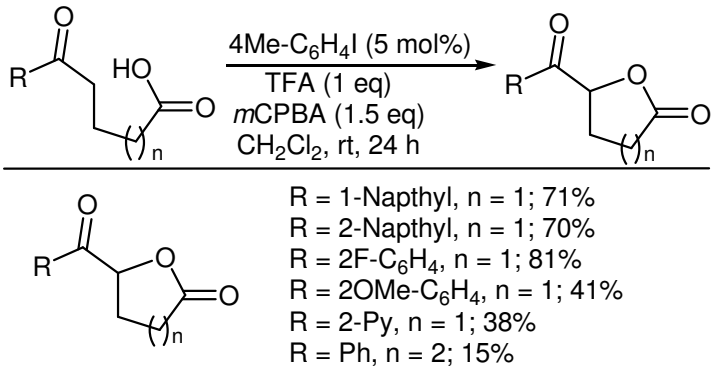
**Scheme 57. Synthesis of electron-rich [hydroxy(tosyloxy)iodo]arenes**




## *8.8. Oxylactonization of ketocarboxylic acids*

Ishihara et al.[562] reported the hypervalent iodine-catalyzed oxylactonization of ketocarboxylic acids to ketolactones in the presence of iodobenzene (10 mol %), *p*-toluenesulfonic acid monohydrate (20 mol %) and *m*CPBA as a stoichiometric co-oxidant (Scheme 58). 1-Napthyl and 2-napthyl ketones afforded the corresponding ketolactones in good yields. In contrast, 2-methoxyphenyl ketone was transformed to the corresponding lactone in only 41% yield, since Baeyer–Villiger products were obtained as the alternative main products. Unfortunately, picolinoyl lactone and six-membered δ-lactones were obtained in only 38% and 15% yield, respectively.

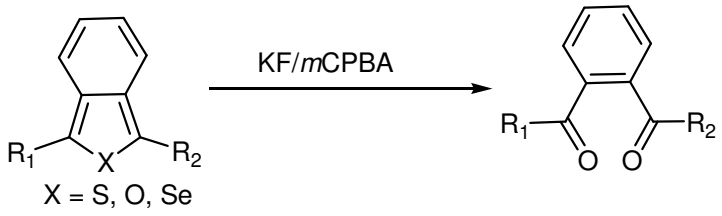
**Scheme 58. In situ-generated hypervalent iodine-catalyzed oxylactonization of ketocarboxylic acids.**




## *8.9. Oxidative ring opening of 1,3-diarylbenzo[c]heterocycles*

Mohanakrishnan et al.[563] reported on the oxidative cleavage of benzo[c]heterocycles using *m*CPBA and the reaction of 1,3-diaryl benzo[*c*]heterocycles with *m*CPBA at room temperature for 5 min led to the formation of 1,2-diaroylbenzenes in good to excellent yields (Scheme 59). In the case of 1,3-dithienylbenzo[c]thiophene, the *m*CPBA-mediated oxidative cleavage provided an unsymmetrical diketone formed through oxidation of a thiophene unit into an S,S-dioxide moiety. However, the reaction with diarylbenzo[c]thiophenes provided their respective diketones in excellent yields. The oxidative ring-opening reaction of 1,3-diarylbenzo[c]furans proceeded with relatively better yields than their respective benzo[*c*]thiophenyl heterocycles. Diarylbenzo[c]selenophenes also underwent oxidative cleavage to furnish the corresponding diketones in slightly reduced yields. In the case of thiophene-tethered benzo[*c*]furans, oxidation of the thiophene unit was not observed. As expected, the benzo[c]furans linked to the dihexylfluorene, pyrene, and diphenylmethane groups also underwent the oxidative cleavage and led to their respective diketones in excellent yields.[563]

**Scheme 59. Oxidative ring opening of 1,3-diarylbenzo[c]heterocycles**

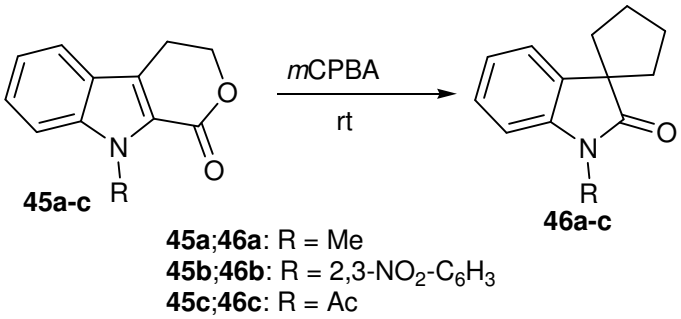



$R_1$ = $R_2$ = Phenyl, thienyl, *p*-tolyl, *p*-anisyl, napthyl, *o*-xylenyl

## *8.10. Oxidation of indoles*

Peracids have been widely used for the oxidation of 2,3-disubstituted indoles.[564] Hino demonstrated that treatment of tetrahydrocarbazole with *m*-CPBA at -60 °C in $CH_2I_2$ provided hydroxy-4a*H*-carbazole as the major product.[565] Similarly the latter hydroxyindolenine could be oxidized in good yield to the corresponding ketoamide by *m*CPBA in the presence of $H_2SO_4$.[565] On the other hand, *m*CPBA oxidation at -40 °C of aristoteline, a piperidino-indole alkaloid, provided the corresponding hydroxyindolenine in 94% yield. In contrast, at 25 °C, the hydroxyindolenine was obtained as the major product (57%) with a 21% yield of the corresponding ketoamide.[566] Furthermore, ketoamides have been synthesized by *m*-CPBA oxidation of a tetrahydrobenzo[*b*][1,8]naphthyridin-5(7*H*)-one.[567] and of *N*-methylazetopyridoindoles.[568] Being inspired by these results, Husson et al.[569] reported on the oxidative cleavage of the indole 2,3 double bond according to Kurihara's experimental conditions[568] (*m*CPBA, room temperature in $CH_2Cl_2$) with *N*-substituted indole δ-lactones **45a-c**. The expected ketoamides were not obtained, but instead new heterocycles were formed to which the structures of 4,5-dihydrospiro[furan-3(2*H*),3′-indole]-2,2′-(1′*H*)-diones **46a-c** were attributed (Scheme 60).

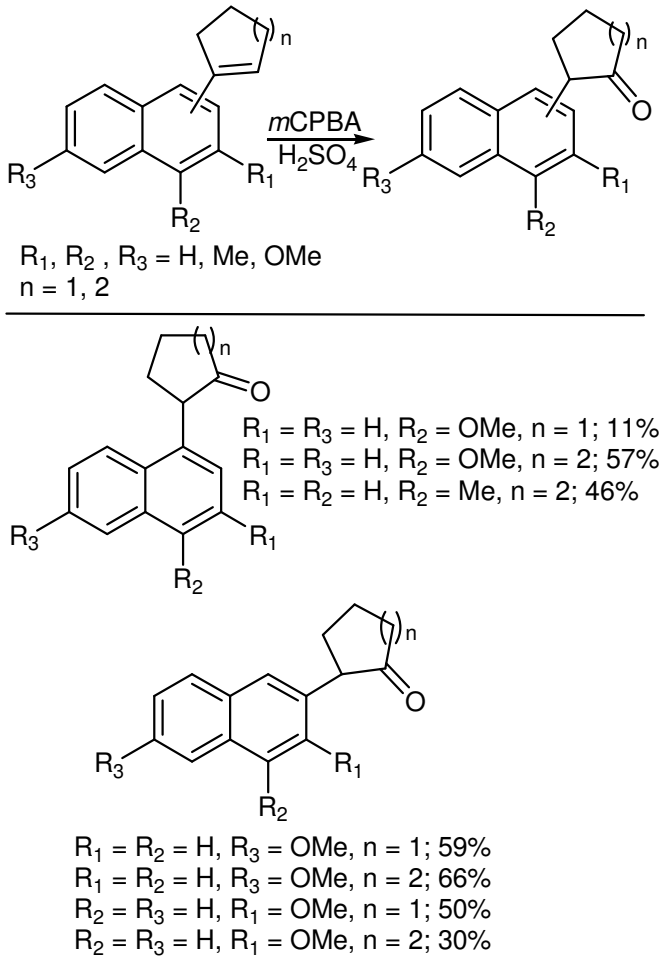
**Scheme 60. Oxidation of indoles with *m*CPBA**




## *8.11. Miscellaneous transformations*

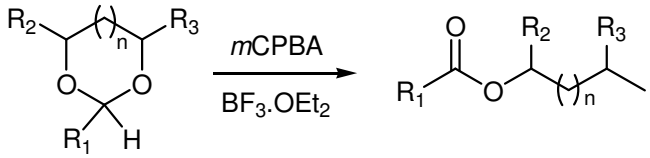
Góra et al.[570] reported on the oxidation of naphthylcycloalkenes with *m*-CPBA followed by acid catalyzed rearrangement of either the diol or epoxide, and provided a series of naphthylcycloalkanones in a very simple manner (Scheme 61). The conditions allow for preparation of naphthylcycloalkanones on a multigram scale. Initialy, most of the substituted naphthylcycloalkenes gave only 10–20% yields of the target naphthylcycloalkanones with $H_2O_2$ but changing the conditions to *m*CPBA gave satisfactory yields.

**Scheme 61. Oxidation of naphthylcycloalkenes with *m*CPBA**



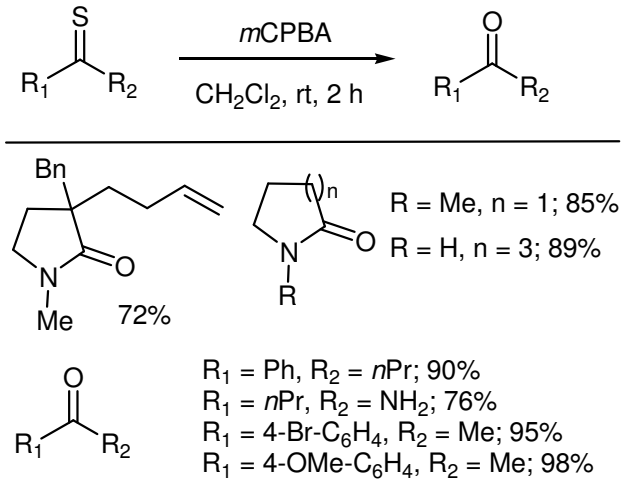

Kim et al.[571] demonstrated an efficient conversion of cyclic acetals to their corresponding hydroxy alkyl esters in good to excellent yields through oxidation using *m*CPBA (Scheme 62). Interestingly all of the cyclic acetals evaluated provided hydroxy alkyl esters without any problems. From these results, it was suggested that aldehydes could be converted to the corresponding hydroxy alkyl esters. Besides symmetrical cyclic acetals, unsymmetrical cyclic acetals were also converted to hydroxy alkyl esters. It is worthy of note that unsymmetrical cyclic acetals afforded only one isomer.

**Scheme 62. Conversion of cyclic acetals into their corresponding hydroxy alkyl esters**



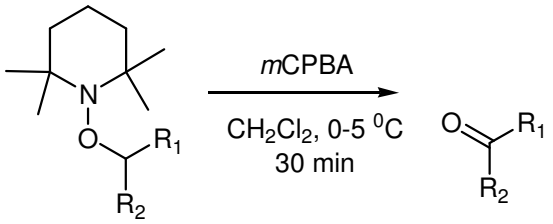

Pinnick et al.[572] reported on the synthesis of amides derived from thioamides using *m*CPBA. This reaction was quite rapid and occurred to the total exclusion of olefin epoxidation of side chain olefins when present (Scheme 63). Furthermore, this methodology applies both to thioamides as well as thiolactams and proceeds in high yield. Primary, secondary and tertiary thioamides undergo this transformation with equal efficiency. For example, butyramide, aprolactam, and *N*-methylpyrrolidone were produced in 76%, 89%, and 82% yield respectively from the thioamide precursors.

**Scheme 63. Synthesis of amides from thioamides**




Inokuchi and Kawafuchi[573] reported that O-benzyl- and O-allyl-TEMPOs were transformed to the corresponding carbonyl compounds by using *m*CPBA (Scheme 64). Different oxidizing reagents viz., $Mn(OAc)_3$, $Cu(OAc)_2$ and *tert*-BuOOH were examined but it turned out that *m*CPBA was the most highly efficient oxidant to effect the reaction the most rapidly at 0–5 ºC to afford the expected products in excellent yields.

**Scheme 64. Conversion of O-benzyl- and O-allyl-TEMPOs to carbonyl compounds**




$R_1 = R_2 = Ar, Alk$

## 9. Summary

The different synthetic methods discussed in this review showed that *m*CPBA is a versatile reagent used in organic synthesis. *m*CPBA is a cheap commercially available oxidant that easily oxidizes numerous functional groups. It is an efficient single oxygen atom donor since it contains a non-symmetrical O–O bond which is heterolytically cleaved during the oxidation cycle. A tactical utilization of *m*-CPBA in synthetic plans is that it may replace tedious organic transformations with simpler routes. One drawback of *m*-CPBA is that this oxidizing regant only epoxidize electron-rich olefins and allylic or homoallylic alcohols and also *m*-CPBA also require a directing group. One other drawback which needs to be mentioned is that a relatively large excess of *m*-CPBA may be required in some reactions to consume all of the starting material. It is interesting to note that militating against this is that *m*-CPBA can be reused when it is in stoichiometric excess. Owing to the discovery of a variety of novel applications, *m*-CPBA is becoming an increasingly important reagent in synthetic organic chemistry. We hope that this review may act as a catalyst in boosting the applications of *m*-CPBA in organic synthesis.

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# *meta*-Chloroperbenzoic acid (*m*-CPBA): A Versatile Reagent in Organic Synthesis

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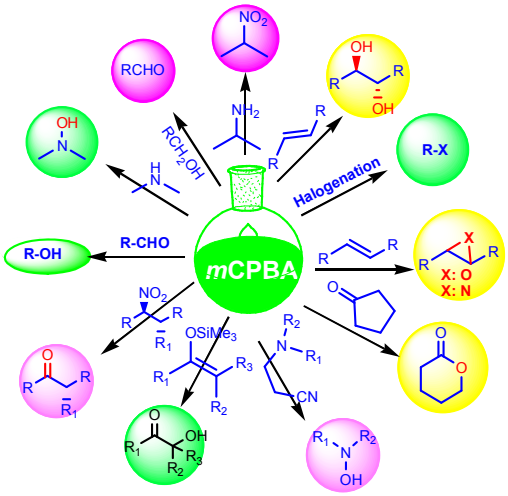

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