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Methods for selective benzylic C – H oxofunctionalization of organic compounds

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The development of methods for the selective oxidation of C – H groups of organic compounds resulting in C – O bond formation is a challenging problem in modern synthetic organic chemistry. Versatile methods for the oxofunctionalization of these groups are currently lacking. Approaches for the oxidation of benzylic C – H groups having a relatively weak C – H bond (the homolytic bond dissociation energy is ~80 – 90 kcal mol^{-1}) differ from the methods used for the oxidation of aliphatic and aromatic C – H groups with stronger C – H bonds. The review summarizes homogeneous catalytic and non-catalytic methods for the selective oxofunctionalization of benzylic groups of organic compounds developed in the past 40 years. Reactions using various oxidizing agents in the presence or in the absence of transition metal compounds are considered. Putative mechanisms of selected transformations are discussed. Particular focus is placed on the selective oxidation of various substrates.
The bibliography includes 278 references.

Contents

1. Introduction 587
2. Oxidation of substrates containing benzylic CH_2 groups to carbonyl compounds 588
2.1. Transition metal-free oxidation 588
2.1.1. Reactions using different oxidants 588
2.1.2. Reactions involving molecular oxygen 593
2.1.3. Electrochemical oxidation 595
2.2. Transition metal-promoted oxidation 597
2.2.1. Oxidation in the presence of iron complexes 598
2.2.2. Oxidation in the presence of manganese complexes 601
2.2.3. Oxidation in the presence of cobalt compounds 605
2.2.4. Oxidation in the presence of copper compounds 607
2.2.5. Oxidation in the presence of ruthenium compounds 608
2.2.6. Oxidation in the presence of rhodium compounds 610
2.2.7. Oxidation in the presence of other metal compounds 610
2.2.8. Transition metal-promoted oxidation by oxygen 612
2.3. Photocatalytic oxidation 614
3. Oxidation of arylalkanes to benzylic alcohols 617
3.1. Transition metal-free hydroxylation of arylalkanes 617
3.2. Benzylic hydroxylation in the presence of transition metal complexes 617
3.2.1. Benzylic hydroxylation in the presence of iron complexes 618
3.2.2. Benzylic hydroxylation in the presence of manganese complexes 619
3.2.3. Benzylic hydroxylation in the presence of ruthenium complexes 623
4. Conclusion 624

1. Introduction

Oxidation processes, including the oxidation of various C – H groups of organic molecules, occur in living systems utilizing haem and non-haem metalloenzymes oxygenases as catalysts under mild conditions. The development of synthetic methods for the selective C – H oxidation is a challenge mainly because of very low reactivity of C – H groups, which show neither basic nor acidic properties and are generally unreactive towards both nucleophilic and electrophilic reagents. The oxofunctionalization accompanied by the homolytic cleavage of strong C – H bonds (the bond dissociation energy D_{CH} = 80 – 110 kcal mol^{-1}) requires highly reactive reactants, the use of which often impairs the selectivity of the overall process. These transformations have attracted great attention and can be identified as a

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high-priority research area of synthetic organic chemistry. Thus, in 2017 Clarivate Analytics has put forward John Bercaw, Robert Bergman and Georgiy Shul'pin as Nobel nominees for the chemistry prize for 'critical contributions to C – H functionalization'.[1]

Most of the available methods for the selective oxidative C – H functionalization are based on the use of transition metal compounds (generally complexes) as catalysts. Metals play a dual role in these processes. On the one hand, the metal should assist the activation of the oxidant to form a catalytically active centre and, on the other hand, it should ensure the regioselective activation of a C – H bond to form the target product containing a new C – O bond. In this respect, the role of metal complexes is similar to that of metalloenzymes catalyzing the C – H oxidation in the living nature. Therefore, significant recent progress in the development of methods for the catalytic C – H oxidation of organic compounds is related to a wide application of the biomimetic approach, which utilizes synthetic metal complexes to mimic the catalytic activity of the natural metalloenzymes oxygenases.

Synthesis methods for the selective oxidation of benzylic groups have specific features regarding lability of the corresponding C – H bonds due to stabilization of transition states *via* conjugation with the aromatic π-system. This generally facilitates the rate-limiting cleavage of the C – H bond. Considerable research on this issue has been done, and high selectivity was achieved in these processes. The present review addresses catalyst-free and homogeneous catalytic methods for the liquid-phase benzylic C – H oxofunctionalization of organic compounds developed over the past four decades. The main trends in the elaboration of heterogeneous benzylic C – H oxidation reactions include the oxidation using transition metal oxides,[2–4] zeolites,[5–7] metal-organic frameworks (MOF),[8,9] solid-supported porphyrin, salen and bis(amino)bis(pyridine) transition metal complexes and so on.[10–12] Approaches to the development of enzyme-catalyzed benzylic C – H hydroxylation reactions have their specific issues and are beyond the scope of the review. They are considered in a number of original publications and literature reviews.[13–27]

The following abbreviations are used in the review:
acac — acetylacetonate,
AIBN — 2,2′-azobis(isobutyronitrile),
BFBF — benzofurobenzofuran,
[bmim]Br — 1-n-butyl-3-methylimidazolium bromide,
Boc — *tert*-butoxycarbonyl,
bpy — 2,2′-bipyridine,
CAN — cerium(IV) ammonium nitrate,
DBDOC — methanodibenzodioxocine,
DDQ — 2,3-dichloro-5,6-dicyano-1,4-benzoquinone,
DFT — density functional theory,
ee — enantiomeric excess,
EHA — 2-ethylhexanoic acid,
er — enantiomeric ratio,
IBA — 2-iodosobenzoic acid,
IBX — 2-iodoxybenzoic acid,
IPr — 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene,
LED — light-emitting diode,
mCPBA — *meta*-chloroperoxybenzoic acid,
MMO — methane monooxygenase,
MW — microwave irradiation,
NBS — *N*-bromosuccinimide,
NHC — *N*-heterocyclic carbene,
NHPI — *N*-hydroxyphthalimide,
opba — *o*-phenylenebis(oxamate),
PCC — pyridinium chlorochromate,
PINO — phthalimide *N*-oxyl radical,
Py — pyridyl,
rt — room temperature,
TBAB — tetra-n-butylammonium bromide,
TBHP — *tert*-butyl hydroperoxide,
TBS — *tert*-butyldimethylsilyl,
TEA — triethanolamine,
TEMPO — 2,2,6,6-tetramethylpiperidine-1-oxyl,
TFE — 2,2,2-trifluoroethanol,
TFDO — methyl(trifluoromethyl)dioxirane,
TFP — 1,1,1-trifluoropropanone,
Tf — trifluoromethanesulfonyl (triflyl),
tmtacn — 1,4,7-trimethyl-1,4,7-triazacyclonane,
TON — turnover number (moles of the substrate converted per mole of the catalyst),
TPP — tetraphenylporphyrin.

2. Oxidation of substrates containing benzylic CH_2 groups to carbonyl compounds

Methods for the selective benzylic C – H oxofunctionalization can be divided into the following groups: transformations, which occur in the absence of transition metals; processes using transition metal compounds; photocatalytic methods. These reactions can be accomplished using such oxidizing agents as organic peroxides, the triple salt $2\,KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$ (oxone), potassium bromate, hypervalent iodine compounds, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and selenium dioxide (SeO_2), as well as green oxidants such as hydrogen peroxide, molecular oxygen, *etc*. Generally, the transition metal-free oxidation proceeds *via* a free-radical mechanism, which impairs the selectivity of these processes. Sections 2.1 – 2.3 deal with methods for the selective benzylic C – H oxofunctionalization of organic compounds to carbonyl derivatives.

2.1. Transition metal-free oxidation

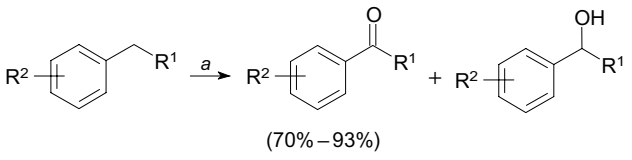
2.1.1. Reactions using different oxidants

The simplest and facile method for the synthesis of aryl ketones is based on the non-catalytic oxidation of substituted alkylbenzenes with organic hydroperoxides, *e.g.*, *tert*-butyl hydroperoxide (TBHP), at high temperatures (Scheme 1).[28] The reactions with simple substrates bearing

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Current research interests: stereoselective transition metal-promoted oxidation catalysis, mechanisms of homogeneous catalytic oxidation reactions.

Translation: T.N.Safonova

Scheme 1

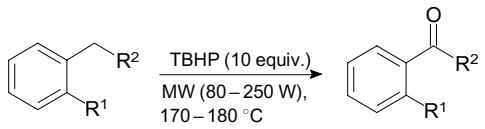


(*a*) TBHP (12 equiv.), hexane, 130 °C;
R^1 = Alk, Ar; R^2 = Alk, Hal, OAlk, *etc.*

alkyl or aryl substituents give ketones in relatively high yields. A significant drawback of this method is that it requires a large excess of an oxidant. Besides, since the oxidation follows a free-radical mechanism, it is of limited use for the oxidation of complex substrates.

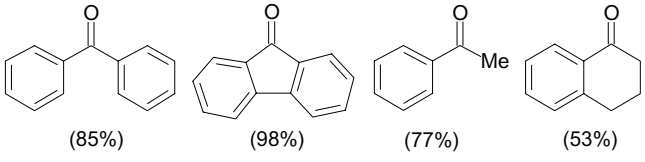
The microwave-assisted organic synthesis is a rapidly emerging area of organic chemistry.[29, 30] Homogeneous heating of the reaction mixture by microwave irradiation leads to a significant decrease in the reaction time and an increase in the selectivity of the reaction and also facilitates an increase in the product yield. Some transformations that are not possible with conventional heating techniques can be accomplished under these conditions. In 2009, Lee and co-workers[31] performed the oxidation of arylalkanes with TBHP (70% aqueous solution) under microwave irradiation (MW) in the absence of an organic solvent (Scheme 2). This procedure afforded ketones in moderate to high yields. The structures of these ketones are shown in Scheme 2. However, the scope of this method is limited to a narrow range of structurally simple substrates.

Scheme 2



$R^2 \neq H$

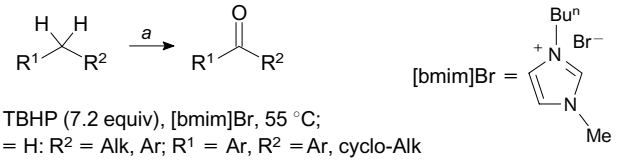
Examples of products



Ionic liquids are widely used as green solvents. Their advantages are non-toxicity, low vapour pressure, non-flammability, high polarity, good dissolution properties, the ease of separation from the reaction mixture and recyclability.[32, 33] Hence, ionic liquids are considered as promising media for oxidation. In 2016, a method was developed for the oxidation of compounds containing a benzylic CH_2 group with TBHP in 1-n-butyl-3-methylimidazolium bromide ([bmim]Br) as the ionic liquid. These conditions made it possible to reduce the reaction temperature to 55 °C and decrease the excess of the oxidant to 7.2 equiv. (Scheme 3).[34] The corresponding ketones were prepared in 58% – 98% yields.

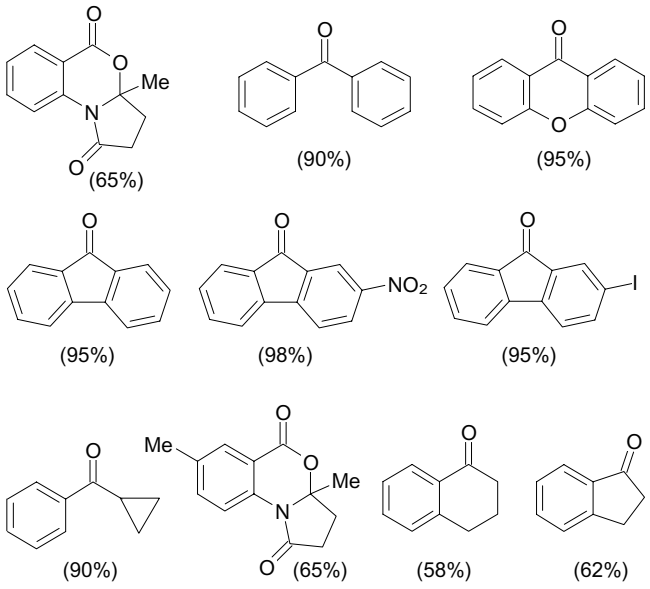
Peroxycarboxylic acids can oxidize certain arylalkanes to carbonyl derivatives. In 1999, Tian and co-workers,[35] in attempting to transform ketone **1** into ester **2** *via* the Baeyer – Villiger oxidation with *m*-chloroperoxybenzoic

Scheme 3



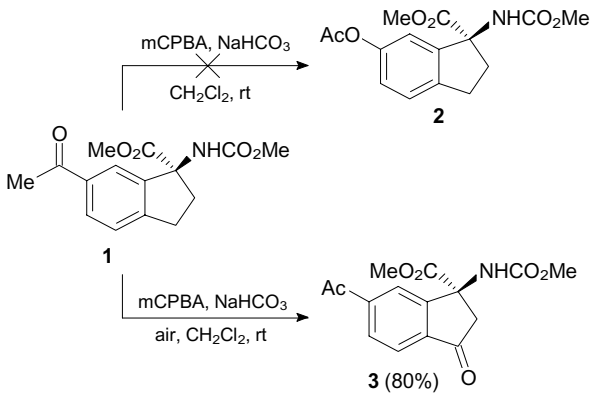
(*a*) TBHP (7.2 equiv), [bmim]Br, 55 °C;
R^1 = H: R^2 = Alk, Ar; R^1 = Ar, R^2 = Ar, cyclo-Alk

Examples of products



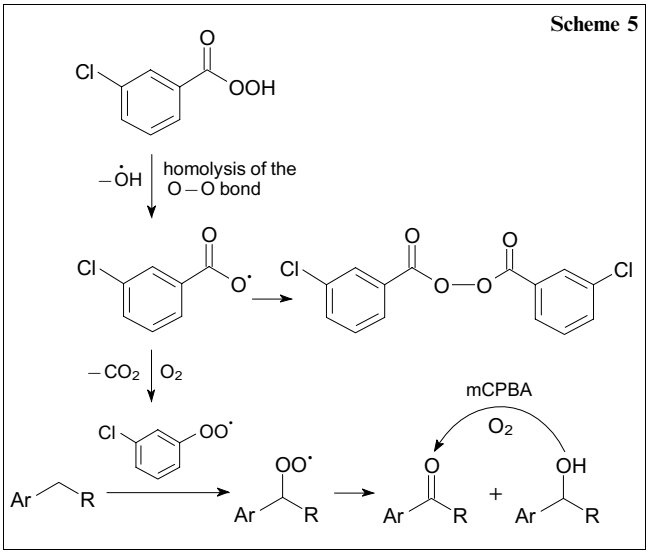
acid (mCPBA), obtained diketone **3** as the major product (Scheme 4). The formation of the latter compound was attributed to the ability of mCPBA to oxidize the benzylic methylene moiety to the carbonyl group in the presence of atmospheric oxygen.

Scheme 4



This method can be applied to oxidize simple arylalkanes and arylcycloalkanes to the corresponding ketones in good yields (67% – 88%). Under these conditions, 3-ethylpyridine and 2-ethylnitrobenzene are stable to the oxidation, which is evidence that the reaction is sensitive to the presence of electron-withdrawing substituents in the substrate. The reaction did not occur under an inert gas atmosphere. Based on this fact and other evidence, a free-radical mechanism was proposed for this reaction (Scheme 5). Molecular oxygen plays a key role in this

Scheme 5

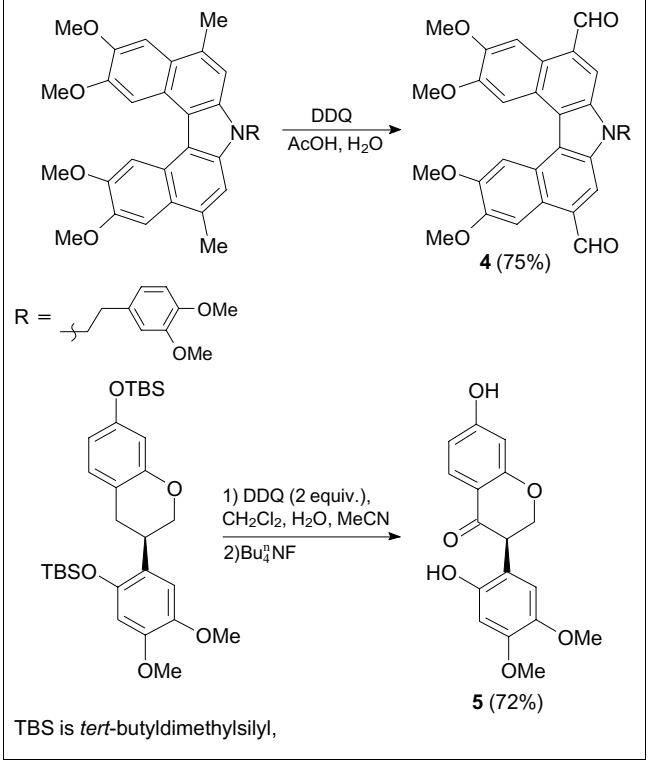


process as it is required for the formation of the arylperoxy radical and subsequent transformation of the alcohol to ketone.

2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) is commonly employed in organic synthesis as a mild oxidant.[36] Lee and Harvey [37, 38] demonstrated that this reagent can be utilized to prepare aryl ketones and aldehydes from appropriate polyaromatic arylalkanes. More recently, DDQ was successfully used to oxidize the benzylic methylene group in total syntheses of natural products, for example, of compound **4** serving as a precursor of the alkaloid ningalin D (Ref. 9) and of isoflavanone **5** isolated from the plant *Dalbergia oliveri* (Scheme 6).[40]

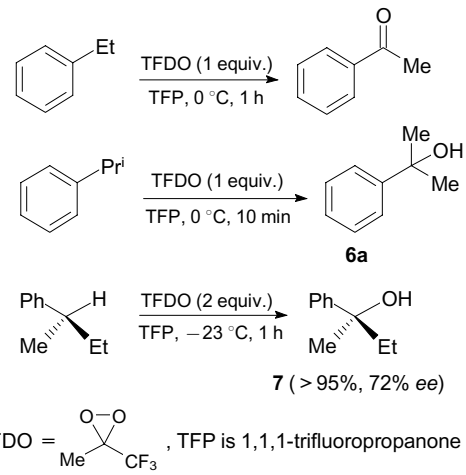
Dimethyldioxirane and its fluorinated analogue, methyl(trifluoromethyl)dioxirane (TFDO), can also be used to oxidize the C–H bond in various hydrocarbons.[41] For

Scheme 6



TBS is *tert*-butyldimethylsilyl,

Scheme 7

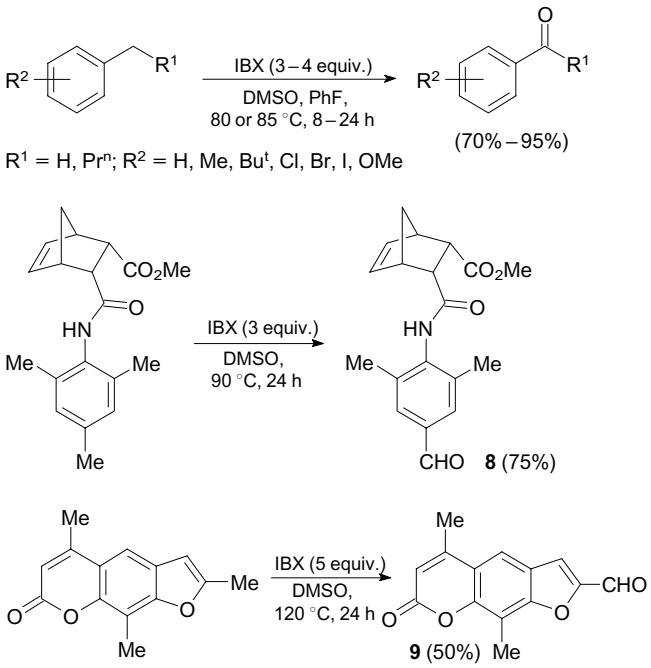


instance, ethylbenzene and cumene were oxidized to acetophenone and cumyl alcohol (**6a**), respectively (Scheme 7); however, the conversion of the substrates was low (10% and 14%).[42] Compounds containing the tertiary C–H group form products in higher yields. It is worth noting that the oxidation of optically pure (*R*)-2-phenylbutane with TFDO in 1,1,1-trifluoropropanone proceeds with partial retention of configuration to give alcohol **7** in high yield with high enantiomeric excess (*ee*). Adam *et al.*[43] suggested that the reaction proceeds through the direct insertion of an oxygen atom into the C–H bond.

Hypervalent iodine compounds can serve as oxidizing agents in the synthesis of aryl ketones. Nicolaou *et al.*[44] used 2-iodoxybenzoic acid (IBX) to oxidize a methyl or methylene group to prepare carbonyl compounds in DMSO on heating (Scheme 8).

The authors demonstrated that one of the two methyl groups can be selectively subjected to oxidation (see Scheme 8, the synthesis of aldehydes **8** and **9**) and predicted the direction of the oxidation based on the proposed

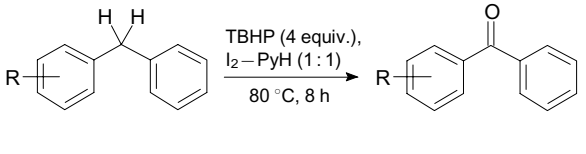
Scheme 8



mechanism through a single-electron transfer from the substrate to IBX. Apart from IBX, the benzylic oxofunctionalization of arylalkanes was performed using NH_4IO_3 – *N*-hydroxyphthalimide,[45] $NaIO_4 - H^+ - LiBr$,[46] $PhI(OAc)_2$ – mCPBA – TBHP,[47] $PhI(OAc)_2 - NaN_3$,[48] PhIO – KBr – Montmorillonite K10 mixtures,[49] as well as catalytic systems, which generate hypervalent iodine intermediates and contain oxone as the oxidant: 2-iodobenzoic acid – oxone,[50] sodium 2-iodobenzenesulfonate – $Bu^n_4NHSO_4$ – oxone[51] and PhI (0.1 equiv.) – KBr (0.3 equiv.) – oxone.[52]

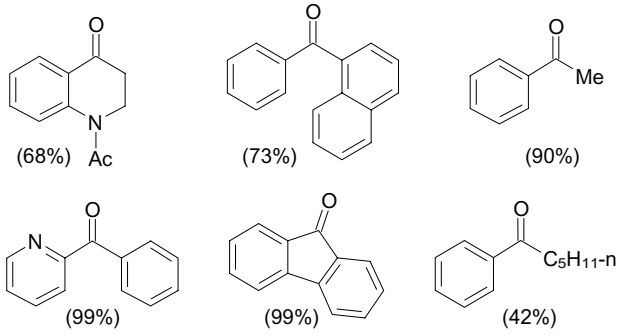
In 2009, a simple I_2 – pyridine – TBHP catalytic system was proposed for the oxidation of the benzylic methylene group of various diarylmethanes to form carbonyl derivatives (Scheme 9).[53] Apart from monosubstituted benzophenones, this catalytic system was used to synthesize other ketones shown in Scheme 9 and to prepare nitriles from primary amides. Advantages of this method are relatively mild conditions and the absence of organic solvents and transition metals.

Scheme 9



R = H (95%), 4-F (94%), 4-Cl (99%), 4-Br (97%), 4-Ph (94%), 4-NO_2 (99%), 4-Me (82%), 4-OAc (86%), 4-OMe (77%), 3-Cl (97%), 2-Cl (93%); PyH is pyridine

Examples of products



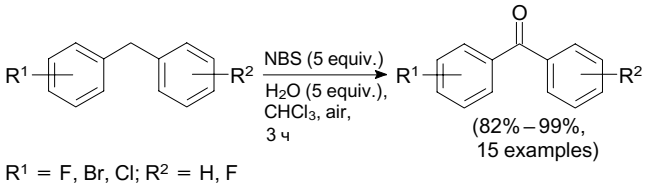
Zhang *et al.*[53] explored the mechanism of oxidation. The substrate was not oxidized in the presence of hydroquinone or benzoquinone. Peroxide intermediate **10** was isolated. It was transformed into benzophenone on heating with TBHP. The oxidation of triphenylmethane afforded peroxide in 49% yield. Diphenylmethanol was not oxidized under these conditions and was not detected as an oxidation product of diphenylmethane. Based on these data, the authors proposed the reaction mechanism shown in Scheme 10.

Khan *et al.*[54] utilized hydrogen peroxide (5 equiv., 30% aqueous solution) and HBr (0.9 equiv., 48% aqueous solution) for the benzylic oxidation of alkyl- and cycloalkylarenes in dichloromethane. An assumption behind this approach was that α-bromo-substituted alkylarenes, generated *via* free-radical halogenation, can be slowly hydrolyzed to the corresponding benzylic alcohols followed by their oxidation to carbonyl compounds. Therefore, acetophenone can be synthesized in 75% yield from ethylbenzene. However, the applicability of this approach is limited due to incomplete hydrolysis of α-bromoalkylarenes and the fact that the reactions with many substrates are accompanied by aromatic bromination as a side process.

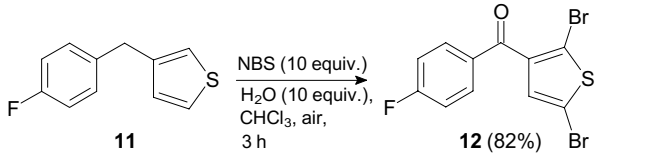
A conceptually similar method was proposed by Xiong and co-workers.[55] This method is based on the treatment of the substrate with an excess of *N*-bromosuccinimide (NBS) in the presence of H_2O in refluxing chloroform (Scheme 11). Substituted benzophenones generated *via* the benzylic oxidation were obtained in 82% – 99% yields. The reactions with substrates containing a thiophene ring (*e.g.*, compound **11**) involve, apart from the transformation of the methylene group to the carbonyl one, the dibromination of the thiophene moiety at the α-position to form product **12**. Isotope-labelling experiments using $H_2{}^{18}O$ and catalytic experiments under an inert atmosphere and in the presence of radical traps confirmed the assumption that ketone **12** is generated through the free-radical dibromination at the benzylic position followed by hydrolysis.

In 2012, Cao and co-workers[56] reported a method for the oxidation of the benzylic methylene group with oxone in

Scheme 11

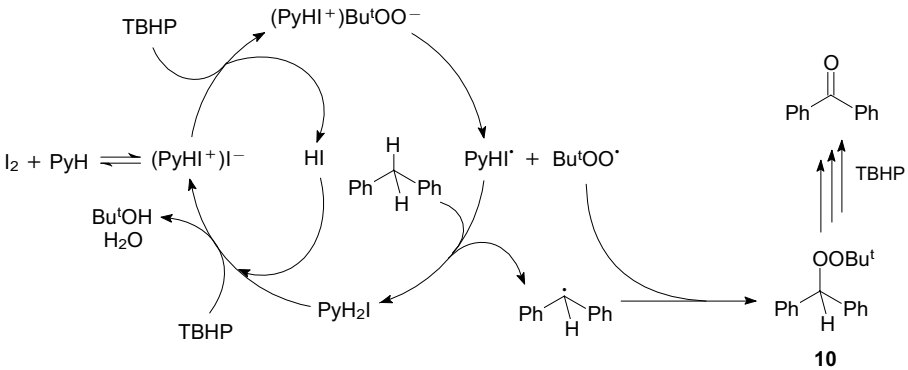


R^1 = F, Br, Cl; R^2 = H, F



11 **12** (82%)

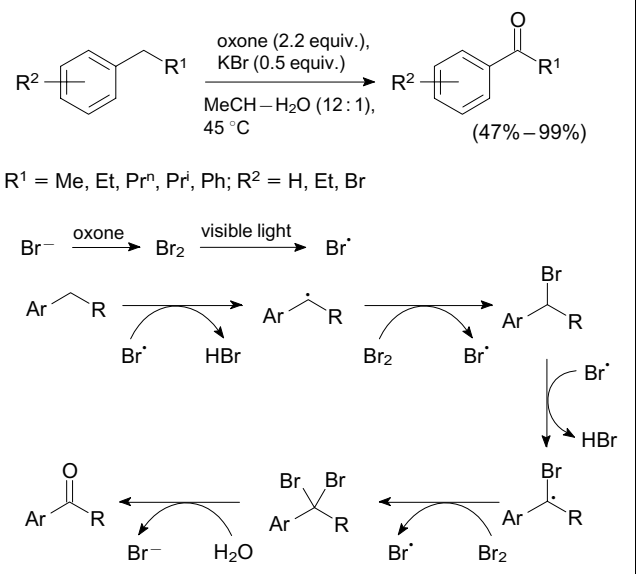
Scheme 10



10

the presence of KBr and H_2O in acetonitrile. This method can be applied to prepare various aryl ketones in high yields (Scheme 12). However, the oxidation of toluene and (4-ethyl)nitrobenzene affords bromination products instead of the corresponding carbonyl compounds.

Scheme 12



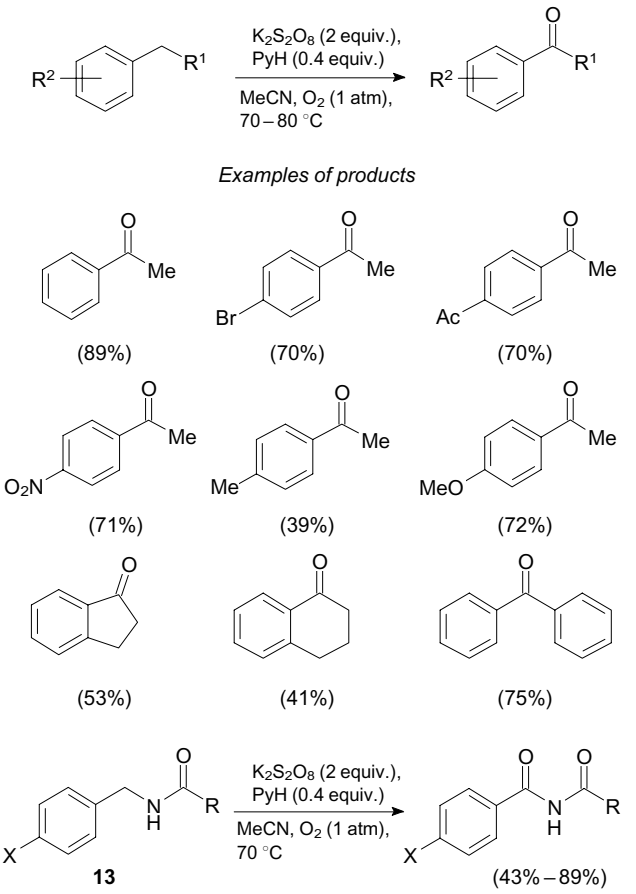
The oxidation was demonstrated to require the presence of KBr and water and exposure to visible light. A free-radical mechanism of the process (see Scheme 12) was proposed based on the results of catalytic experiments in the presence of isotope-labelled water ($H_2{}^{18}O$). Similar reaction conditions were described by Togo and co-workers.[57]

Apart from oxone, the oxidative C – H functionalization of arylalkanes was accomplished using other inorganic compounds as oxidants. Thus, commercially available sodium chlorite ($NaClO_2$) was used to oxidize allylic and benzylic substrates to carbonyl compounds in the presence of TBHP or catalytic amounts of *N*-hydroxyphthalimide (NHPI).[58] Advantages of this approach are operational simplicity and the use of available reagents. However, its applicability is limited to the oxidation of a narrow range of diarylmethanes and arylcycloalkanes.

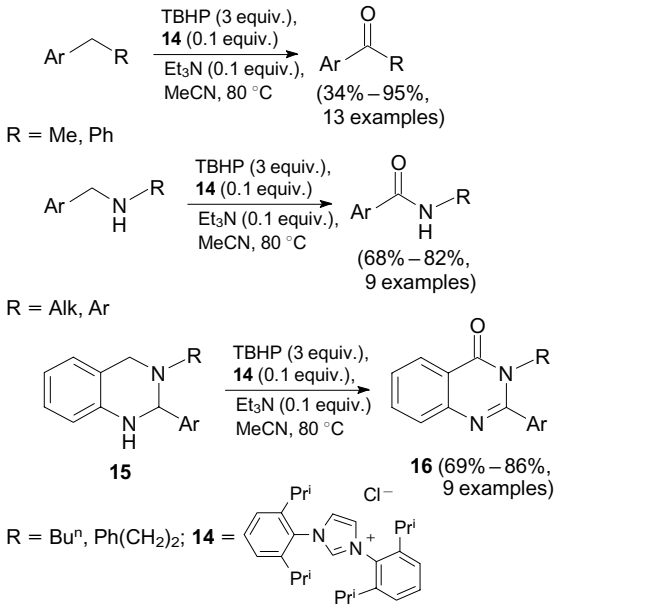
In 2017, Hu *et al.*[59] demonstrated that potassium persulfate can also be used for the benzylic C – H oxidation of various alkylarenes and *N*-benzylamides **13** (Scheme 13) under aerobic conditions in the presence of pyridine acting as a phase-transfer catalyst. The proposed mechanism involves the persulfate-promoted generation of a benzylic radical from the substrate followed by the formation of hydroperoxide and subsequent decomposition of the latter to form the corresponding carbonlyl compound.

N-Heterocyclic carbenes (NHC) can catalyze benzylic C – H oxidation reactions under transition metal-free conditions. In 2016, Maheswari and co-workers[60] demonstrated that NHC-carbenes, generated *in situ* from imidazolium salts in the presence of triethylamine, catalyze the oxidation of arylalkanes and *N*-benzylamines with TBHP in acetonitrile at 80 °C (Scheme 14). The authors examined a series of compounds as precatalysts and found that 1,3-bis(2,6-diisopropylphenyl)-1*H*-imidazolium chloride (**14**) is the most active one in this series. Under similar

Scheme 13



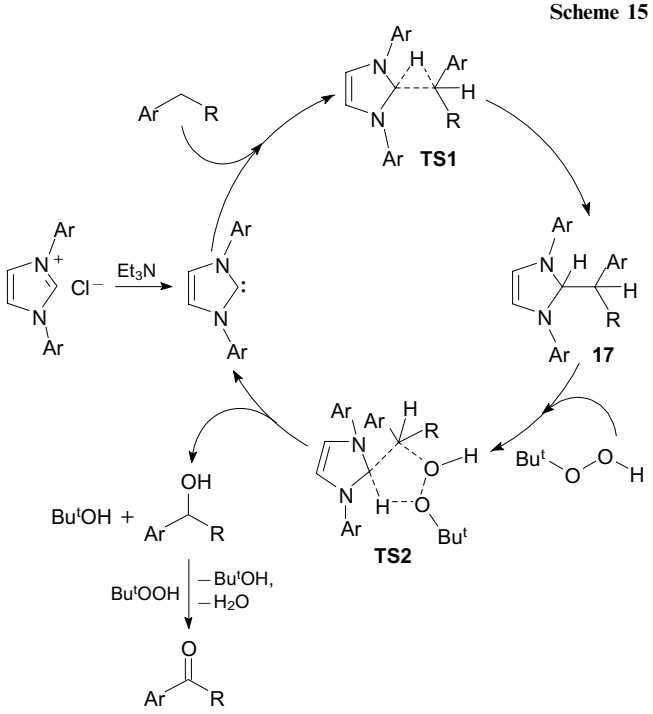
Scheme 14



conditions, 3-alkyl-1,2,3,4-tetrahydroquinazolines **15** can be transformed into 2,3-disubstituted 3*H*-quinazolin-4-ones **16** possessing pharmacological activity in good yields.

The plausible mechanism for the oxidation is consistent with the results of quantum chemical calculations [the

Scheme 15



density functional theory (DFT), M06-2X/6-31G(d,p) level] and is presented in Scheme 15. In the first step, free carbene is generated from the imidazolium salt in the presence of a base followed by C – H activation of the benzylic position of the substrate through the transition state **TS1** to form intermediate **17**. The subsequent reaction with TBHP occurs through the transition state **TS2** and is accompanied by the release of carbene and the formation of secondary alcohol, which is oxidized with TBHP to form a carbonyl product.

2.1.2. Reactions involving molecular oxygen

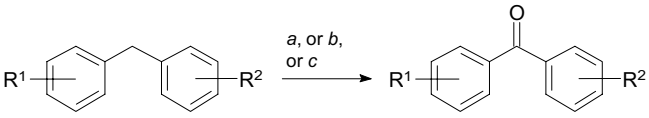
Molecular oxygen is considered as a promising oxidizing agent in selective benzylic oxidation reactions as it can be obtained at virtually no cost, has a high active oxygen content (50 mass %) and generates water as an oxidation by-product.

The available methods for the oxidation of C – H groups by molecular oxygen under transition metal-free conditions can be divided into several groups. One group includes methods using *N*-hydroxyphthalimide or related compounds (Scheme 16). Quite a few methods utilize various promoters of oxidation, which generate the reactive oxidation species PINO (phthalimide-*N*-oxyl radical). Mention should also be made of the employment of different quinones,[61 – 63] methyl violet,[64] 2,2′-azobis(isobutyronitrile) (AIBN)[65] and acetaldehyde.[66, 67] Another group includes photocatalytic oxidation methods using light-sensitive compounds.[68 – 72] These approaches are attractive due to operational simplicity, high product yields, the ease of scale-up, high atom economy, *etc*. However, their applicability is limited to simple substrates because of low regioselectivity associated with the free-radical character of oxidation. In a number of methods, bases serve as catalysts. Examples of the oxidation by molecular oxygen in the absence of NHPI are presented below. These transformations are considered in detail in the review,[73] which summarizes methods for the benzylic and allylic oxidation under metal-free conditions published up to 2014.

Diarylmethanes with different substituents can be oxidized by molecular oxygen in the presence of bases.[74 – 77] For example, sodium *tert*-butoxide in DMSO promotes aerobic oxidation of the benzylic methylene group to the carbonyl one (Scheme 17, conditions *a*).[75] Lithium bis(trimethylsilyl)amide in THF can act as the base (conditions *b*), and dipyridylmethanes can serve as substrates.[76] In this case, the autoxidation can proceed by a radical-anion mechanism (Scheme 18).

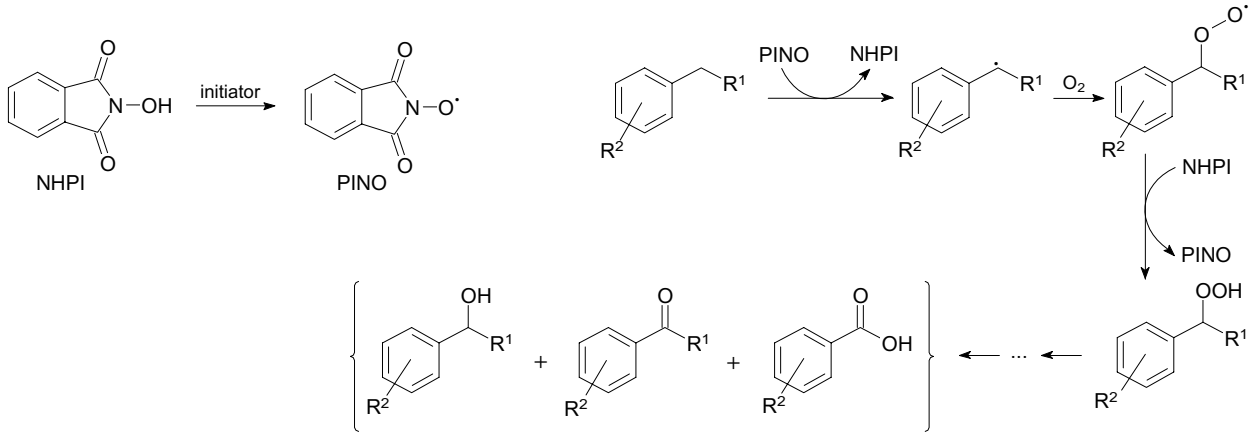
A similar method for the oxidation of diarylmethanes was proposed by Xu and co-workers.[77] The authors used 1 equiv. of potassium *tert*-butoxide in the presence of 1 equiv. of 18-crown-6 ether (18-crown-6) in DMF at room temperature or on slight heating (conditions *c* in Scheme 17). Based on the results of kinetic studies, the authors proposed two possible reaction pathways: a radical

Scheme 17

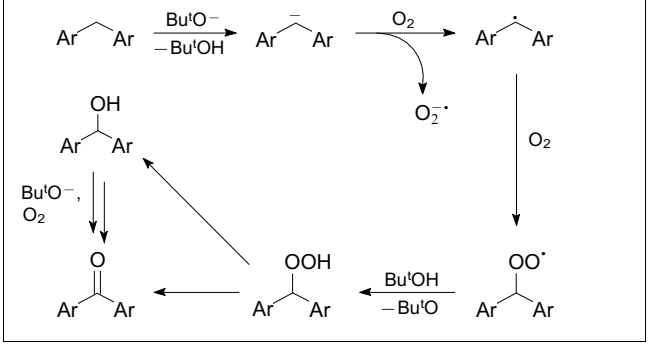


(*a*) O_2 (1 atm), ButONa (2 equiv.), DMSO, 50 °C (80% – 98% yields, 22 examples); (*b*) O_2 (1 atm), $LiN(SiMe_3)_2$ (1.5 equiv.), THF, 60 °C (79% – 91% yields, 14 examples); (*c*) O_2 (1 atm), ButOK (1 equiv.), 18-crown-6 (1 equiv.), DMF, rt (70% – 96% yields, 19 examples); R^1, R^2 = H, Me, OMe, Hal, *etc*.

Scheme 16



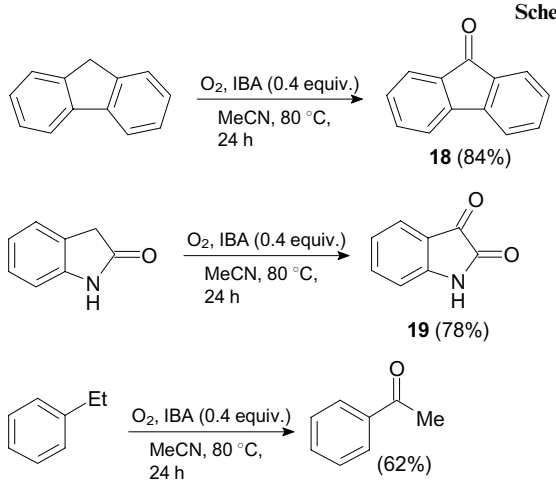
Scheme 18



pathway (involving a radical intermediate generated from DMF) and an ionic pathway (similar to that shown in Scheme 18).

2-Iodosobenzoic acid (IBA) can serve as the catalyst for the aerobic oxidation of the methylene group to the carbonyl one.[78] For example, fluorenone (**18**) was synthesized from fluorene; isatin (**19**), from 2-oxindole; acetophenone, from ethylbenzene (Scheme 19).

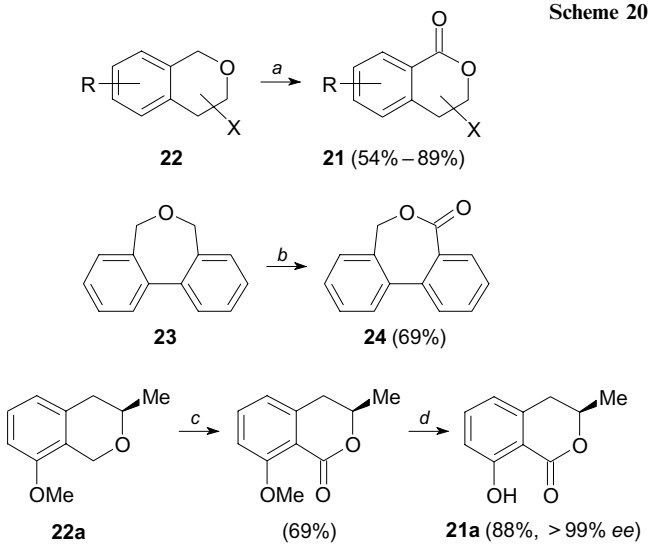
Scheme 19

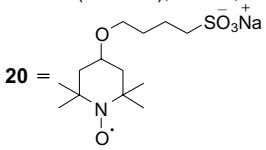


Shen and co-workers[79] reported a method for the oxidation of diarylalkanes in the presence of catalytic amounts of DDQ and *tert*-butyl nitrite in 1,1,2,2-tetrachloroethane on heating. The yields of diaryl ketone varied from 65% (for substrates containing electron-withdrawing substituents on the aromatic ring) to 99%. More recently, Brasholz and co-workers[80] accomplished a photochemical version of this reaction under much milder conditions. The authors used acetonitrile instead of 1,1,2,2-tetrachloroethane and atmospheric air (1 atm) instead of oxygen (0.3 – 0.5 MPa) and performed the reaction at room temperature. However, good outcome was achieved only in the oxidation of diarylmethanes, while a sharp decrease in selectivity was observed in the case of alkylarenes. Thus, the oxidation of ethylbenzene affords alcohol and ketone in a ratio of 1 : 1 in a total yield of 64% with a substrate conversion of 100%.

Wang and co-workers[81] oxidized the methylene group of cyclic benzyl ethers by molecular oxygen in the presence of the 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) derivative (compound **20**) as the catalyst (Scheme 20). Isochromanones **21** were obtained in 73% – 89% yields in the reactions with substrates **22**, which do not contain elec-

Scheme 20



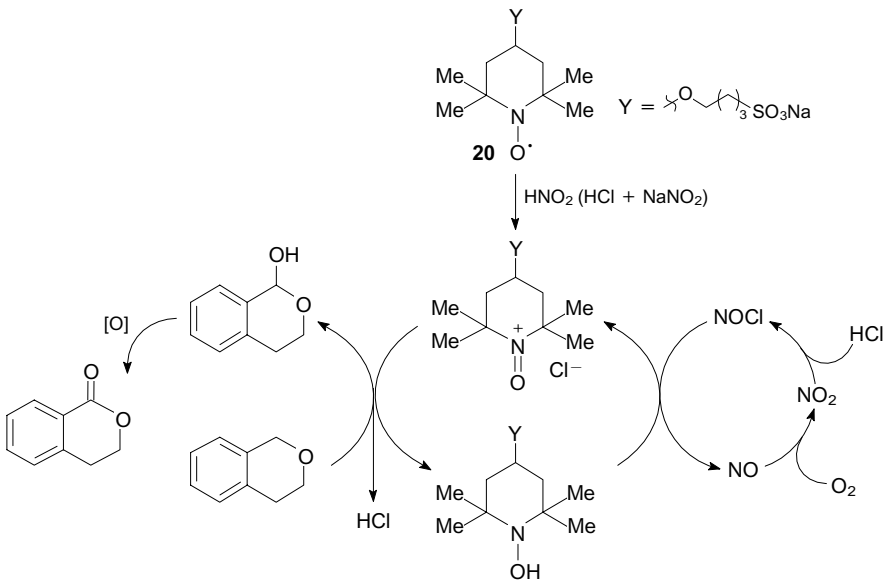
(*a*) O_2 (1 atm), **20** (0.5 mol.%), HCl (aq., 10 mol.%), $NaNO_2$ (4 mol.%), MeCN, 35 °C; (*b*) O_2 (1 atm), **20** (2 mol.%), HCl (aq., 10 mol.%), $NaNO_2$ (4 mol.%), MeCN, 35 °C, 10 h; (*c*) O_2 (1 atm), **20** (0.5 mol.%), HCl (aq., 10 mol.%), $NaNO_2$ (4 mol.%), MeCN, 35 °C, 10 h; (*d*) BBr_3, CH_2Cl_2, −78 °C; **20** =  **21**, **22**: X = 3-Me, 4-Me; R = 5-Me, 7-Me, 7-F, 7-Bu^t, 7-OMe

tron-withdrawing substituents on the aromatic ring (the presence of such substituents leads to a decrease in the yield of oxidation products). The catalyst is quite stable. It can be recovered from the mixture after the completion of the reaction by water extraction and reused. The applicability of this method in organic synthesis was demonstrated by several examples. For instance, the reaction with ether **23** gave 7*H*-dibenzo[*c*,*e*]oxepin-5-one (**24**), which is an important precursor in the synthesis of polymer materials; (*S*)-mellein (**21a**) possessing antibacterial and antifungal activity was synthesized from compound **22a** in two steps. The proposed mechanism for the oxidation is presented in Scheme 21 (for X = R = H).

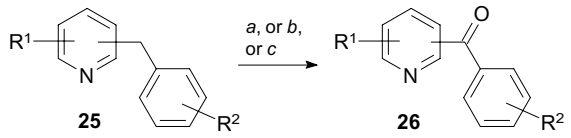
In recent years, significant progress was achieved in the development of methods for the C – H oxidation of the methylene group in *N*-heterocyclic compounds by molecular oxygen. In 2015, a method was proposed for the aerobic oxidation in the presence of catalytic amounts of NH_4I and AcOH (Scheme 22, conditions *a*).[82] Acetic acid promotes the reaction through the formation of pyridinium salt from the starting substrate. In the course of the reaction, ammonium iodide is apparently oxidized by oxygen to form molecular iodine, which serves as a source of radicals that can promote homolytic cleavage of the benzylic C – H bond in the pyridinium salt. Experiments using the $I_2 - AcONH_4$ mixture instead of $NH_4I - AcOH$ gave products in similar yields and with a similar selectivity of oxidation.

Law's research group tested organic derivatives of selenium as catalysts for the aerobic oxidation.[83] They found that phenylselenyl bromide in the presence of acetic acid efficiently catalyzes the C – H oxidation of the methylene group of benzylpyridines **25** (see Scheme 22, conditions *b*). The method was examined using several

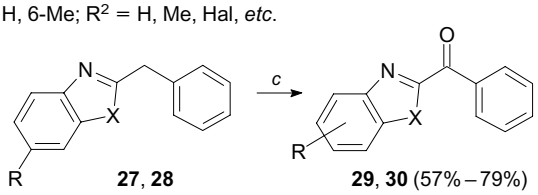
Scheme 21



Scheme 22



R^1 = H, 6-Me; R^2 = H, Me, Hal, *etc.*



R = H, 6-Cl; (*a*) O_2 (1 atm), NH_4I (0.5 mol.%), AcOH (10 mol.%), 100 °C, 24 h (61% – 97% yields); (*b*) O_2 (1 atm), AcOH (1 equiv.), PhSeBr (5 mol.%), DMSO – H_2O (1 : 1), 100 °C, 22 h (58% – 97% yields); (*c*) O_2 (1 atm), DMSO, 130 °C, 48 h; X = S (**27**, **29**), NH (**28**, **30**)

substrates; ketones **26** were obtained in moderate to high yields.

In the above-described oxidation reactions of hetarylalkanes, the efficient formation of benzylic radicals was achieved in the presence of an activator, which reacted with a heterocyclic moiety of the substrate (*e.g.*, Brønsted acids that react with the substrate to form pyridinium salts). Guha and Sekar [84] suggested that the oxidation of benzylpyridines with NBS (20 mol.%) in DMSO at 120 °C is promoted by halogen bonding between pyridine and NBS, *i.e.*, the latter acts as the activator. This assumption is consistent with the results of catalytic experiments, spectroscopic measurements and DFT calculations. Carbonyl products were obtained in 57% – 95% yields.

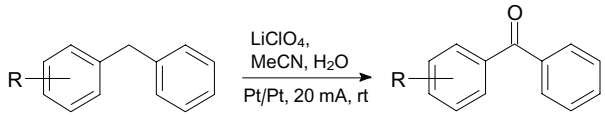
In 2018, Liu and co-workers [85] demonstrated that benzylpyridines **25** can be oxidized to the corresponding diaryl ketones (58% – 95% yields) by molecular oxygen in DMSO at 130 °C in the absence of additives (see Scheme 22, conditions *c*). This method proved to be applicable to the oxidation of benzothiazoles **27** and benzimidazoles **28** giving *N*-heterocyclic ketones **29** and **30** in good yields (see Scheme 22).

It should be noted that most of the methods for the benzylic C – H oxidation by molecular oxygen under transition metal-free conditions are efficient only with diarylmethanes, whereas the oxidation of alkylarenes does not occur or is characterized by low conversion and selectivity values.

2.1.3. Electrochemical oxidation

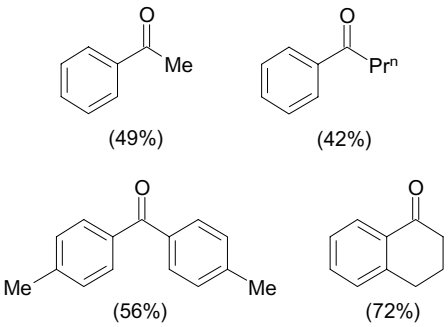
In recent years, electrochemical methods have been extensively developed and are considered as a good alternative to the conventional C – H bond activation using oxidizing agents and to photoredox catalytic methods.[86] In 2013, Wang and co-workers [87] proposed a method for the oxidation of diarylmethanes in the MeCN – H_2O mixture (Pt electrodes, $LiClO_4$ as an electrolyte) giving the corresponding ketones in good yields (Scheme 23). Ketones presented in Scheme 22 were prepared under similar conditions.

Scheme 23

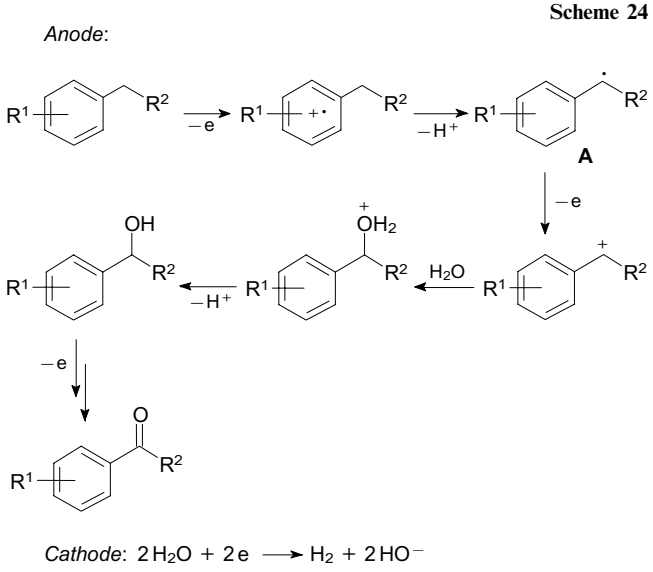


R = H (84%), 4-F (87%), 4-Br (83%), 4-CF_3 (84%), 4-NO_2 (48%), 4-Ph (42%), 4-OMe (63%), 3-F (83%), 3-Me (75%), 2-F (66%), 2-Me (64%)

Examples of products



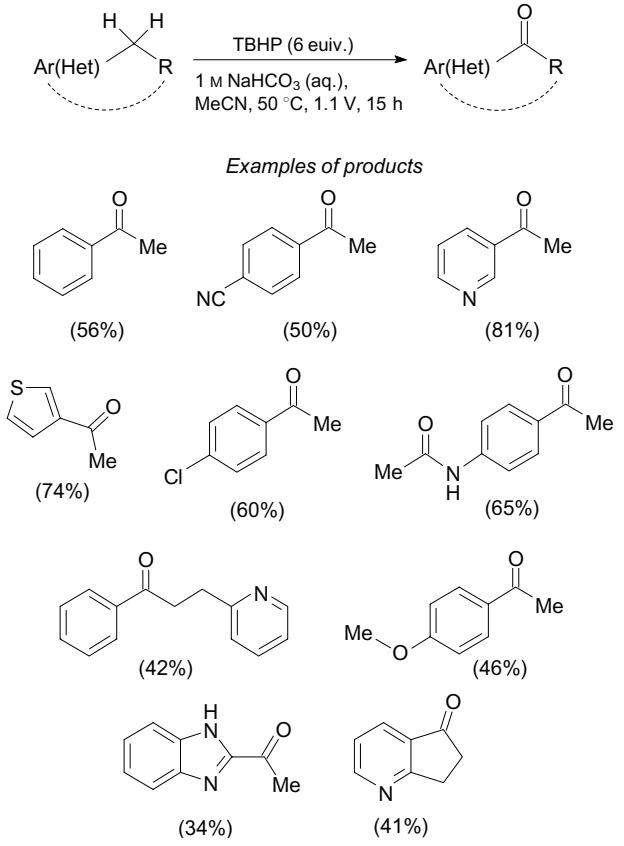
Scheme 24



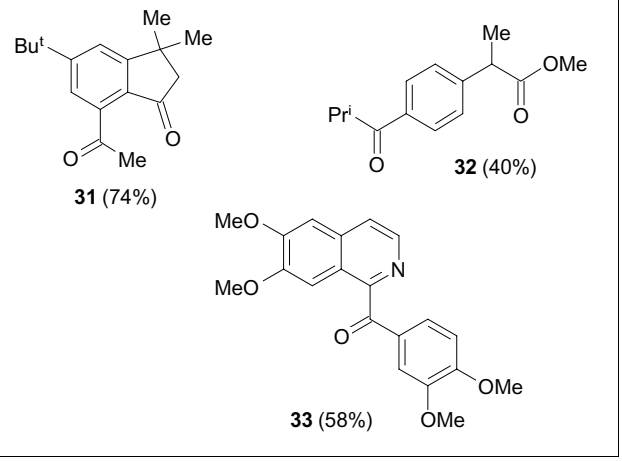
The authors investigated the mechanism for the oxidation reaction (Scheme 24). Benzylic radical **A** was detected as the key intermediate by EPR spectroscopy.[87]

In 2019, an electrochemical method was developed for the direct benzylic C–H oxidation through the formation of *tert*-butyl peroxide radicals using an aqueous $NaHCO_3$ solution as the electrolyte.[88] This method was applied to oxidize a series of substrates, in particular those containing heterocyclic moieties, to prepare ketones (Scheme 25). It is worth noting that compounds **31** – **33** exhibited biological activity.

Scheme 25



Structures 31 – 33



Francke and Little[89] reported the application of indirect electrolysis in the presence of redox catalysts that act as electron-transfer agents (mediators) in electroorganic synthesis. Generally, these transformations occur at lower potentials compared to those required for direct electrolysis, resulting in their higher chemoselectivity. For example, the electrochemical oxidation of tetrahydroisoquinolines **34** in the presence of the NaBr–TEMPO catalytic system in a two-phase medium (CH_2Cl_2/H_2O) afforded amides **35** in good yields.[90] The proposed mechanism for the oxidation is shown in Scheme 26.

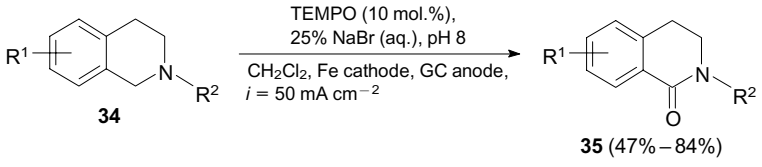
Utley and Rozenberg[91] performed the anodic oxidation of 2-methyl- and 2-benzylnaphthalenes **36** to the corresponding carbonyl derivatives using catalytic amounts of DDQ in dilute acetic acid (Scheme 27). Aryl ketones **37** were prepared in yields of up to 76%; benzylic alcohol acetates **38** were isolated as the major by-products (in yields of up to 16%).

In 2017, Stahl and co-workers[92] demonstrated that NHPI can act as a mediator in the electrochemical oxidation of hetarylalkanes under aerobic conditions (Scheme 28). They prepared 2-pyridyl and benzimidazol-2-yl methyl ketones in high yields. However, the target products were obtained in much lower yields (48% and 15%, respectively) in the presence of the $Co(OAc)_2$–NHPI–O_2 system, which was successfully used by this research group for the oxidation of the methylene group of diarylmethanes and substituted ethylbenzenes.

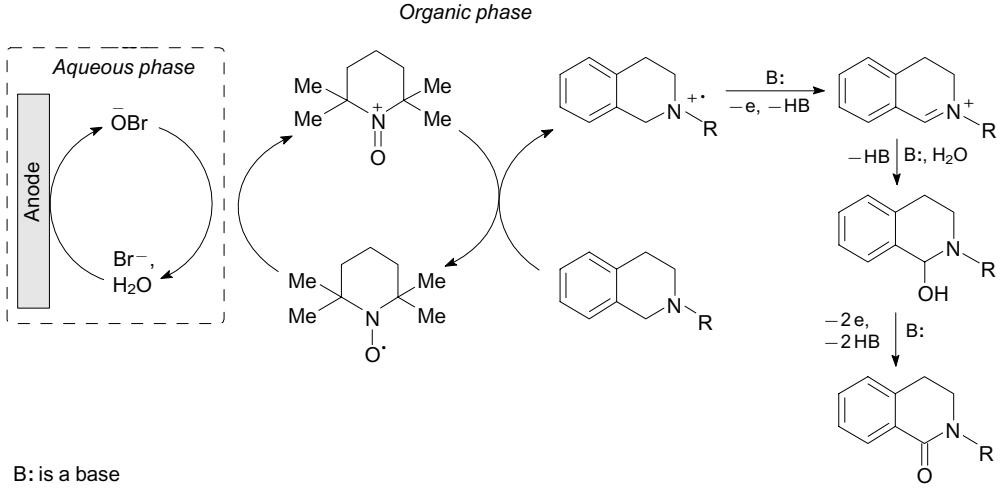
Little and co-workers[93] used triarylimidazoles **39a** – **e** with different substituents on aromatic rings as mediators in the electrochemical oxidation of organic compounds (Scheme 29). The insertion of electron-donating or electron-withdrawing substituents makes it possible to vary the redox potential in a wide range. For instance, the selective oxidation of the methylene group in unsymmetrical benzyl ethers **40** in the presence of mediator **39a** gave *p*-hydroxybenzoate esters **41a** – **f** (see Scheme 29).

In some cases, carbenium cations, generated by low-temperature electrochemical oxidation, can be accumulated and then involved as electrophiles in reactions with the added nucleophilic reagents. This method, known as the cation-pool method,[94,95] was applied by Yoshida and co-workers[96] to the benzylic C–H oxidation of diarylmethanes and toluene derivatives to prepare the corresponding carbonyl compounds. The generation of diarylcarbenium cations followed by their reaction with dimethyl sulfoxide

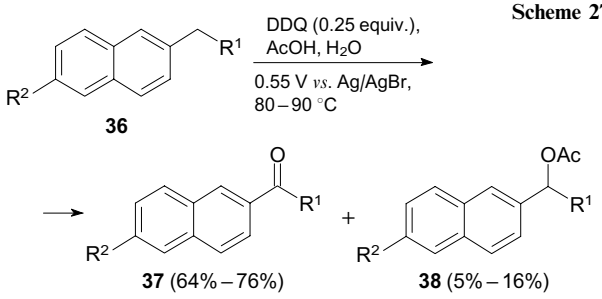
Scheme 26



R^1 = H, 6-OMe, 7-OMe; R^2 = H, Boc, Bu^n, 4-$XC_6H_4CH_2$ (X = Cl, Br, OMe);
GC electrode is a glassy-carbon electrode

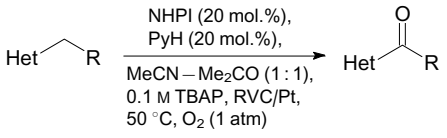


Scheme 27



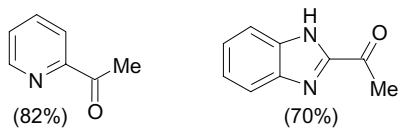
R^1 = H, Ph, 4-MeC_6H_4, 4-ClC_6H_4, 4-$MeOC_6H_4$; R^2 = H, Me, OMe

Scheme 28



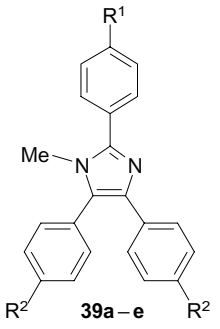
TBAP = $Bu^n_4NH_2PO_4$, RVC is a reticulated vitreous carbon electrode

Examples of products



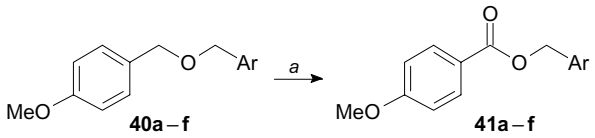
afforded suflonium cations **42**, which can be transformed into target ketones by the treatment with triethylamine (Scheme 30).

Structures 39



R^1 = Br: R^2 = H (**a**), OMe (**b**), Br (**c**);
R^1 = OMe:
R^2 = H (**d**), OMe (**e**)

Scheme 29



(*a*) **39a** (20 mol.%), 0.2 M $LiClO_4$, MeCN, CH_2Cl_2, Pt electrodes

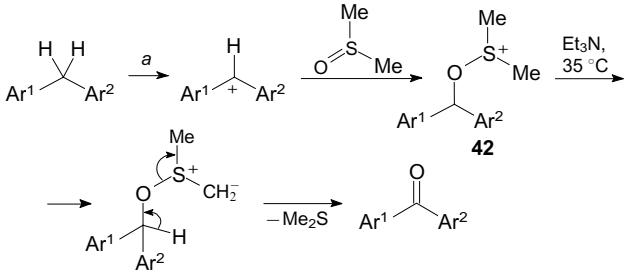
Compounds **40**, **41**	Ar	Yield (%)	See [a]
a	4-BrC_6H_4	55	87
b	4-ClC_6H_4	54	89
c	Ph	40	92
d	3-BrC_6H_4	42	88
e	4-MeC_6H_4	45	86
f	4-$MeOC_6H_4$	50	89

[a] The yield based on the recovered starting material.

2.2. Transition metal-promoted oxidation

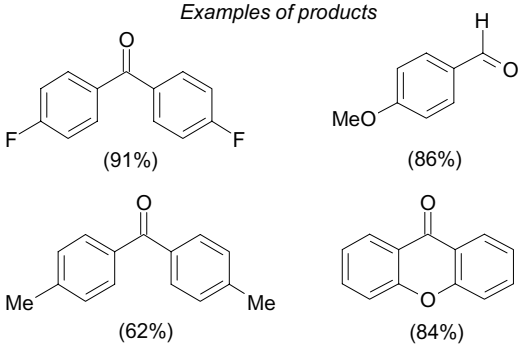
There has been a lot of transition metal-promoted benzylic C–H oxofunctionalization reactions. The simplest approach utilizes stoichiometric amounts of inorganic oxidizing agents, such as potassium permanganate,[97–99] chromium(VI) compounds,[100–102] cerium(IV) ammonium nitrate (CAN),[103, 104] $Ce(OTf)_4$,[105] $Ag(Py)_4S_2O_8$,[106]

Scheme 30



(*a*) $Bu^n_4NBF_4$, CH_2Cl_2, −78 °C (anodic oxidation)

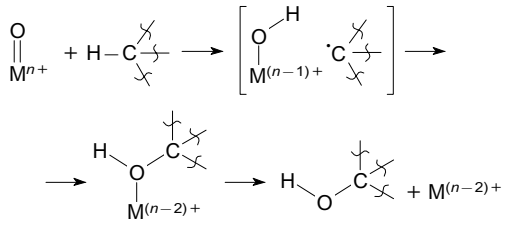
Examples of products



$Pd(OAc)_2$,[107,108] *etc*. However, these methods are of little use in chemo- and regioselective oxidation reactions of complex molecules. In the past two decades, catalytic processes using various transition metals (Co, Cr, Mn, Ir, Cu, Ru, Zn and Fe) were reported.[109] However, these reactions often proceed *via* a free-radical mechanism, which impairs the selectivity of the oxidation of complex substrates.

Transition metal-promoted biomimetic catalytic oxidation processes, which are mediated by an oxygen rebound mechanism and occur without formation of a metal−carbon bond, comprise a special group of methods for the selective oxofunctionalization of the methylene group of arylalkanes (Scheme 31).

Scheme 31



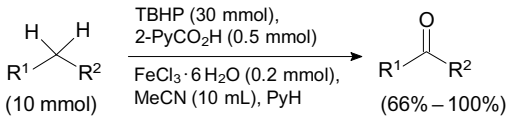
These reactions are usually performed in the presence of Fe and Mn complexes as the catalysts.[109–114] Important characteristic features of these transformations are high selectivity (due to the reaction mechanism) and the possibility of employing green oxidants such as peroxides, in particular hydrogen peroxide.[115]

The oxidation reactions of methylarenes (in the simplest case, toluene) giving carbonyl derivatives are considered in detail in the review[116] published in 2015. Most of the methods summarized in the cited review are characterized by low selectivity of oxidation and are applicable only to simple methylarenes. Hence, these methods are beyond the scope of the present review.

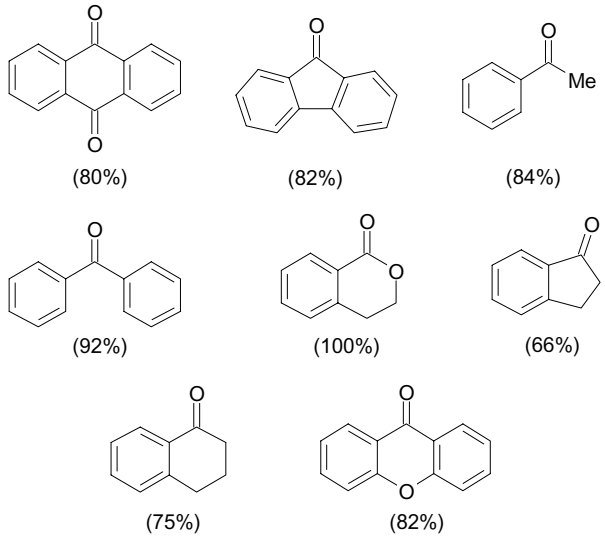
2.2.1. Oxidation in the presence of iron complexes

Iron is present in active sites of various enzymes catalyzing C−H oxidation reactions. Among these enzymes are soluble methane monooxygenase (sMMO) and cytochrome P450 enzymes. Iron compounds are commonly used as catalysts in organic synthesis.[117,118] In the 1980s, Barton and Doller[119,120] were the first to utilize iron inorganic salts in the presence of organic additives as catalysts for the selective benzylic C−H oxofunctionalization of organic compounds with peroxides. These catalytic systems included a Fe^{II} or Fe^{III} salt, organic acid, pyridine as the solvent and oxygen or peroxides as the oxidant. More recently, Tamrakar and co-workers[121] used the Fe^{III}–TBHP–2-picolinic acid system for the selective oxidation of the benzylic methylene group in a MeCN–PyH mixture (Scheme 32).

Scheme 32



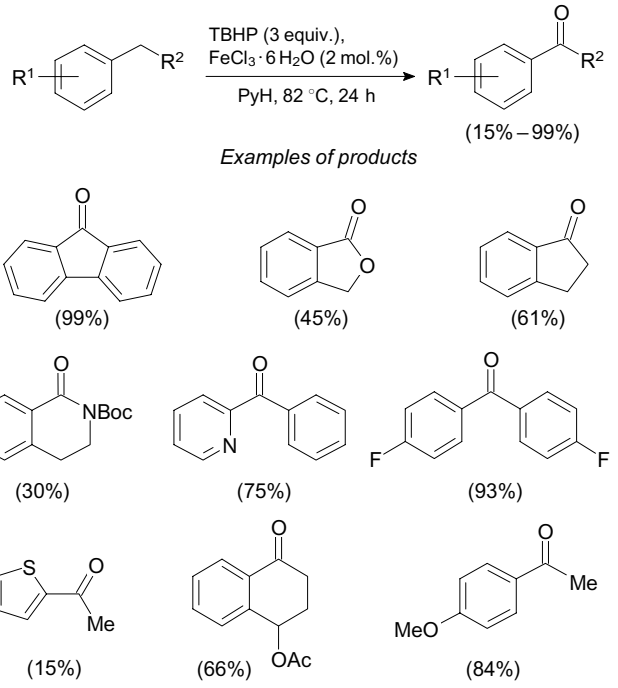
Examples of products



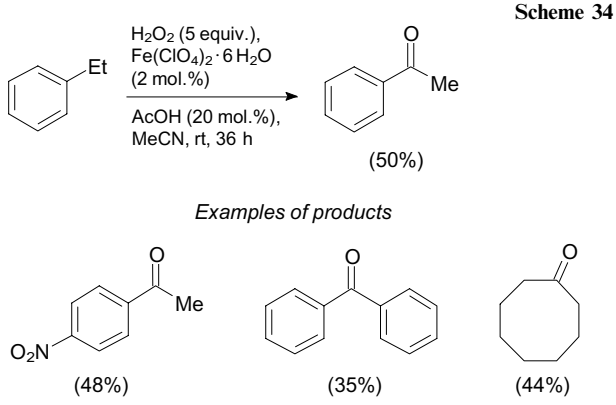
In 2007, Nakanishi and Bolm[122] accomplished the benzylic oxidation of arylalkanes by TBHP in pyridine at 82 °C in the presence of $FeCl_3$ as the catalyst (Scheme 33; Boc is *tert*-butoxycarbonyl). The practical advantages of this method are the use of commercially available iron(III) chloride in the absence of organic ligands and additives and the possibility of utilizing an oxidant (TBHP) in an aqueous solution rather than in a solution in hydrocarbons. These conditions allow the synthesis of various ketones in moderate to high yields.

It was found that arylalkanes and cycloalkanes can be oxidized to the corresponding ketones by hydrogen peroxide (5 equiv.) in acetonitrile at room temperature in moderate yields (35% – 50%).[123] Various iron(II) salts were tested as catalysts. Iron perchlorate $Fe(ClO_4)_2 \cdot 6H_2O$ demonstrated the highest conversion and selectivity (Scheme 34). This method requires the presence of carboxylic acids (*e.g.*,

Scheme 33



Scheme 34

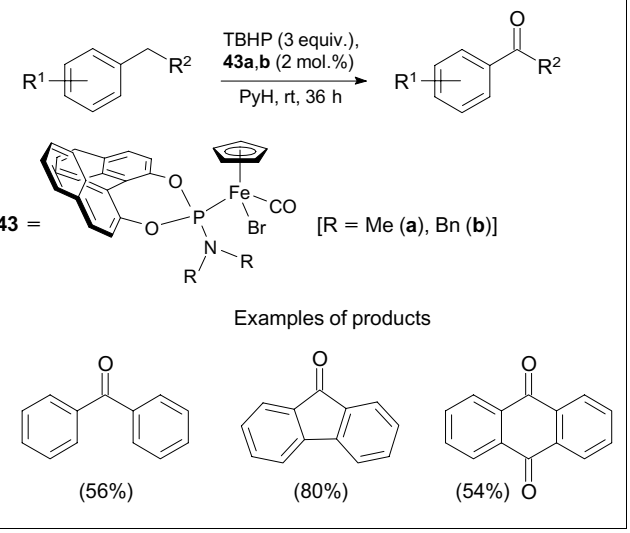


acetic acid) as additives to increase the efficiency of oxidation apparently through the formation of carboxylate complexes as intermediates.[124, 125] In the case of cyclohexane, the reaction affords an equimolar mixture of cyclohexanone and cyclohexanol (40% total yield).

Nagano and Kobayashi [126] investigated the oxidation by peroxides in the presence of iron salts and demonstrated that the binuclear iron(III) μ-oxo complex $Fe_2O(DS)_4$ ($DS = n\text{-}C_{12}H_{25}OSO_3^-$) is an efficient catalyst for the oxidation of arylalkanes by TBHP (5 equiv.) in an aqueous solution at 30 °C. Under these conditions, various arylalkanes containing one benzylic group can be oxidized to aryl ketones in good yields (71% – 99%). The reaction proceeds *via* a free-radical mechanism through the formation of $Bu^tOO^\bullet$ and the benzylic radical.

In 2010, Bauer and co-workers [127] synthesized iron carbonyl complexes with phosphoramidite ligands **43a**,**b** (Scheme 35). These complexes proved to be efficient catalysts for the oxidation of the benzylic methylene group of arylalkanes by TBHP giving the corresponding ketones in yields from 31% to 80%. The examples of the reaction products are presented in Scheme 35.

Scheme 35



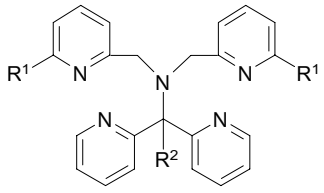
Feringa and co-workers [128] performed the screening of a series of non-haem iron complexes with ligands **44** – **55** to evaluate their activity in the benzylic oxidation by hydrogen peroxide and oxygen. Ethylbenzene and 4-ethylanisole served as model substrates. They were oxidized by iron complexes with pentadentate (**44a** – **d**, **45**, **46**, **48a** and **49b**), hexadentate (**48b**), tetradentate (**49a**, **50a**,**b**, **51**, **52a**,**b**, **53** and **54**) and tridentate (**47** and **55a**,**b**) ligands. The high-throughput screening was performed using a Chemspeed ASW 2000 automated synthesis workstation. The oxidation was carried out with an excess of the substrate (1.75 mmol) in the presence of 1.75 μmol catalyst and 87.5 μmol H_2O_2 in acetonitrile at 30 °C under a nitrogen atmosphere. The aerobic oxidation was performed using the same amounts of the substrate and the catalyst, but the reaction was initially carried out at 30 °C and then at 80 °C. Iron complexes with pentadentate ligands **44a** and **46** and with imines **50a**,**b** and **51** were found to be the most efficient catalysts for the oxidation by hydrogen peroxide. The highest alcohol to ketone ratio was observed for the complexes with imines (up to 6 in the reaction with 4-ethylanisole). The complexes with pentadentate ligands **44a** and **48a** and with tetradentate ligands **49a** and **52a** were the most efficient in the reaction with O_2. The oxidation by hydrogen peroxide gave alcohol as the major product, while ketone was obtained as the major product of oxidation by oxygen.

Liu *et al.*[129] proposed a method for the benzylic oxidation catalyzed by complex **56**. The oxidation was performed with oxone in a $MeCN - H_2O$ mixture at 80 °C (Scheme 36). This method was applied to transformations of a series of substrates into the corresponding ketones in moderate yields. In the synthesis of fluorenone (**18**), the conversion of the substrate was 93%. Xanthene (**57**) was oxidized to xanthone (**58**) with a conversion of 100%. Under these conditions, tetrahydronaphthalene (**59**) was oxidized to 3,4-dihydronaphthalen-1(2*H*)-one (**60**), 1,2,3,4-tetrahydronaphthalen-1-ol (**61**) and 4-hydroxy-3,4-dihydronaphthalen-1(2*H*)-one (**62**) with a conversion of 96%.

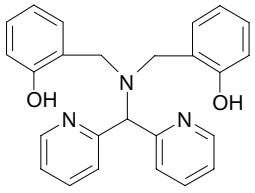
Table 1 presents the results of experiments on the oxidation of other substrates under these conditions.

In 2011, Bauer and co-workers [130] synthesized and structurally characterized a series of new iron iminopyridine complexes with ligands **63a** – **c** (Scheme 37) and evaluated the catalytic activity of the complex $[Fe(OTf)_2(\mathbf{63a})_2]$ [Tf is

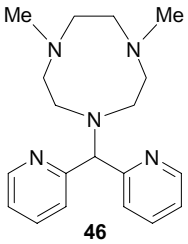
Structures 44 – 55



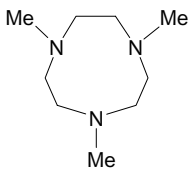
44a – d



45

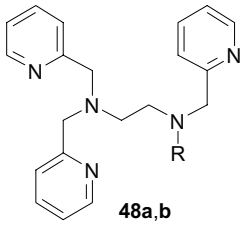


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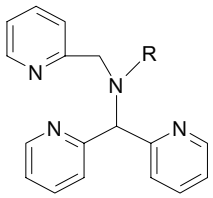


47

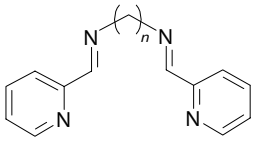
R^2 = H: R^1 = H (**a**), Br (**b**), OMe (**c**);
R^1 = H, R^2 = Me (**d**)



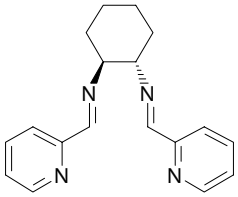
48a,b



49a,b



50a,b

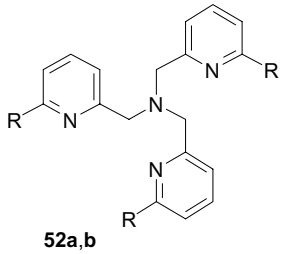


rac-**51**

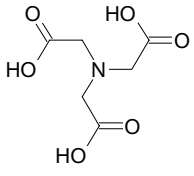
R = Me (**a**), $(CH_2)_2OH$ (**b**)

R = Me (**a**), CH_2CO_2H (**b**)

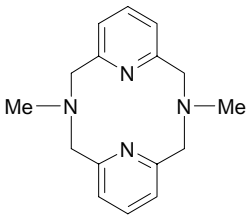
n = 2 (**a**), 3 (**b**)



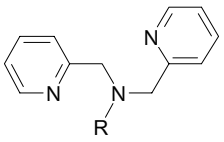
52a,b



53



54

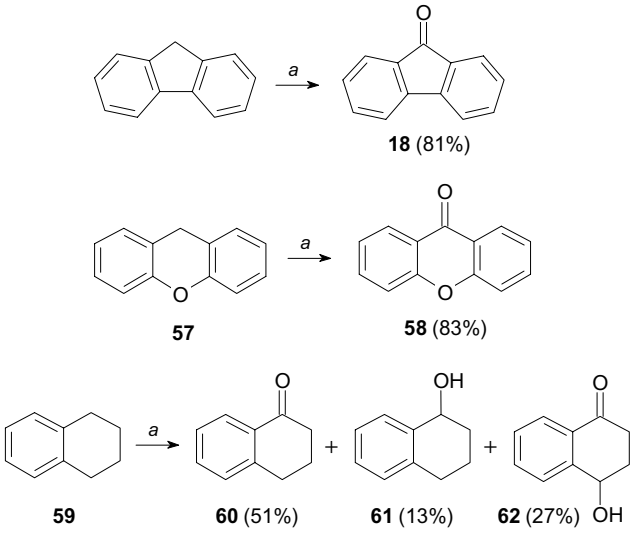


55a,b

R = H (**a**), Me (**b**)

R = Me (**a**), Bu^n (**b**)

Scheme 36



(*a*) oxone (1.2 equiv.), **56** (5 mol.%), MeCN, H_2O, 80 °C;

56 =

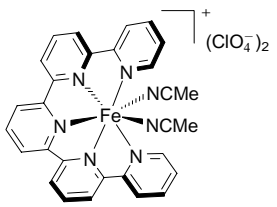
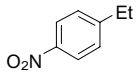
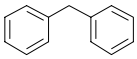


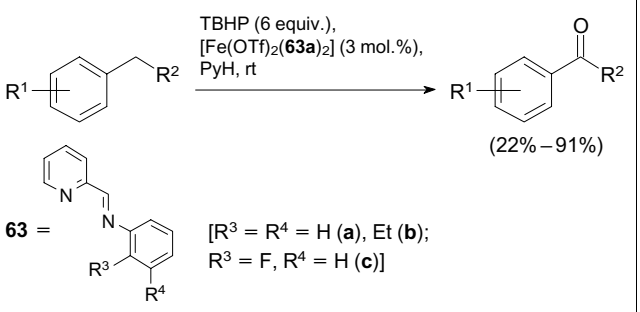
Table 1. Oxidation of alkylarenes by oxone in the presence of iron complex **56** (MeCN – H_2O, 80 °C).[129]

Substrate	Conversion (%)	Yield of ketone (%)	Yield of alcohol (%)
	63	41	5
	58	42	6
	73	42	10
	72	55	2

trifluoromethanesulfonyl (triflyl)] in the oxidation of the benzylic methylene group by *tert*-butyl hydroperoxide. The oxidation of simple substrates (ethylbenzene, diphenylmethane and fluorene) afforded ketones in 22% – 91% yields. The formation of the [Fe – O – O – Bu^t] intermediate was detected by spectroscopy. The oxidation of diphenylmethane is not inhibited in the presence of 2,4,6-tri-*tert*-butylphenol, which may indicate that free *O*-centred radicals are not generated in this reaction.

Recently, Kühn and co-workers[131] synthesized iron complexes **64a – c** with tetradentate pyridine-bis-*N*-hetero-

Scheme 37

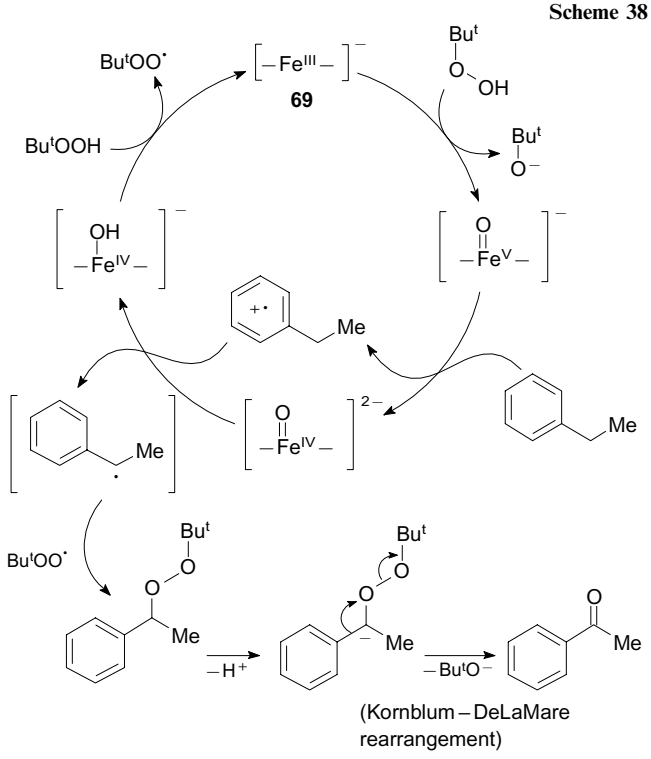


cyclic carbene ligands. These complexes were found to catalyze the C – H oxidation by hydrogen peroxide. Only xanthene (**57**) and 9,10-dihydroanthracene were tested as substrates in the benzylic C – H oxidation. Hence, it impossible to judge the practical applicability of this approach.

Claver and co-workers [132] synthesized iron complexes with ligands **65** – **68** based on benzofurobenzofuran (BFBF) and methanodibenzodioxocine (DBDOC). These complexes catalyzed the oxidation of arylalkanes by such oxidants as H_2O_2, mCPBA, cumene hydroperoxide and TBHP; the best results were obtained with the latter oxidant. Diphenylmethane, ethylbenzene and its R-substituted analogues (R = 4-OMe, 2-OMe, 4-CF_3) served as model substrates for the oxidation. The complexes $[FeL_2(MeCN)_2](BF_4)_2$, where L = **65** – **67**, demonstrated higher performance compared to the complex with ligand **68**. In the former case, the oxidation gave acetophenone and 4-trifluoromethylacetophenone in 40% and 30% yields, respectively; in the latter case, the yields were < 10% and 5%.

Andrioletti and co-workers [133] showed that the iron complex [Fe(TAML)(H_2O)]Li (**69**) (TAML is a tetraamidomacrocyclic ligand) can act as the catalyst for the benzylic C – H oxidation by TBHP in an acetone – buffer mixture (pH 12) at −10 °C (Scheme 38). The yields of ketones were 82 – 93% in the reactions with different substituted ethylbenzenes, 52% – 99% in the oxidation of substrates containing the diaryl-substituted methylene group and 8% – 21% in the oxidation of ethylpyridines. The proposed mechanism for the oxidation is presented in Scheme 38. The free-radical mechanism is evidenced by the fact that the

Scheme 38



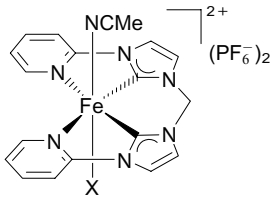
reaction is inhibited by 2,6-di-*tert*-butyl-4-methylphenol (ionol).

2.2.2. Oxidation in the presence of manganese complexes

Manganese compounds are extensively studied as catalysts for the benzylic C – H oxidation. Manganese(II) and manganese(III) salts in the presence of peroxide oxidants are the simplest systems used for the selective C – H oxofunctionalization. For instance, manganese(III) acetate catalyzes the oxidation of allylic and benzylic methylene groups by *tert*-butyl hydroperoxide to give carbonyl derivatives.[134] Tietze *et al.*[135] applied this method in the total synthesis of (−)-diversonol (**70**) to oxidize chromane system **71** at the benzylic position (Scheme 39).

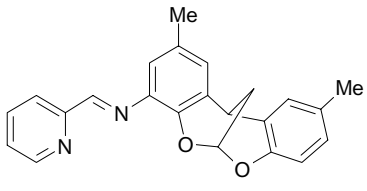
The manganese(II) triflate (0.1 mol.%) – bipyridine (1 mol.%) system can be employed to catalyze the oxidation of benzylic methylene groups to carbonyl groups and to

Structures 64 – 69

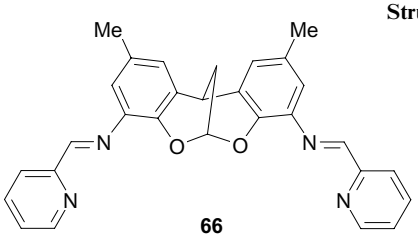


64a – c

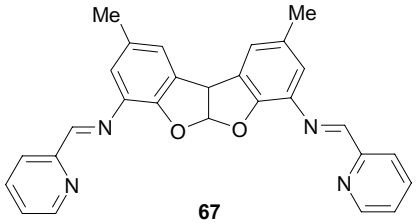
X = MeCN (**a**), PMe_3 (**b**), Bu^tCN (**c**)



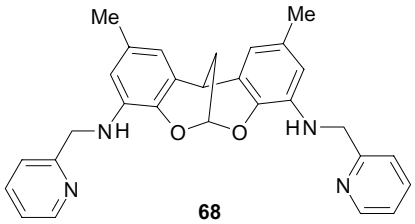
65



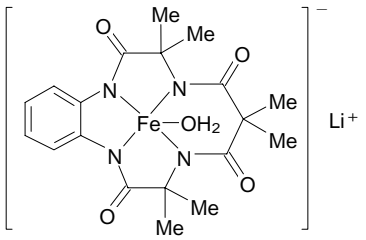
66



67

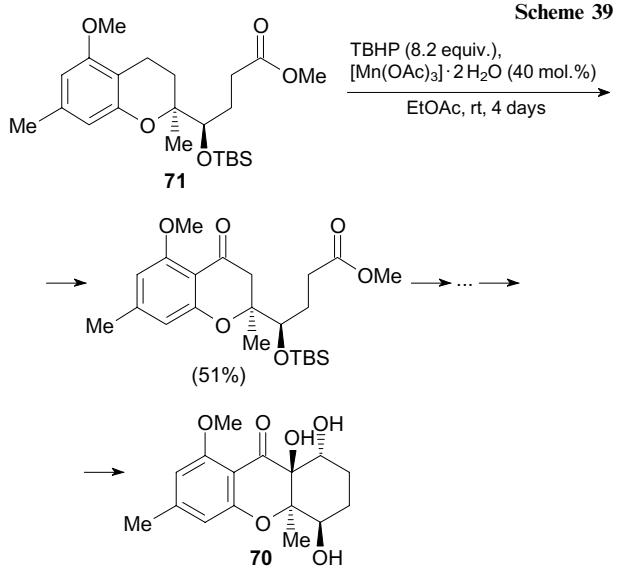


68



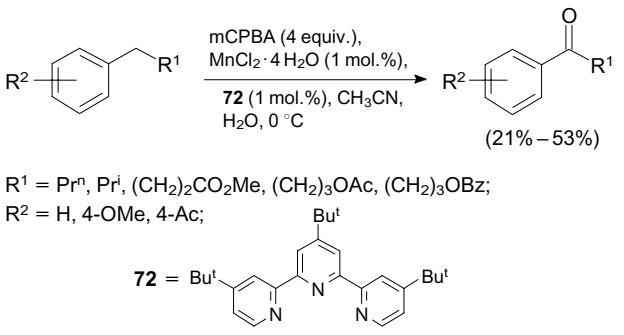
69

Scheme 39



hydroxylate substituted cumenes with peracetic acid giving the target products in 34% – 48% yields.[136] Oxone and mCPBA oxidize arylalkanes and secondary alcohols to form carbonyl derivatives in the presence of the catalyst generated *in situ* from manganese(II) chloride and terpyridine ligand **72** containing three *tert*-butyl substituents (Scheme 40).[137] This reaction produces aryl ketones in moderate yields. For example, the oxidation of diphenylmethane affords benzophenone in 53% yield.

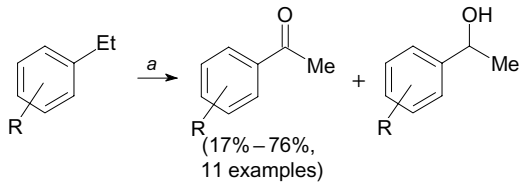
Scheme 40



Browne and co-workers[138] proposed a method for the oxidation of secondary alcohols and arylalkanes by hydrogen peroxide in the presence of the manganese(II) perchlorate – pyridine-2-carboxylic acid – butanedione system (Scheme 41). The oxidation of ethylbenzene derivatives affords aryl ketones in yields usually not higher than 50% (in the case of diarylmethanes, the product yields were higher and varied from 60% to 99%). In some cases, the reactions gave significant amounts of alcohol as a by-product, *i.e.*, the selectivity to ketones was not sufficiently high.

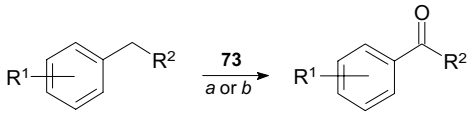
In 1997, Lee *et al.*[139] tested manganese(III) salen complexes **73a**,**b**, which have been previously designed for the enantioselective epoxidation of alkenes, as catalysts for the benzylic C – H oxidation. The oxidation of ethylbenzene in the presence of commercially available chiral Jacobsen's catalyst **73b** or related complex **73a** lacking *tert*-butyl substituents (Scheme 42) gave acetophenone as the major

Scheme 41

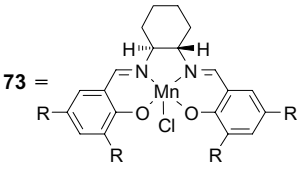


(*a*) butanedione (1.5 equiv.), AcOH (0.2 equiv.), H_2O_2 (4 equiv.), $Mn(ClO_4)_2 \cdot 6H_2O$ (0.1 mol.%), 2-$PyCO_2H$ (1 mol.%), NaOAc (2 mol.%), MeCN, 0 °C; R = H, 4-Me, 4-OMe, 3-NO_2

Scheme 42

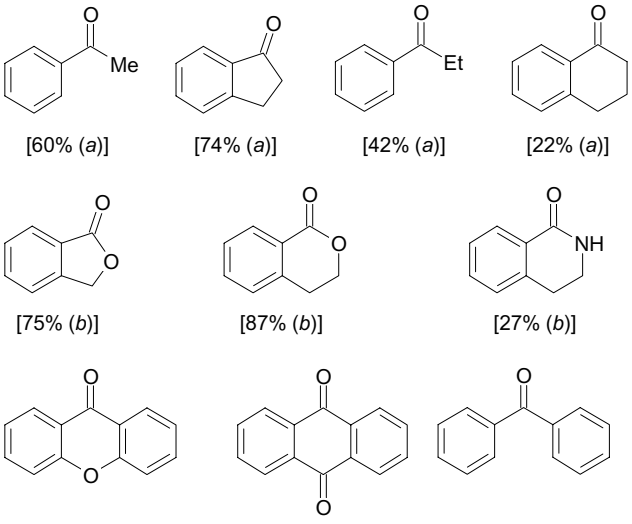


(*a*) PhIO, MeCN; (*b*) NaClO, CH_2Cl_2



[R = H (**a**), But (**b**)]

Examples of products (conditions)



[60% (*a*)] [74% (*a*)] [42% (*a*)] [22% (*a*)]

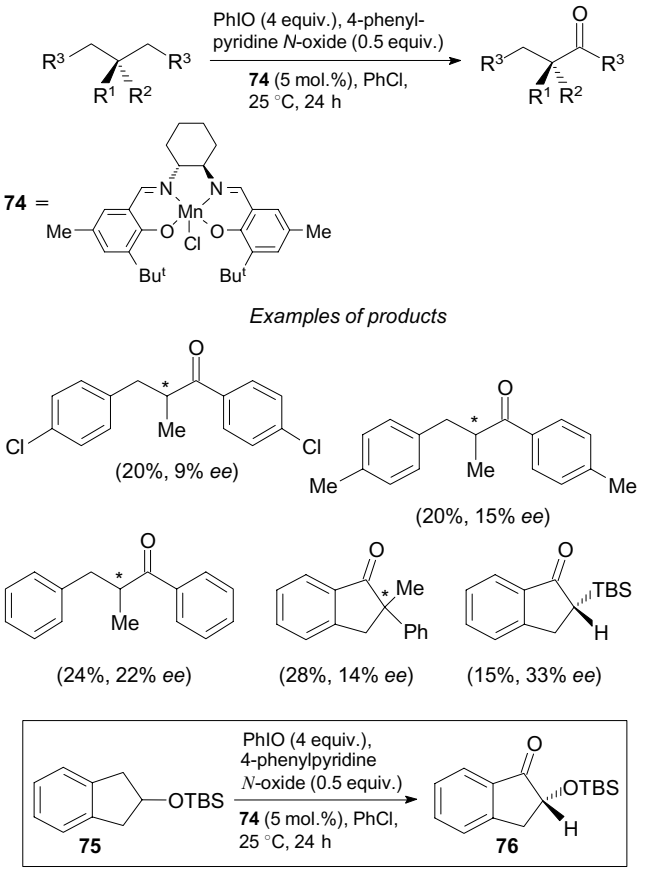
[75% (*b*)] [87% (*b*)] [27% (*b*)]

[92% (*b*)] [66% (*b*)] [72% (*a*)]

product and 1-phenylethanol as a by-product. The best selectivity to acetophenone was achieved using PhIO (the conversion of the substrate was 77%, the ratio alcohol : ketone = 6 : 94), whereas NaClO (15%, 11 : 89) and H_2O_2 (12%, 38 : 62) proved to be least efficient. The authors proposed to oxidize arylalkanes to aryl ketones using racemic manganese salen complex **73a** in an amount of 15 mol.% in the presence of 3 equiv. of PhIO in acetonitrile (conditions *a*) or in an amount of 8 mol.% in the presence of 3 equiv. of NaClO in CH_2Cl_2 (conditions *b*) under an inert atmosphere (N_2) at 0 °C.

Komiya and co-workers[140, 141] reported the catalytic oxidative desymmetrization of alkanes and 1,3-disilyl esters with PhIO in the presence of chiral manganese(III) salen complex **74**. This reaction affords the corresponding chiral

Scheme 43



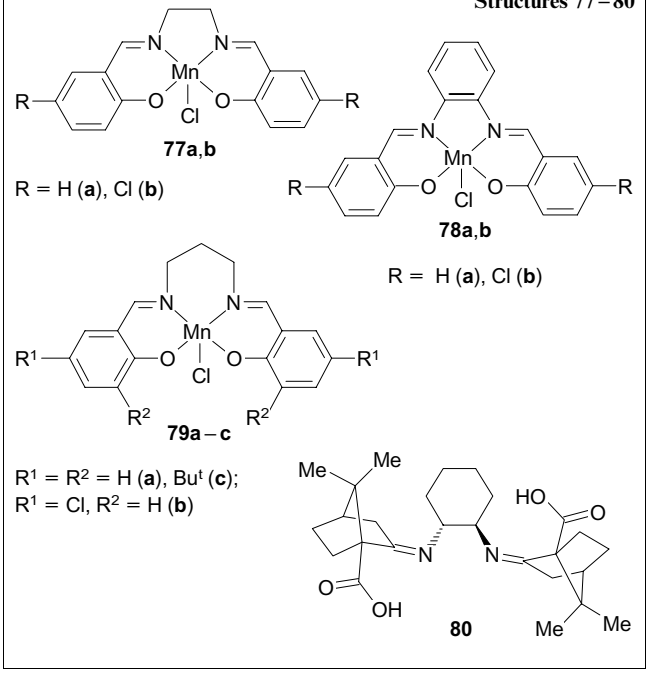
carbonyl compounds in an optical yield of up to 33% *ee* (Scheme 43).

A strong non-linear temperature dependence of the enantioselectivity was observed in the study of the oxidation of 2-siloxindane (**75**) in the presence of complex **74**.[142] Thus, the maximum enantioselectivity (42% *ee* for product **76**) was achieved at 40 °C. This effect persisted in the reaction catalyzed by a complex that differs in the nature of substituents in the ligand, but the temperature range changed. The authors attributed this observation to the influence of two opposing factors on the formation of diastereomeric intermediates: the steric repulsion and the chelation effect between the reactive, presumably, Mn=O species and the substrate. This result is a single example of the so-called isoinversion principle in asymmetric C–H oxidation reactions of organic compounds.

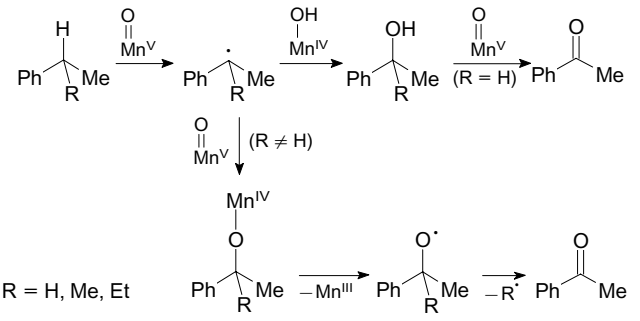
Lee *et al.*[143] continued to investigate the catalytic activity of Mn^{III} complexes **77** – **79** with Schiff base ligands in the benzylic C–H oxidation by PhIO in acetonitrile. Manganese(III) complex **78a** was found to provide the highest yield (65% – 80%) and selectivity to ketones.

Apart from tertiary alcohol generated as the major product, the oxidation of PhIO by cumene and *sec*-butylbenzene affords acetophenone as a by-product. In the case of cumene, the alcohol to acetophenone ratio was 58 : 42; in the case of *sec*-butylbenzene, the alcohol and ketone were prepared in equal amounts. The presence of oxygen has only a slight effect on the amount of the resulting acetophenone. The proposed mechanism for the oxidation involves the formation of reactive Mn(V)=O species and is presented in Scheme 44. The formation of such reactive species from manganese complexes in the presence of strong oxidants (PhIO and NaClO) was predicted by Jacobsen and co-

Structures 77 – 80



Scheme 44



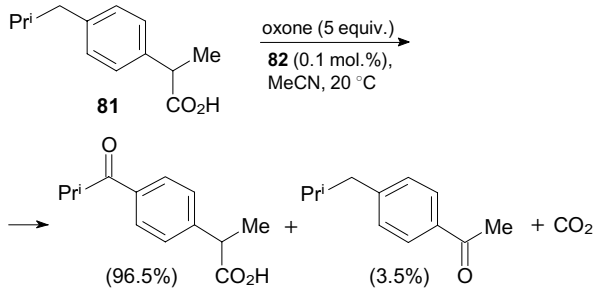
workers[144] and was then experimentally confirmed by Talsi and co-workers.[145]

In 2001, Pedro and co-workers[146] synthesized a new dimeric manganese(III) oxamate complex of the general formula $(Ph_4P)_2[Mn_2(opba)_2(H_2O)_3]\cdot 3\,H_2O\cdot MeCN$, where opba is *o*-phenylenebis(oxamate). This complex was structurally and magnetically characterized and was proved to be catalytically active in C–H oxidation of alkanes by *tert*-butyl hydroperoxide at room temperature. For example, the oxidation of ethylbenzene with 3 equiv. of TBHP affords acetophenone (17%) and 1-phenylethanol (4.2%); the oxidation of diphenylmethane gives benzophenone (37%) and diphenylmethanol (5.2%).

Pan and Chen[147] synthesized ligand **80** based on a camphor derivative and used it for the catalytic oxidation of various allylic and benzylic substrates by *tert*-butyl hydroperoxide in the presence of $Mn(OAc)_2\cdot 4\,H_2O$ to prepare carbonyl derivatives. The oxidation of simple arylalkanes (toluene, ethylbenzene, n-propylbenzene, 1,2,3,4-tetrahydronaphthalene and fluorene) afforded ketones in 63% – 91% yields.

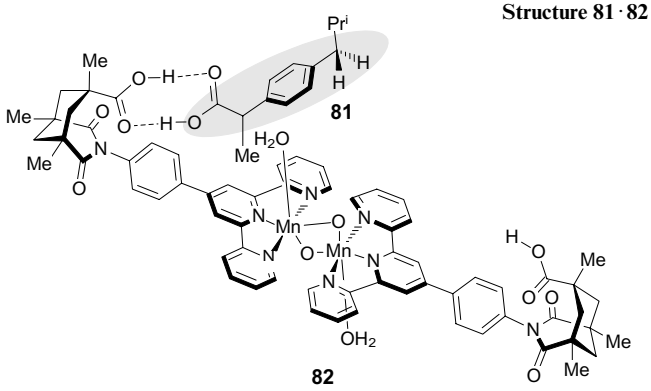
In oxidation processes that occur in biological systems, high selectivity is achieved due to non-covalent interactions between the substrate and amino acids in the active sites of enzymes.[148 – 150] In 2006, Crabtree and co-workers[151] used the molecular recognition strategy in the regioselective oxidation of ibuprofen (**81**) by oxone (Scheme 45).

Scheme 45



The authors synthesized binuclear manganese oxo complex **82** with the terpyridine ligand containing a substituent derived from Kemp's acid, with the free CO_2H group. The carboxyl group of the ligand is involved in hydrogen bonding with the CO_2H group of ibuprofen to form structures **81**·**82**. This allows the regioselective oxidation of the methylene group, which is coordinated above the dimanganese dioxo core, in acetonitrile at 20 °C to give carbonyl derivatives. The conversion of the substrate was 71%, the turnover number (moles of the substrate converted per mole of the catalyst, TON) was 710, and the selectivity was 96.5% (see Scheme 45).

Structure 81·**82**

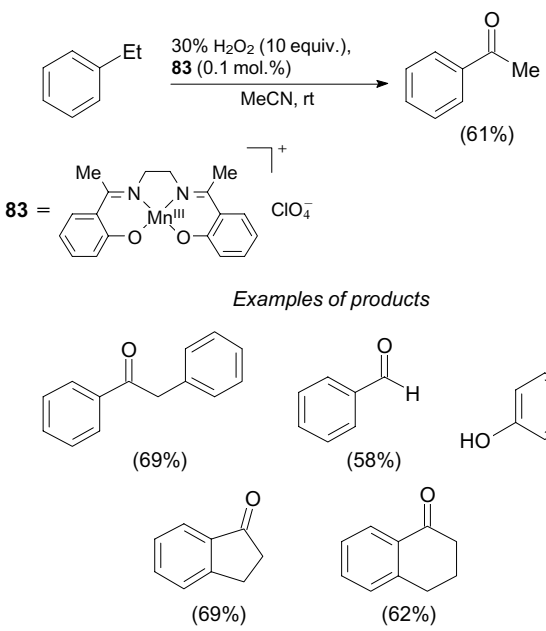


In 2006, Mardani and Golchoubian [152] developed a procedure for the oxidation of arylalkanes by hydrogen peroxide in the presence of manganese complex **83** with a salen-type Schiff base ligand as the catalyst in acetonitrile (Scheme 46). Various mono- and disubstituted arylalkanes were oxidized to the corresponding ketones in moderate yields.

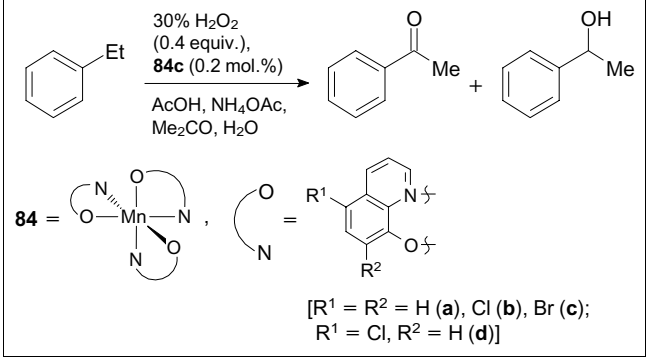
Fu and co-workers [153] used Mn^{III} 8-quinolinolate complexes **84a**–**d** as the catalysts for the oxidation of ethylbenzene by 30% hydrogen peroxide (Scheme 47). The reaction in the presence of complex **84c** with 5,7-dibrominated ligands afforded acetophenone in a yield of up to 65%. The free-radical mechanism rather than the mechanism involving high-valent Mn oxo species was proposed as the main reaction pathway.

Manganese(III) complexes with polyfluoroaryl-substituted corrole ligands (**85** and **86a**,**b**; the letter F in the ring designates the perfluorinated substituent) can catalyze the oxidation of alkanes and alkylbenzenes (toluene, ethylbenzene and diphenylmethane) by mCPBA. These complexes exhibit moderate catalytic activity and display moderate selectivity, as was demonstrated by Bandyopadhyay and coworkers [154] in 2010 (Scheme 48, the yields are given with respect to the oxidant). The high-valent manganese(V) oxo

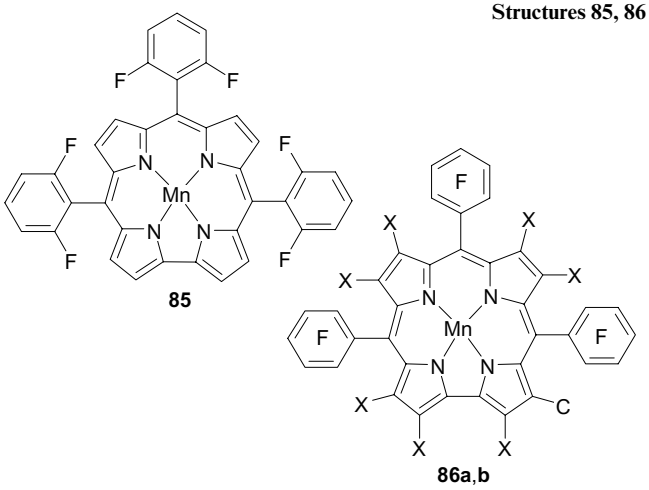
Scheme 46



Scheme 47



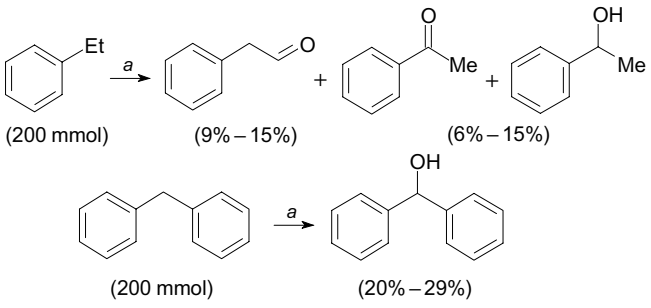
Structures 85, 86



corrole complexes were considered as reactive species responsible for the transfer of the oxygen atom.

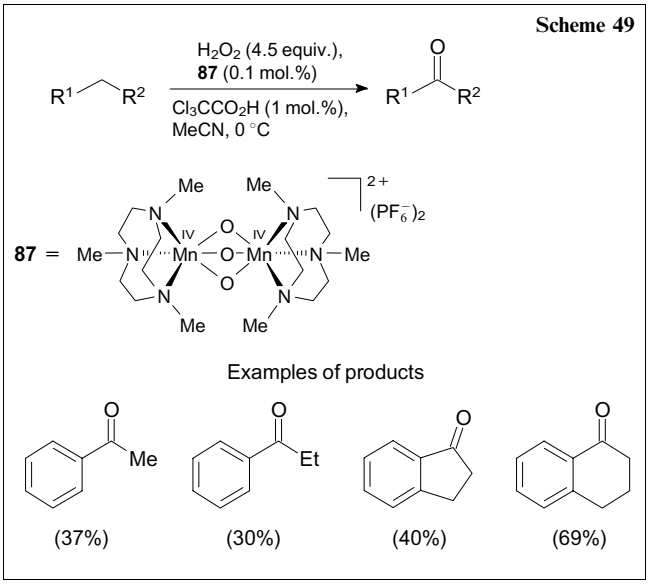
In 2013, de Boer and co-workers [155] used the binuclear manganese complex $[Mn_2O_3(tmtacn)](PF_6)_2$ (**87**, tmtacn is 1,4,7-trimethyl-1,4,7-triazacyclononane) as the catalyst for the oxidation of various substrates (alcohols, aldehydes,

Scheme 48



(*a*) mCPBA (2 mmol), **85** or **86a**,**b** (25 μmol), MeCN, rt

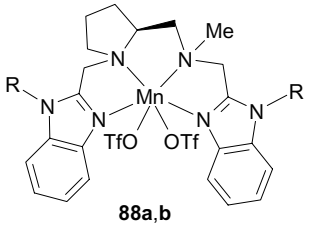
Scheme 49



alkanes and alkenes) by hydrogen peroxide in the presence of trichloroacetic acid (Scheme 49). The oxidation of arylalkanes afforded ketones in 30% – 69% yields.

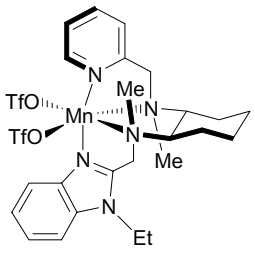
Recently, biomimetic complexes of manganese(II) with tetradentate bis(amino)bis(pyridine) and related tetradentate ligands have attracted considerable attention and are considered as promising catalysts for various chemo- and stereoselective oxidation reactions, in particular for the C – H-oxidation.[156] In 2014, Sun and co-workers[157] demonstrated that the manganese complex [(*S*)-PMB]Mn(OTf)$_2$ (**88a**) efficiently catalyzes the benzylic C – H oxidation by hydrogen peroxide in the presence of carboxylic acid (*e.g.*, AcOH). The reactions with most substrates produced ketones in high yields (> 60%).

Structures 88, 89



88a,**b**

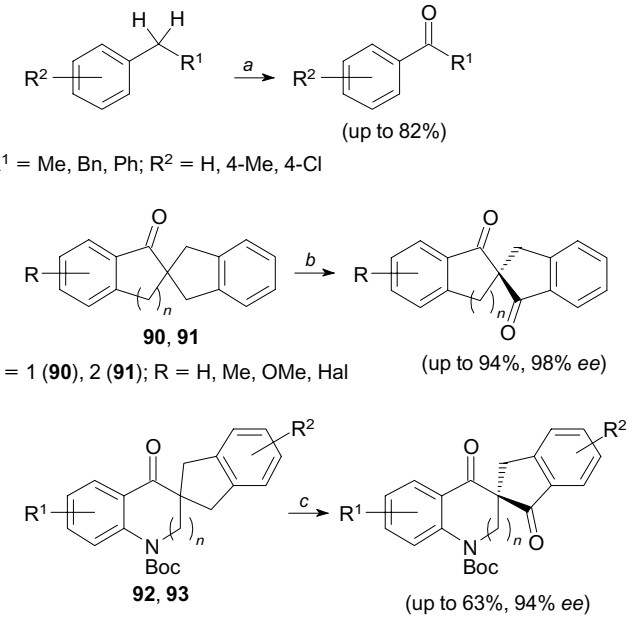
R = Me [(*S*)-PMB)Mn(OTf)$_2$, **a**],
Et [(*S*)-PEB)Mn(OTf)$_2$, **b**]



89

Subsequently, it was shown that complex **89** exhibits similar catalytic activity in the oxidation of the benzylic methylene group by hydrogen peroxide.[158] In 2018, this research group[159] developed a procedure for the oxidative desymmetrization of spirocyclic indanones **90** and tetralones **91** with hydrogen peroxide giving the corresponding β,β′-diketones in high yields with high enantioselectivity (Scheme 50). The oxidation was accomplished using the manganese complex [(*S*)-PEB]Mn(OTf)$_2$ (**88b**) with a tetradentate N$_4$-donor ligand as the catalyst.

Scheme 50



(*a*) H_2O_2 (3.5 equiv.), **88a** (0.5 mol.%), AcOH (14.0 equiv.), MeCN, rt, 0.5 h;
(*b*) 30% H_2O_2 (5 equiv.), carboxylic acid (14.0 equiv.),
88b (0.5 mol.%), MeCN – CH_2Cl_2 (1 : 1), – 30 °C;
(*c*) 30% H_2O_2 (3.5 equiv.), 2,2′-dimethylbutyric acid (14.0 equiv.),
88b (2 mol.%), MeCN – CH_2Cl_2 (1 : 1), argon, 0 °C

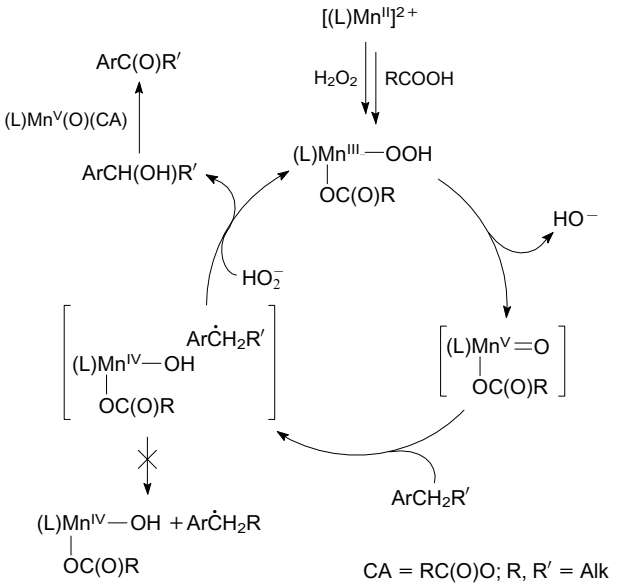
It was suggested that the oxidation occurs through the formation of the oxo species (L)Mn(V)=O, which abstract a hydrogen atom from the substrate accompanied by the generation of a benzylic radical and the (L)Mn^{IV} – OH species in the solvent cage. This is followed by the recombination of the radical species with the manganese-coordinated OH group to give an alcohol molecule (Scheme 51) and the subsequent oxidation of the alcohol to ketone.

In 2019, Sun and co-workers[160] showed that complex **88a**, which has been successfully used for the oxidation of spirocyclic indanones **90** and tetralones **91**, is also an efficient catalyst for the enantioselective oxidation of methylene groups of spirocyclic oxindoles **92** and dihydroquinolinones **93** giving the corresponding carbonyl derivatives (see Scheme 50). The conditions were found for the asymmetric synthesis of secondary alcohols in moderate yields (22% – 41%) with high enantioselectivity (70% – 99% *ee*) starting from dihydroquinolinones **93**.

2.2.3. Oxidation in the presence of cobalt compounds

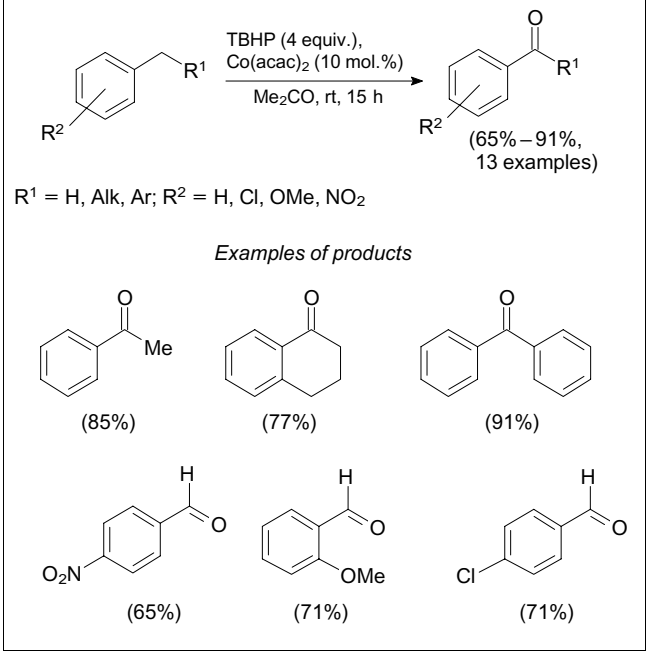
Cobalt salts can act as catalysts for the benzylic oxidation of arylalkanes by various oxidants, such as TBHP, oxone,

Scheme 51



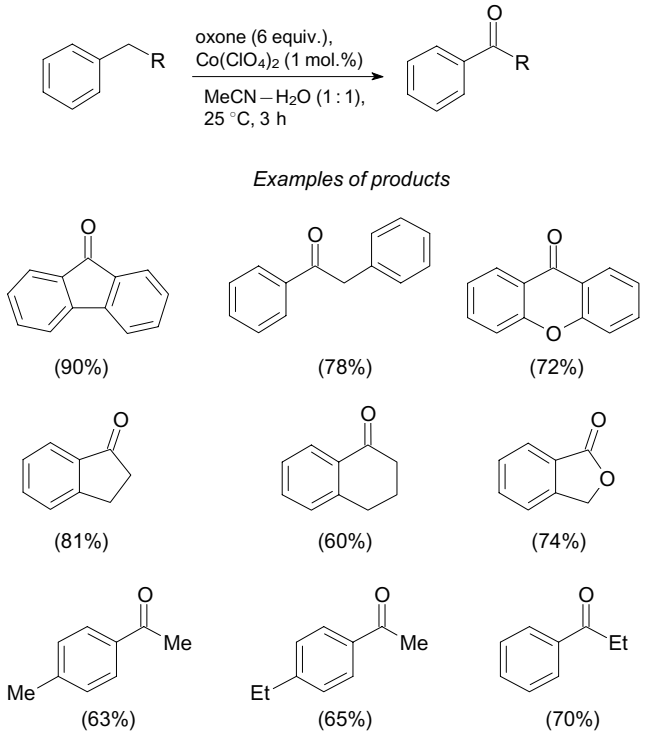
sodium hypochlorite and molecular oxygen. For example, various allylic and benzylic substrates were oxidized by *tert*-butyl hydroperoxide in the presence of cobalt(II) acetylacetonate [Co(acac)$_2$] to form the corresponding enones and aryl ketones at room temperature (Scheme 52).[161] This method was applied to synthesize carbonyl derivatives not only from substrates containing the benzylic methylene group but also from various toluene derivatives containing both electron-donating and electron-withdrawing substituents. The yields of aldehydes were 65%–91%.

Scheme 52

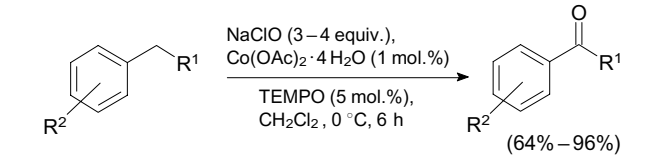


In 2016, Yang and Ma[162] showed that the Co(ClO$_4$)$_2$ (0.1 equiv.)–oxone (6 equiv.) system allows the synthesis of ketones from arylalkanes in acetonitrile at room temperature in 60%–90% yields.[162] The reactions of diarylmethanes afforded ketones in 72%–90% yields; the yields of

Scheme 53

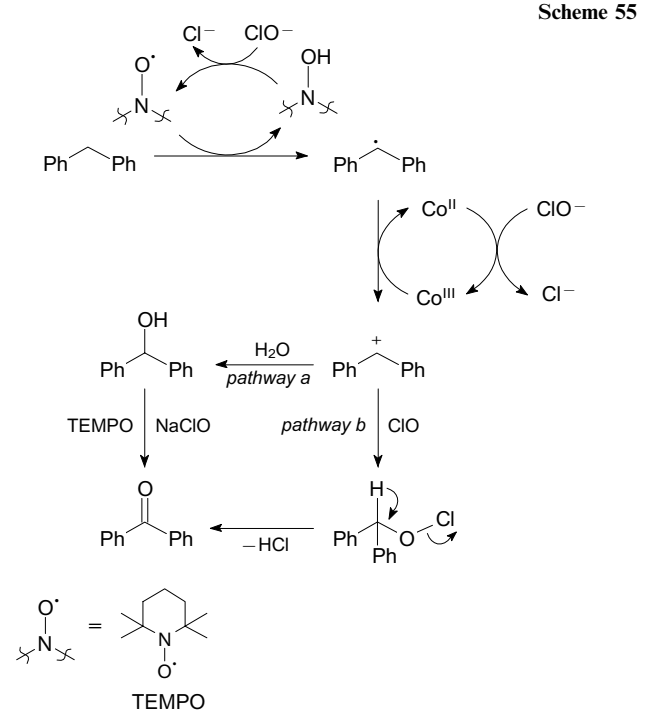


Scheme 54



R^1 = H, Alk, Ar; R^2 = H, Cl, Br, OMe

Scheme 55



ketones derived from the substrates containing one aryl group were 60% – 81% (Scheme 53).

The NaClO – TEMPO – $Co(OAc)_2$ system was utilized to oxidize a series of arylalkanes in good yields (Scheme 54).[163]

The following mechanism was proposed for this process (Scheme 55). The radical initially generated upon TEMPO-induced hydrogen abstraction from the substrate is oxidized to the benzylic cation by the Co^{III} complex, which is produced by the oxidation of Co^{II} with hypochlorite. The subsequent ketone formation can occur by two pathways: through the formation of alcohol followed by its oxidation (pathway *a*) or through the reaction of the cation with hypochlorite followed by the elimination of HCl (pathway *b*).

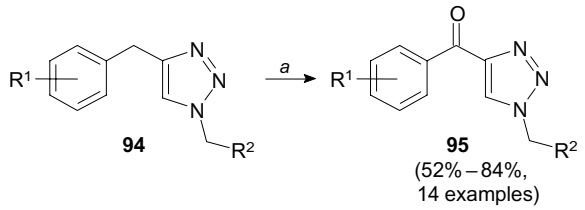
2.2.4. Oxidation in the presence of copper compounds

Many enzymes that catalyze the C – H oxidation contain copper in their active sites. One such enzyme is membrane-associated methane monooxygenase (pMMO). Copper complexes are considered as promising catalysts for the selective C – H oxidation. For example, Yuan and co-workers[164] used copper triethanolamine complexes for the benzylic oxidation by TBHP. Of the four synthesized complexes, the tetrameric complex $[OCu_4(TEA)_4(BOH)_4][BF_4]_2$ (TEA is triethanolamine) displayed the highest activity. The oxidation of simple substrates bearing the benzylic methylene group by TBHP (2 equiv.) at 70 °C gave ketones in yields from 32% to 74%. The oxidation of cumene afforded acetophenone as the major reaction product (20% yield).

Benzyltriazoles **94** were oxidized by TBHP to the corresponding α-ketotriazoles **95** in the presence of copper(I) iodide (Scheme 56).[165] This method was tested with other diarylmethanes; however, the yields of the carbonyl products were not higher than 50%.

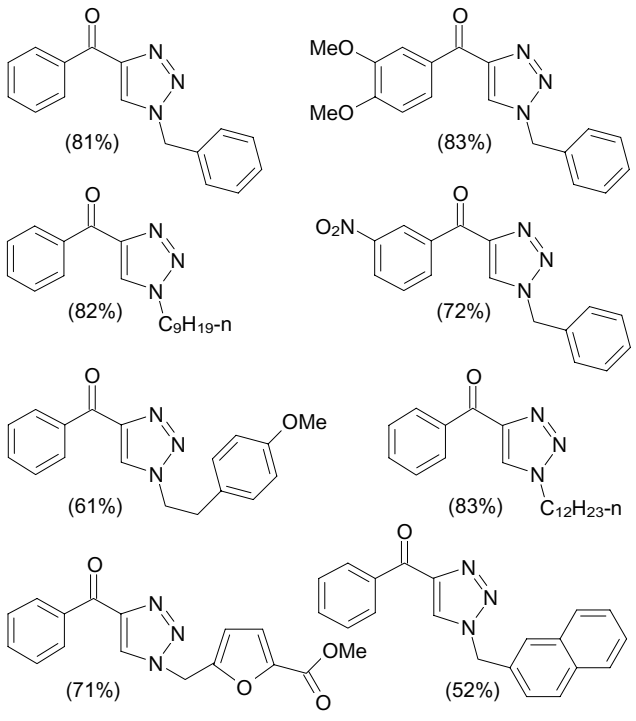
In 2003, Velusamy and Punniyamurthy[166] utilized copper complex **96** with an *N*,*N*,*O*,*O*-donor ligand for the oxidation of arylalkanes by hydrogen peroxide (Scheme 57). The oxidation of ethylbenzene afforded acetophenone in 86% yield. Under these conditions, a series of other ketones, *e.g.*, α-tetralone **60** (89% yield), were synthesized.

Scheme 56

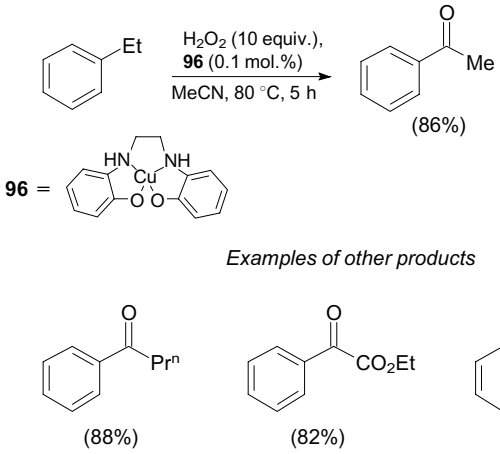


(*a*) TBHP (4 equiv.), CuI (10 mol.%), MeCN, rt

Examples of products



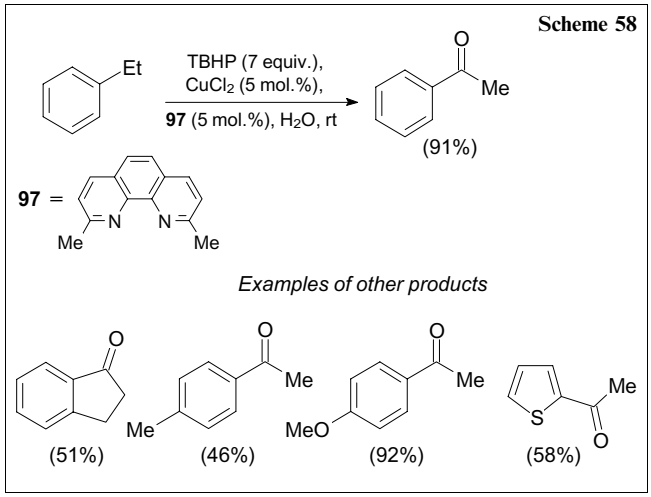
Scheme 57



Kumar and co-workers[167] showed that arylalkanes can be transformed into the corresponding ketones by the reactions with NaOCl in the presence of the complex [Gmim]Cl-Cu^{II} (Gmim is 1-glycyl-3-methyl imidazolium) in 80% – 88% yields.

In 2016, Hossain and Shyu[168] proposed a method for the oxidation of arylalkanes to ketones by *tert*-butyl hydroperoxide in an aqueous solution at room temperature in the presence of copper(II) chloride and neocuprine (**97**) (Scheme 58). Advantages of this system are operational simplicity (the absence of bases and phase-transfer catalysts), the ease of isolation of the product from the reaction mixture by extraction and recyclability of the catalyst.

Scheme 58



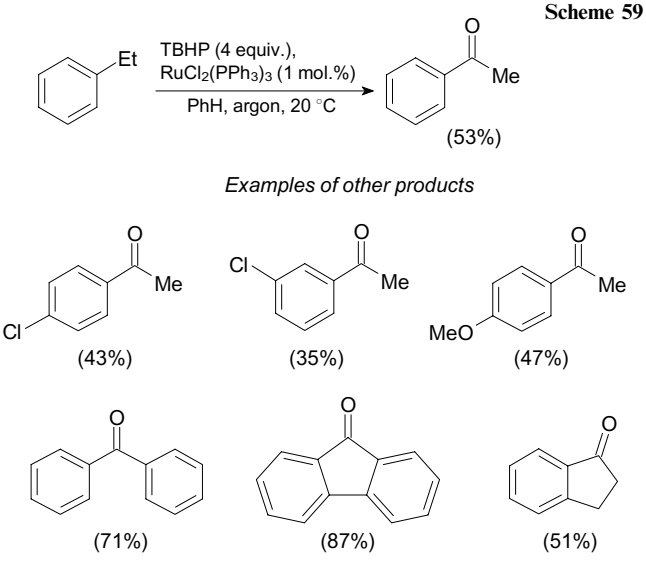
Under these conditions, ethylbenzene was transformed into acetophenone in high yield. Hossain and Shyu [168] described other examples of the oxidation of various mono- and diaryl-substituted substrates in moderate (25% for 3-ethylpyridine) to excellent (95% for fluorene) yields.

2.2.5. Oxidation in the presence of ruthenium compounds

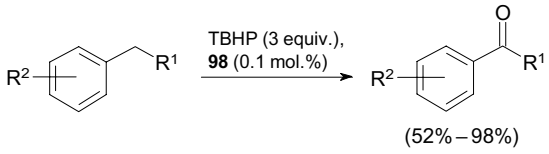
In 1988, Murahashi *et al.*[169] found that non-haem (non-porphyrin) ruthenium complexes can catalyze the oxidation of alkanes by alkyl hydroperoxides. For instance, $RuCl_2(PPh_3)_3$ catalyzes the oxidation of alkylarenes to form carbonyl compounds in moderate yields (see Scheme 59, ethylbenzene as an example, the conversion is 58%). Murahashi *et al.*[170] performed a series of experiments in order to elucidate the reaction mechanism. The relative rates of oxidation of substituted toluenes (k_{rel}) were found to correlate well with the polar Brown – Okamoto substituent constants (σ^+) in the linear free energy relationships. It should be noted that the parameter $\rho^+ = -1.39$ is close to the values obtained for the oxidation with cytochrome P450 (-1.6) and the Fe(TPP)Cl – PhIO (-1.69) system (TPP is tetraphenylporphyrin), in which the metal oxo complexes act as reactive species, and is quite different from those obtained for the oxidation by $Bu^tOO^\bullet$ radicals (-0.6) and $Bu^tO^\bullet$ radicals (-0.4). These kinetic data are indicative of the formation of ruthenium oxo complexes similar to the Fe=O compounds involved in the cytochrome P450 catalytic cycle. The intramolecular isotope effect (k_H/k_D) was examined for the oxidation of 1,1-dideuterio-1,3-diphenylpropane. This effect was determined to be 9, which is similar to that obtained for the oxidation with cytochrome P450 ($k_H/k_D = 11$). Consequently, the C – H bond cleavage is the rate-limiting step. These results and other data provide evidence that the oxidation occurs through a mechanism involving metal oxo species rather than *via* the free-radical mechanism. Examples of other ketones described in the study [169] are presented in Scheme 59.

Zhao and co-workers [171] demonstrated that ruthenium complex **98** can efficiently catalyze the benzylic oxidation of arylalkanes to ketones under solvent-free conditions (Scheme 60); TON reached 980. The products can easily be separated from the catalyst as the latter is water-soluble and is transferred to an aqueous phase.

Scheme 59

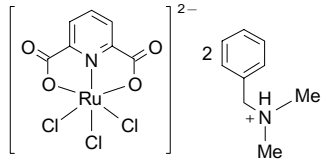


Scheme 60



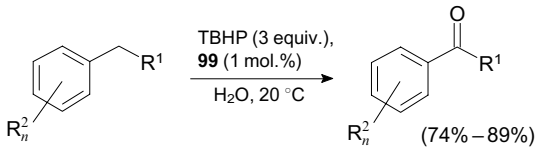
R^1 = Me: R^2 = 4-NO_2, 4-Br, 4-CHO, 4-Me, 3-Me, 2-Me, 2-Br;
R^2 = H: R^1 = Et, Pr^i, Ph, *etc.*

98 =



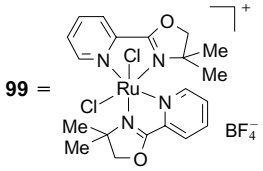
Cationic ruthenium complex **99** is an efficient catalyst for the benzylic C – H oxidation of various arylalkanes by *tert*-butyl hydroperoxide in an aqueous solution (Scheme 61).[172] High conversions of the substrate and high yields of the reaction products were achieved. It was assumed that the reaction occurs *via* a a solvent-caged oxygen rebound mechanism through Ru^{IV} oxo intermediate species. This is evidenced by the large kinetic isotope effect for the oxidation of ethylbenzene ($k_H/k_D = 14$), the large parameter $\rho = -1.1$ in terms of linear free energy relationships and the absence of inhibition upon the addition of radical traps (*e.g.*, TEMPO) to the reaction mixture.

Scheme 61



R^1 = Me: R^2_n = 4-OMe, 4-Cl, 3,4-benzo;
R^2_n = H: R^1 = Me, Et, *etc.*

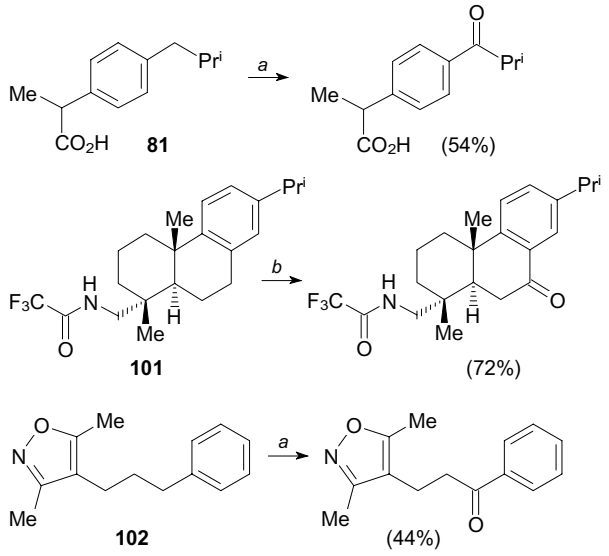
99 =



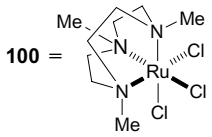
McNeill and Du Bois [173] used (1,4,7-trimethyl-1,4,7-triazacyclonane)ruthenium(III) chloride [(tmtacn)$RuCl_3$, **100**] as the catalyst for the oxidation of tertiary and benzylic C – H groups of compounds **81**, **101** and **102** by cerium(IV) ammonium nitrate (CAN). In the former two cases, the selective oxidation of the benzylic methylene group of compounds **81** and **101** in the presence of the tertiary C – H group affords the corresponding carbonyl derivatives in moderate yields (Scheme 62).

In 2013, Hsu and Plietker [174] synthesized ruthenium complex **103** with a tetradentate ligand (Scheme 63, conditions *a*). Under the optimal conditions (1 mol.% of the catalyst, benzene as the solvent, room temperature), complex **103** catalyzes the benzylic C – H oxidation by *tert*-butyl hydroperoxide. The oxidation of cyclic substrates containing an annulated aryl group [*e.g.*, tetralin (**59**)] gave ketones in 45% – 73% yields; in the case of substituted ethylbenzenes, the yields were 31% – 57%. The reaction mechanism

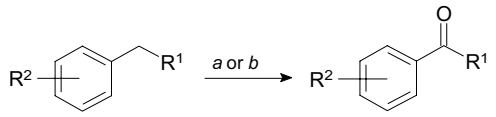
Scheme 62



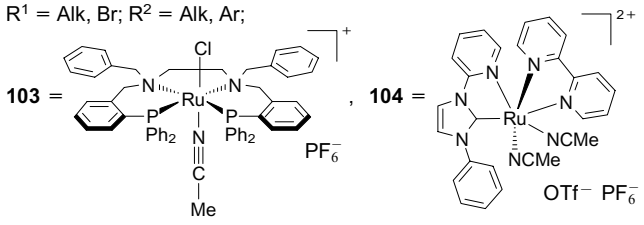
(*a*) CAN (6 equiv.), **100** (2 mol.%), $AgClO_4$ (8 mol.%), Bu^tOH-H_2O (1 : 1); (*b*) CAN (6 equiv.), **100** (4 mol.%), $AgClO_4$ (16 mol.%), Bu^tOH-H_2O (1 : 1);



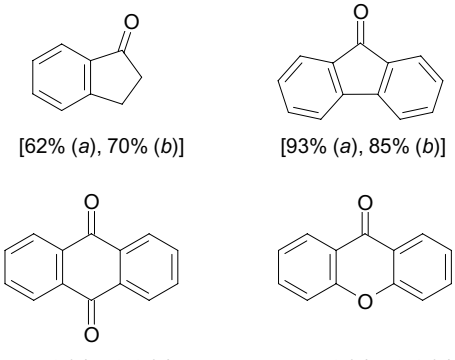
Scheme 63



(*a*) TBHP (3 – 6 equiv.), **103** (1 mol.%), PhH, 25 °C, 18 h (31% – 96% yields, 15 examples); (*b*) $NaIO_4$ (10 equiv.), **104** (3 mol.%), $MeCN-H_2O$ (2 : 1), 70 °C, 4 h (65% – 90% yields, 10 examples); R^1 = Alk, Br; R^2 = Alk, Ar;



Examples of products (conditions)



[62% (*a*), 70% (*b*)] [93% (*a*), 85% (*b*)]

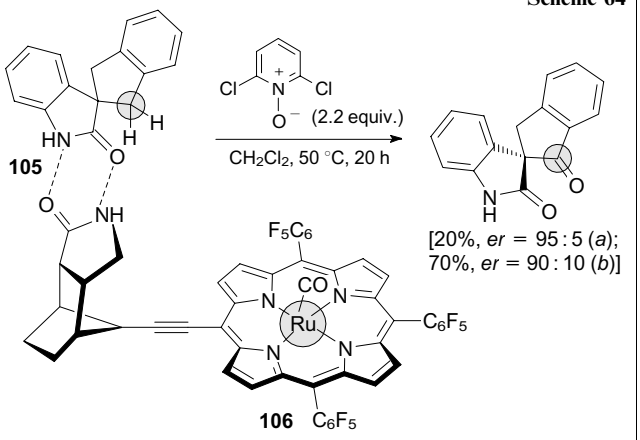
[49% (*a*), 90% (*b*)] [96% (*a*), 90% (*b*)]

was not investigated, but the authors proposed a free-radical pathway because they isolated peroxide products after the oxidation of tetrahydroquinoline derivatives. Besides, the oxidation of tertiary C – H groups, *e.g.*, of triphenylmethane, produced the corresponding triphenylmethyl hydroperoxide.

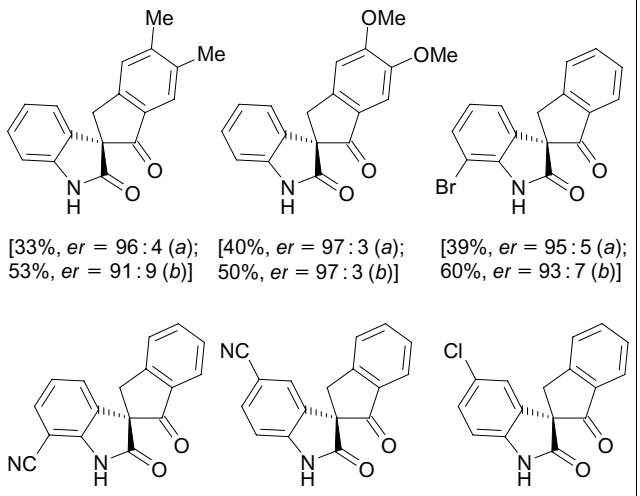
Four years later, Gupta and Choudhury [175] used ruthenium complex **104** with an NHC-carbene ligand and 2,2′-bipyridine as the catalyst for the benzylic oxidation by sodium periodate (see Scheme 63, conditions *b*). Control experiments showed that the reaction mechanism involves the formation of high-valent ruthenium dioxo complexes, the hydrogen atom transfer *via* an oxygen-rebound mechanism and the subsequent oxidation to a carbonyl compound. The formation of Ru^{VI} dioxo and Ru^{V} dioxo species from ruthenium(III) complexes in the reactions with $NaIO_4$ was confirmed by desorption electrospray ionization mass spectrometry (DESI-MS).[176]

In the past two decades, supramolecular catalytic processes have attracted considerable attention.[177, 178] The supramolecular catalysis is based on the ability of the catalyst to recognize a specific substrate *via* weak supramolecular interactions (hydrogen bonds, cation – π, CH – π and π – π interactions) and steric repulsions, which are of secondary importance in the conventional catalysis. In 2015, Bach and co-workers [179] proposed an elegant method

Scheme 64



Examples of products (conditions)



[33%, *er* = 96 : 4 (*a*); 53%, *er* = 91 : 9 (*b*)] [40%, *er* = 97 : 3 (*a*); 50%, *er* = 97 : 3 (*b*)] [39%, *er* = 95 : 5 (*a*); 60%, *er* = 93 : 7 (*b*)]

[24%, *er* = 91 : 9 (*a*); 42%, *er* = 81 : 19 (*b*)] [32%, *er* = 90 : 10 (*a*); 50%, *er* = 85 : 15 (*b*)] [35%, *er* = 80 : 20 (*a*); 59%, *er* = 74 : 26 (*b*)]

for the enantioselective oxidation of spirocyclic oxindoles **105** in the presence of 1 mol.% ruthenium porphyrin complex **106** (Scheme 64; *er* is the enantiomeric ratio). This method is based on the molecular recognition. The enantioselectivity of oxidation is provided by hydrogen bonding between the substrate and the ligand. The reaction proceeds in CH_2Cl_2 at 50 °C in the presence of 2,6-dichloropyridine *N*-oxide as the oxidant. The modification of the ligand demonstrated that the polyfluorination of aryl groups at *meso* positions of the porphyrin moiety of the ligand, on the one hand, enhances the stability of the complex towards oxidative degradation and, on the other hand, increases the electophilicity of the reactive metal oxygen species. This leads to a significant increase in the conversion of the substrate and the enantioselectivity of the process.

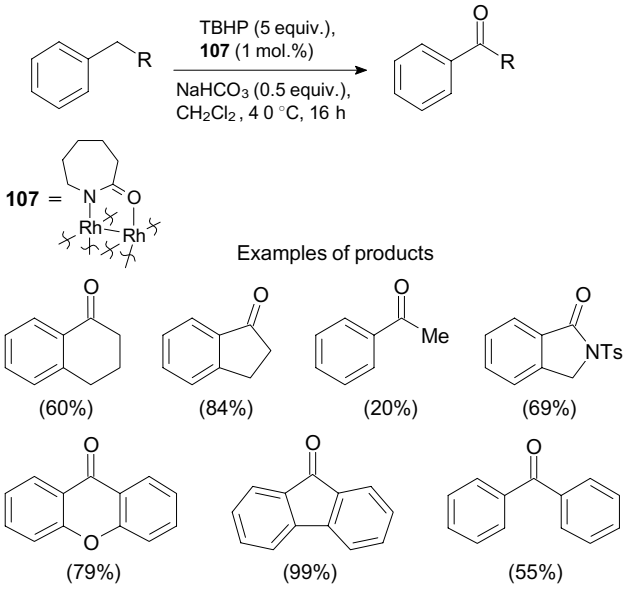
This method for the oxidation (conditions *a*) is characterized by high conversion, but the yields of the products are low because of incomplete oxidation of the alcohol intermediate. The authors performed the further oxidation of the reaction mixture. The main problem is that the ketone can undergo the retro-aldol reaction, resulting in racemization of the product. The best outcome was obtained with the use of pyridinium chlorochromate (PCC) as the oxidant (conditions *b*). Presumably, the oxidation occurs through the formation of the Ru^V oxo complex and the oxygen atom transfer *via* an oxygen-rebound mechanism. This is consistent with experimental results and DFT quantum chemical calculations.

2.2.6. Oxidation in the presence of rhodium compounds

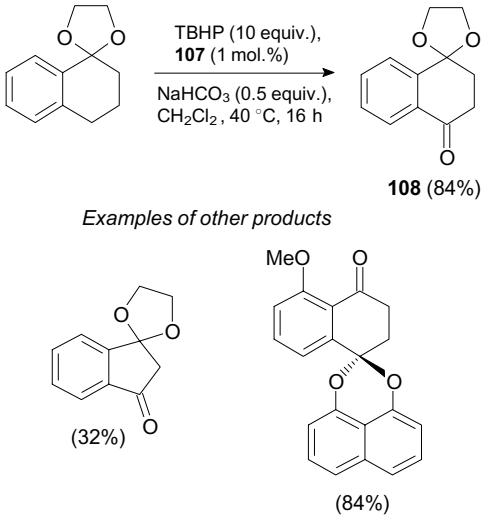
Doyle and co-workers[180] used dirhodium caprolactam [$Rh_2(cap)_4$, **107**] as the catalyst for the benzylic oxidation by *tert*-butyl hydroperoxide. High conversions (> 95%) and high product yields were achieved for most substrates (Scheme 65). Substrates containing strong coordinating groups (pyridine, nitrile) or strong electron-withdrawing substituents were not oxidized under these conditions.

This method was successfully applied to oxidize benzylic CH_2 groups of acetals and ethers (Scheme 66) and can be used to synthesize diketones (after the removal of the dioxolane protecting group, for example, in compound **108**).[180]

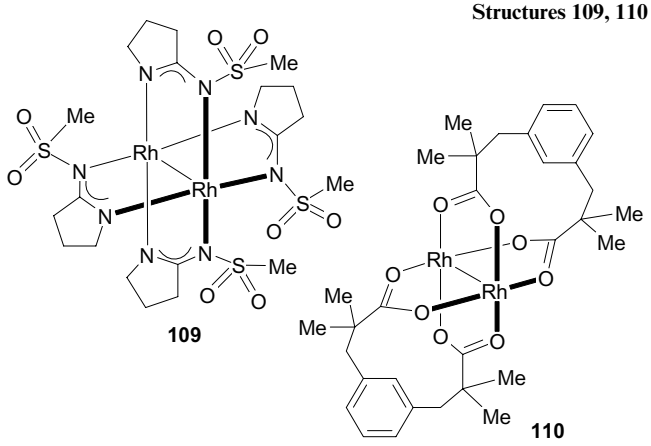
Scheme 65



Scheme 66



Structures 109, 110



Later, similar catalysts based on binuclear rhodium with other ligands, such as (2-sulfonylimino)pyrrolidines [*e.g.*, $Rh_2(Msip)_4$, **109**][181] and tetramethyl-substituted *m*-benzenedipropionic acid [Du Bois's catalyst, $Rh_2(esp)_2$, **110**],[182] were tested as catalysts for the benzylic oxidation by *tert*-butyl hydroperoxide. Complex **110** makes it possible to decrease the amount of the catalyst to 0.1 mol.%, but leads to some decrease in the selectivity of the process.

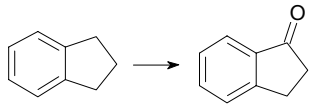
In 2013, dirhodium(II) complexes with NHC-carbene ligands were utilized for the first time in allylic and benzylic C – H oxidation by *tert*-butyl hydroperoxide.[183] These complexes exhibit catalytic activity in the oxidation of arylalkanes similar to that of compound **107** but they significantly increase the efficiency of the oxidant. Thus, the oxidation of fluorene by TBHP (1 equiv.) in the presence of the complex [$Rh_2(OAc)_4(IPr)$] [IPr is 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene] afforded fluorenone (**18**) in 83% yield, whereas this reaction in the presence of catalyst **107** gave the target product in 43% yield.

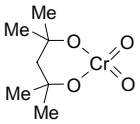
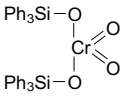
2.2.7. Oxidation in the presence of other metal compounds

The catalytic C – H oxidation of alkanes in the presence of chromium(VI) compounds, primarily allylic and benzylic oxidation reactions, have been known since the 1980s. The research group of Muzart made a significant contribution to the investigation and development of these reactions (see, for example, the review[184]). Selected chromium(VI) com-

pounds, which were tested by Muzart and co-workers [184–186] and by other research teams [187–189] as catalysts for the benzylic oxidation by *tert*-butyl hydroperoxide, are presented in Scheme 67. Chromium(VI) compounds can act as catalysts for the benzylic oxidation by other oxidizing agents. For example, pyridinium dichromate catalyzes the oxidation of arylalkanes by sodium percarbonate ($Na_2CO_3 \cdot 1.5\,H_2O_2$);[190] CrO_3 catalyzes the oxidation by periodate (H_5IO_6).[191]

Scheme 67

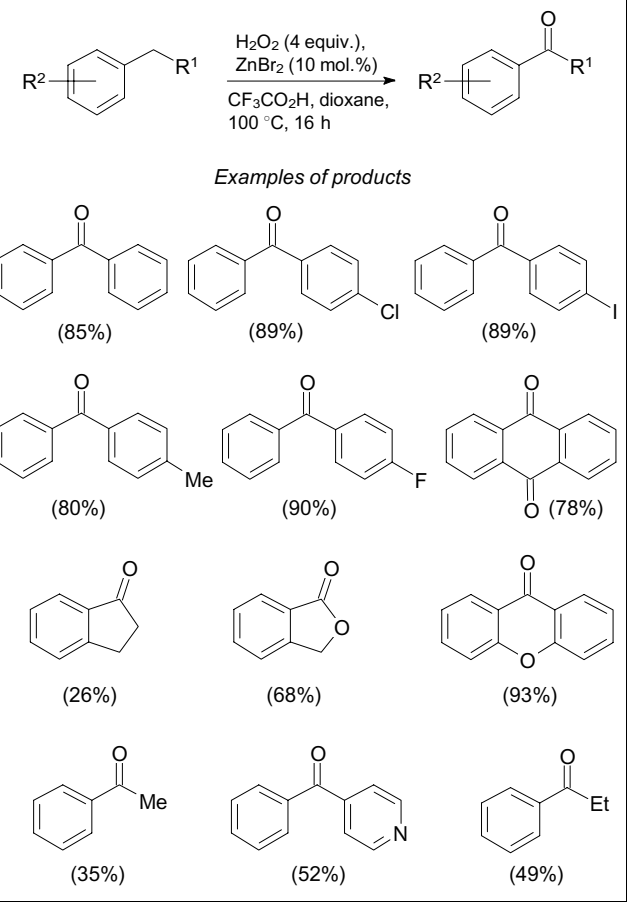


Catalyst (amount, equiv.)	Oxidant (amount, equiv.)	Conditions	Yield (%)
 (0.1)	anhydrous. TBHP (7)	CH_2Cl_2, 0 °C, 8 h	60
 (0.05)	70% aq. TBHP (4)	CH_2Cl_2, rt, 24 h	86
 (0.05)	70% aq. TBHP (4)	$PhCF_3$, rt, 21 h	92

In 2012, Wu [192] reported a method for the zinc-catalyzed benzylic oxidation by hydrogen peroxide (Scheme 68). It was shown that diphenylmethanes containing different substituents are oxidized to benzophenones with high yield and selectivity. The reaction of 9,10-dihydroanthracene is accompanied by excessive oxidation to form anthraquinone as the major product in 78% yield. Apart from substrates with aromatic substituents, this method can be employed to oxidize a number of alkylarenes in moderate yields. For instance, acetophenone and propiophenone were prepared with high selectivity in 35% and 49% yields, respectively.

In 1999, Yamazaki [193] described the benzylic C–H oxidation by sodium hypochlorite in the presence of the nickel complex $Ni(bpy)_2Cl_2$ (bpy is 2,2′-bipyridine). Under these conditions, various toluene derivatives are oxidized to the corresponding benzoic acids in 85%–98% yields; ethylbenzene gives a mixture of benzoic acid and acetophenone in a ratio of 1 : 1 (in a total yield of 89%). The highest yields of reaction products were achieved in the oxidation of electron-deficient substrates. It was assumed that the reaction of the oxidant with the starting complex generates catalytically active $LNi^{IV}{=}O$ or $LNi^{III}OCl$ oxo species. The initial step of substrate oxidation apparently involves the abstraction of a benzylic hydrogen atom by the $LNi^{IV}{=}O$ species or the $OCl^{\bullet}$ radical, which is generated through the dissociation of $LNi^{III}OCl$. The proposed free-radical mechanism is supported by the fact that the reaction affords α-chlorine-substituted alkylbenzenes as by-products.

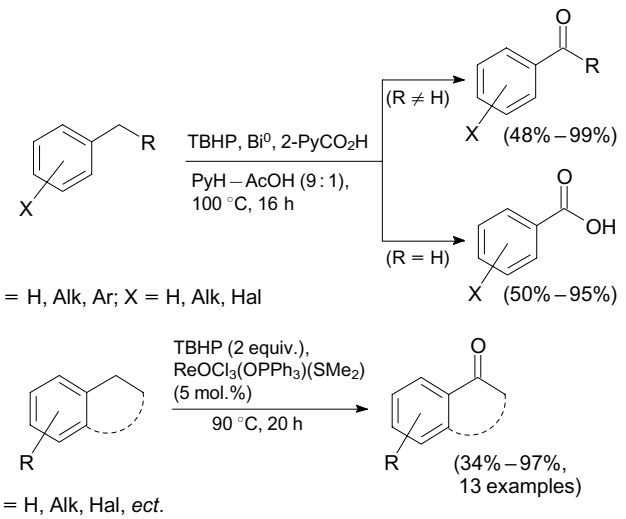
Scheme 68



In 2005, Bonvin *et al.*[194] developed a method for the oxidation of alkylarenes to ketones by *tert*-butyl hydroperoxide in the presence of bismuth(0) and α-picolinic acid in a mixture of pyridine and acetic acid (Scheme 69). Ketones were obtained in yields from 48% to 99%. The oxidation of methylarenes gives benzoic acids in high yields. It was suggested that the oxidation occurs by a free-radical mechanism.[195]

In 2012, Zhu and co-workers [196] reported an efficient procedure for the oxidation of the benzylic methylene group

Scheme 69

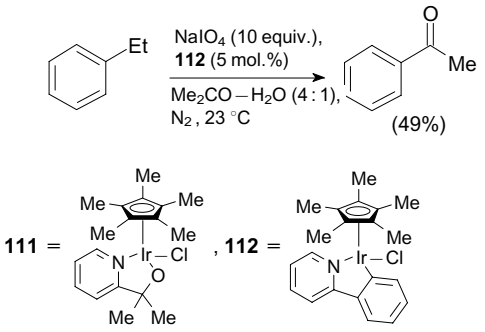


of arylalkanes by TBHP in the presence of the rhenium(V) complex $ReOCl_3(OPPh_3)(SMe_2)$ (see Scheme 69).

Gold(III) compounds can also be used as catalysts for the benzylic oxidation of arylalkanes. For instance, 5 mol.% potassium tetrachloroaurate(III) ($KAuCl_4 \cdot 0.5\,H_2O$) catalyzes the oxidation of the benzylic methylene group by *tert*-butyl hydroperoxide (2 equiv.) in pyridine to form carbonyl derivatives.[197] The reactions of diarylmethane derivatives give ketones in 66% – 99% yields; the oxidation of less reactive substrates containing one aryl group (indane, tetralin, *etc.*) affords products in yields from 57% to 65%.

In 2010, Crabtree and co-workers[198,199] used iridium(III) cyclopentadienyl complexes **111** and **112** (Scheme 70) as catalysts in C – H oxidation reactions. Initially, cerium(IV) ammonium nitrate was utilized as the stoichiometric oxidant. Later, sodium periodate ($NaIO_4$) was shown to be a more efficient oxidant providing higher selectivity.[199] This method can be employed to oxidize various alkanes to carbonyl compounds. For example, ethylbenzene is oxidized in the presence of complex **112** to give acetophenone in 49% yield (TON 10); the oxidation of ethane provides acetic acid in 25% yield (TON 3.9). The mechanism for the oxidation in the presence of iridium complexes is unclear. Iridium(V) oxo complexes were considered as possible key intermediates in the C – H oxidation; however, the known iridium oxo complex $[(Mes)_3Ir^V{=}O]$ (Mes = 2,4,6-$Me_3C_6H_2$) revealed no activity in the catalytic oxidation of alkanes.[200]

Scheme 70

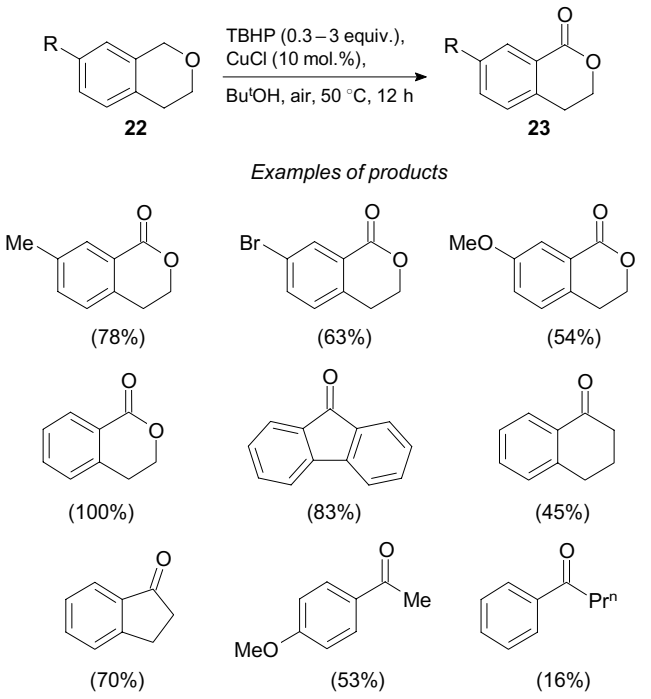


2.2.8. Transition metal-promoted oxidation by oxygen

Many oxidation reactions with molecular oxygen proceed with the participation of NHPI in the presence of transition metal salts (Co^{II},[92,201–204] Cu^I/Cu^{II},[205,206] Fe^{III},[207] V^{IV},[208] Mg^{II},[209] *etc*). Methods for the homogeneous benzylic oxidation by molecular oxygen are discussed in the review,[210] which summarizes the data published in the period from 2000 to 2018. Biomimetic aerobic oxidation reactions and the mechanisms of oxidation by methane monooxygenases and biomimetic complexes are considered in a review.[211] Selected methods for the oxidation in the absence of NHPI are outlined below.

Catalysts based on copper compounds are commonly included in catalytic systems for aerobic oxidation. In 2017, Kanai and co-workers[212] proposed a CuCl – TBHP system, which proved to be efficient in the oxidation of benzylic methylene groups of isochromanes **22** giving lactones **21** in high yields (Scheme 71). Under these conditions, the oxidation of compounds containing benzylic methylene groups, which have no C – O bonds or the second aryl moiety, afford ketones in much lower yields.

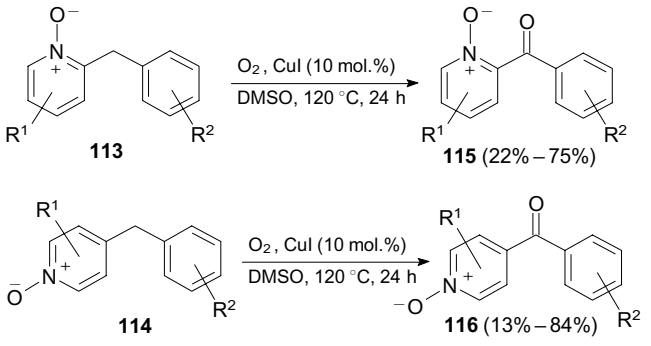
Scheme 71



The methylene group of benzylpyridine *N*-oxides **113** and **114** is oxidized by atmospheric oxygen using copper(I) iodide as the ligand-free catalyst (Scheme 72).[213] The reaction affords benzoylpyridine *N*-oxides **115** and **116**, which can be functionalized in different ways (for example, by the reduction of the carbonyl group, *via* cross-coupling resulting in C – C or C – N bond formation in the α position of the pyridine ring, *etc.*) and transformed into biologically active compounds. A new method was proposed for the synthesis of the antihistamine Acrivastine (**117**) from available 2-picoline *N*-oxide (**118**) *via* three consecutive activated C – H functionalization processes (Scheme 73).[213] The classical route for the synthesis of Acrivastine is based on less available 2,6-dibromopyridine and proceeds through compound **119** to give the target product in lower yield.[214,215]

Earlier, copper(I) iodide and iron(II) chloride ($FeCl_2 \cdot 4\,H_2O$) were employed as catalysts for the aerobic oxidation of benzylpyridines **25** in DMSO at 100 °C in the

Scheme 72



113, **115**: R^1, R^2 = Me, Cl, OMe, CO_2Me, CN, CF_3 (in different positions);
114, **116**: R^1, R^2 = Me, Cl, OMe, CN, NO_2 (in different positions)

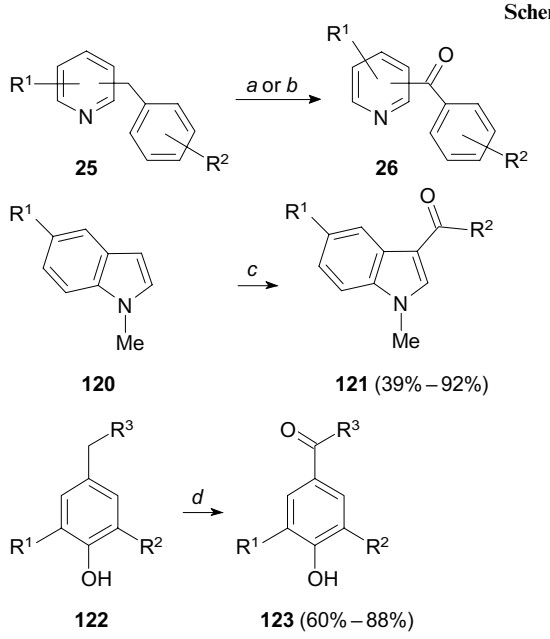
presence of acetic acid (1 equiv.) to form benzoylpyridines **26**.[216,217] Besides, copper(II) chloride in the presence of ethyl chloroacetate[218] and the $CuBr \cdot SMe_2$ – 1,4-diazabicyclo[2.2.2]octane (DABCO) system[219] were tested as catalysts for the C – H oxidation of methylene groups of *N*-heterocyclic compounds, pyridines **25** and indoles **120**, respectively (Scheme 74). Ketones **26** and **121** were obtained in relatively high yields.

Methyl and methylene groups in *para* positions of sterically hindered phenols **122** are oxidized by atmospheric oxygen in the presence of copper(II) acetate in ethylene glycol to form carbonyl derivatives **123** (see Scheme 74).[220]

Copper(II) compounds [the $CuCl_2$ – 18-crown-6 system or $Cu(OAc)_2$] in the presence of acetaldehyde were used in the catalytic C – H oxidation by molecular oxygen (1 atm) at 70 °C.[221,222] The process is characterized by high turnover numbers (TON up to 3.9×10^4) but moderate ketone selectivity [the ketone to alcohol yield ratio was 4.5 – 6 for the $CuCl_2$ – 18-crown-6 system and 1.3 – 1.8 for $Cu(OAc)_2$]. Presumably, the oxidation occurs through the formation of peracid, which is produced by oxidation of aldehyde with divalent copper(II) compounds and oxygen and which then generates copper oxo species (L)Cu(II) – O$^{\bullet}$ directly involved in the C – H bond cleavage of the substrate.

An interesting example of C – H oxidation was reported by Xiao and co-workers[223] in 2014. They synthesized new catalysts based on iron complexes with tridentate pyridine bis(sulfonylimidazolidine) ligands **124**, which can catalyze the chemoselective α-oxidation of a series of cyclic ethers by oxygen (Scheme 75). An unusual fact is that molecular hydrogen is released as a by-product, as opposed to the oxidation by metalloenzymes and biomimetic catalysts based on iron complexes. The oxidation of isochromanes **22** occurs with high chemoselectivity to form compounds **23** and also ethers in small amounts. The yields of oxidation products strongly depend on the electronic effects of substituents on the aromatic ring. The highest catalyst turnover numbers were observed for substrates containing electron-withdrawing substituents, whereas the presence of electron-donating substituents leads to the opposite outcome. Under these conditions, ketones were synthesized from isochromane analogues **22** containing a five-membered oxygen-containing ring and(or) a pyridine moiety instead of the benzene ring (see Scheme 75).

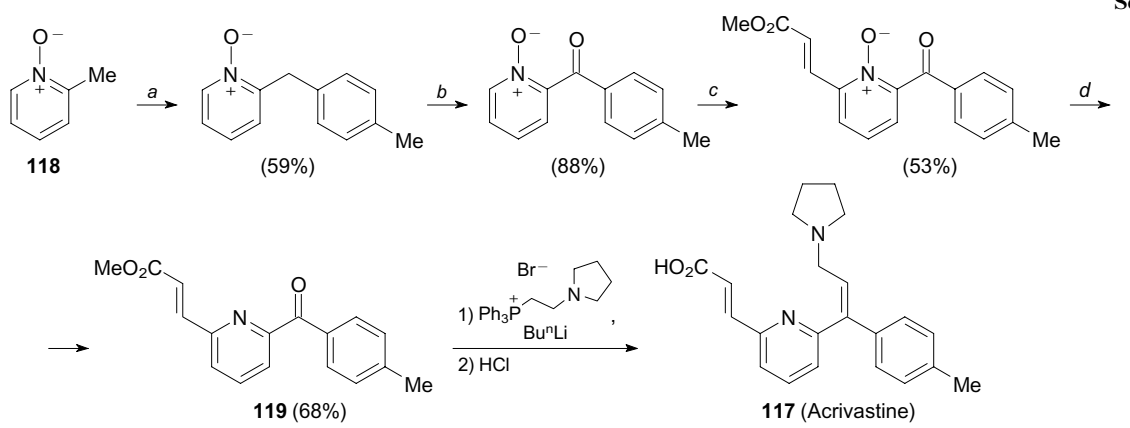
Scheme 74



(*a*) O_2 (1 atm), CuI (10 mol.%), AcOH (1 equiv.), DMSO, 100 °C, 24 h (R^1 = H: R^2 = H, 4-Me, 4-Hal, *etc.*; 61% – 97% yields);
(*b*) O_2 (1 atm), $CuCl_2 \cdot 2H_2O$ (10 mol.%), $ClCH_2CO_2Et$ (1 equiv.), DMF, 130 °C, 24 h (R^1 = R^2 = H, Cl; 66% – 92% yields);
(*c*) $CuBr \cdot SMe_2$ (15 mol.%), DABCO (0.25 equiv.), DMSO, 100 °C;
(*d*) air, $Cu(OAc)_2$ (1 mol.%), ethylene glycol, 50 – 100 °C;
120, **121**: R^1 = H, OMe, Br; R^2 = H, Me, Ph, 4-Py;
122, **123**: R^1, R^2 = Me, Bu^t, OMe, F, Cl, Br, CN; R^3 = H, Me, Et, Pr^i, Bu^n, Bu^t, Bn, Ph

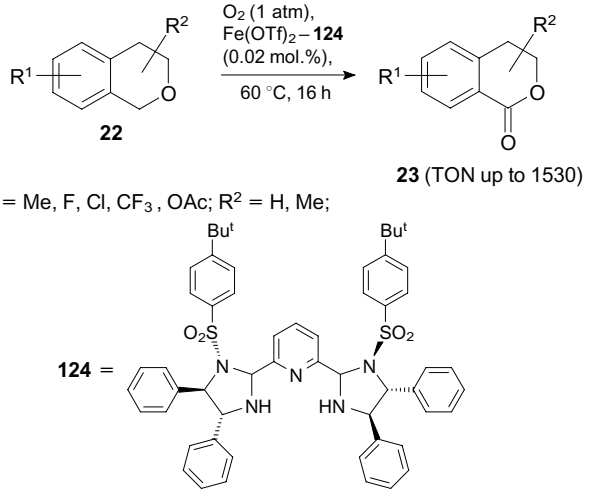
Domínguez and co-workers[224] found that palladium acetate in the presence of triazole bidentate ligand **125** at very low concentrations can catalyzes benzylic oxidation of arylalkanes by molecular oxygen (Scheme 76). This approach was tested with a small series of substrates [ethylbenzene, diphenylmethane, benzyl phenyl ketone, fluorene, 9,10-dihydroanthracene, xanthene (**57**)]. In all cases, the yields of ketones were higher than 90%. Previously, this research team[225] proposed a procedure using ligand **125** and $NiBr_2$ under similar conditions and prepared aryl ketones in 50% – 98% yields.

Scheme 73

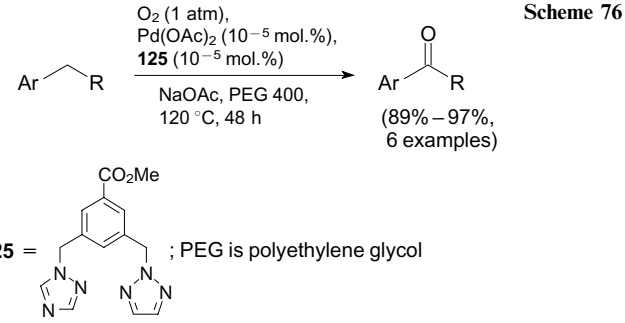


(*a*) 4-ClC_6H_4Me (0.5 equiv.), $Pd_2(dba)_3$ (2.5 mol.%), XPhos (5 mol.%), Bu^{t}ONa (3 equiv.), PhMe, 110 °C, 24 h; (*b*) O_2, CuI (10 mol.%), Bu^{t}OAc, 120 °C, 24 h; (*c*) $MeO_2CCH{=}CH_2$ (0.25 equiv.), $Pd(OAc)_2$ (15 mol.%), PyH (0.25 equiv.), $AgCO_3$ (0.37 equiv.), dioxane, 120 °C, 24 h;
(*d*) PCl_3 (3 equiv.), $CHCl_3$, 80 °C, 1 h; dba is dibenzylideneacetone, XPhos is 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl

Scheme 75

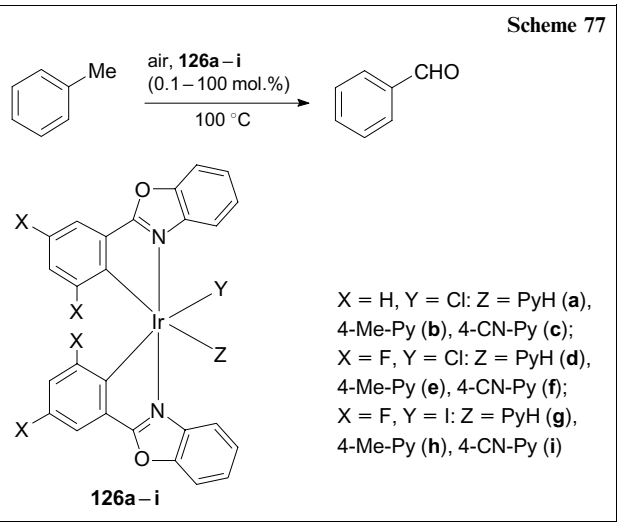


Scheme 76



Chen and co-workers [226] synthesized a series of iridium complexes **126a – i** of the general formula $[(C^{\wedge}N)_2Ir(Y)(Z)]$, where C^N is a monoanionic bidentate cyclometalating ligand, Y = Cl or I, Z is pyridine or its derivatives, 4-cyano- (4-CN-Py) and 4-methylpyridine (4-Me-Py). These complexes were employed to transform toluene into benzaldehyde by the reaction with molecular oxygen at 100 °C with high catalytic performance (the substrate conversion 1.55% – 4.66%, TON was 1460 – 2810; in some cases, TON reached 4200) (Scheme 77).

Scheme 77



2.3. Photocatalytic oxidation

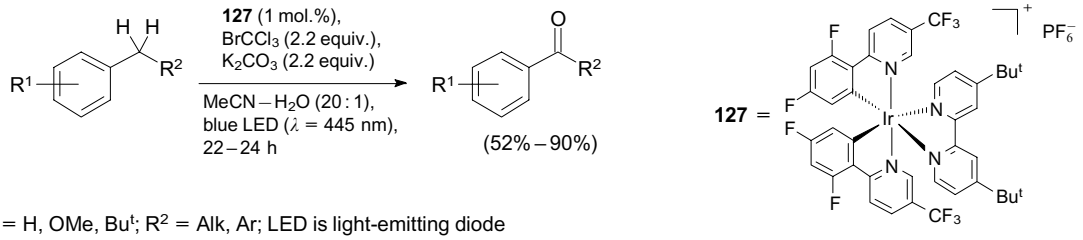
In the past decades, visible-light photoredox catalysis was a rapidly emerging field in organic synthesis.[227, 228] Photocatalysis served as the basis for several promising approaches to oxidation of benzylic $C(sp^3)-H$ groups.[229 – 241] For instance, Pandey *et al.*[235] described the visible light-mediated photocatalytic activation of the benzylic C – H bond in the presence of iridium complex **127** (Scheme 78). The proposed reaction mechanism involves the Ir^{III}/Ir^{IV} catalytic cycle, including a single-electron transfer from the substrate to metal to form the radical cation and subsequent hydrogen atom abstraction by the $Cl_3C^{\bullet}$ radical followed by hydration of the resulting cation to form benzylic alcohol. The latter is oxidized to a carbonyl compound.

The visible light-mediated aerobic oxidation is an attractive strategy from the viewpoint of green chemistry principles applied to organic synthesis. The design of photocatalytic systems has attracted great attention. Efforts were made to improve the selectivity, increase product yields and extend the applicability of these approaches to different substrates. Lei and co-workers [232] proposed a procedure for the synthesis of diaryl ketones by the oxidation of diarylalkanes by molecular oxygen in the presence of 9-mesityl-10-methylacridinium perchlorate (**128**) as the visible light organic photocatalyst (Scheme 79).

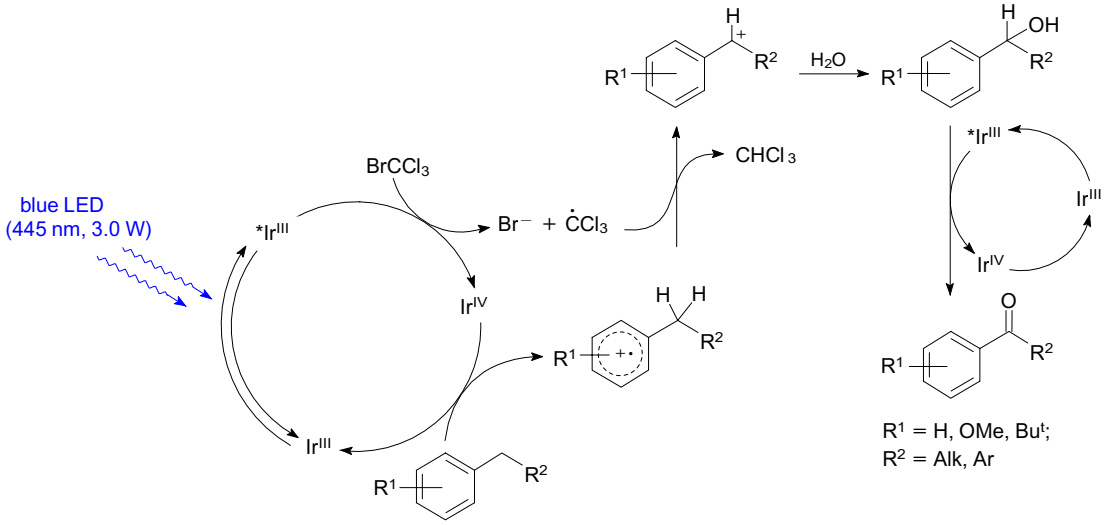
Kanai and co-workers [231] designed a system based on a ruthenium(II) tris(bipyridyl) complex and tetrakis(acetonitrile)copper(I) triflate for the selective photooxidation of substituted fluorenes under mild conditions (Scheme 80). This method proved to be applicable to a wide range of derivatives giving fluoren-9-ones **18** ($R^1 = R^2 = R^2 = H$) and **129** in moderate to high yields.

In 2016, Mühldorf and Wolf [236] described a system for the visible light-mediated benzylic oxidation by oxygen in the presence of riboflavin tetraacetate **130** combined with iron complex **131** (2 mol.%) as the photocatalyst (Scheme 81). The reaction mechanism was proposed. Under visible light irradiation, riboflavin activates oxygen and oxidizes the substrate. This is accompanied by the formation of H_2O_2 as a by-product, which can degrade the photocatalyst. Iron complex **131** was utilized to avoid the latter process. Complex **131** catalyzes the oxidation of the

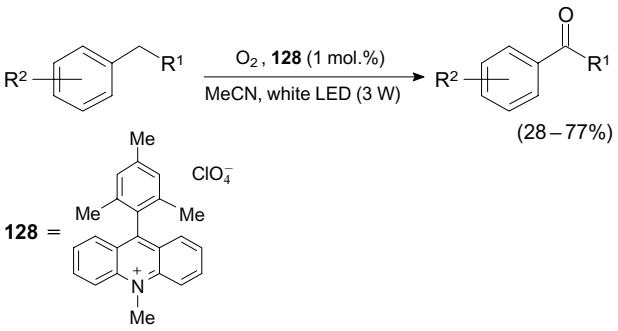
Scheme 78



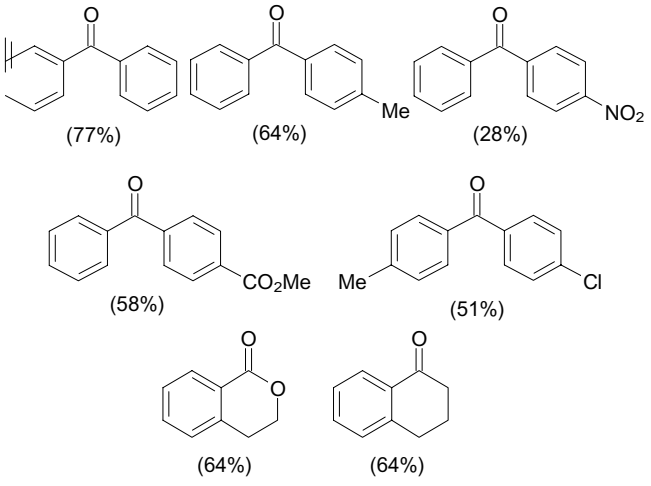
R^1 = H, OMe, Bu^t; R^2 = Alk, Ar; LED is light-emitting diode



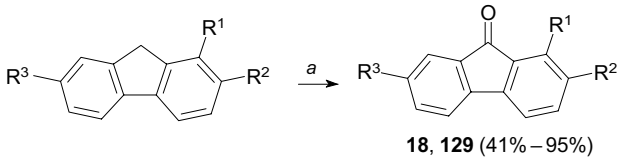
Scheme 79



Examples of products



Scheme 80



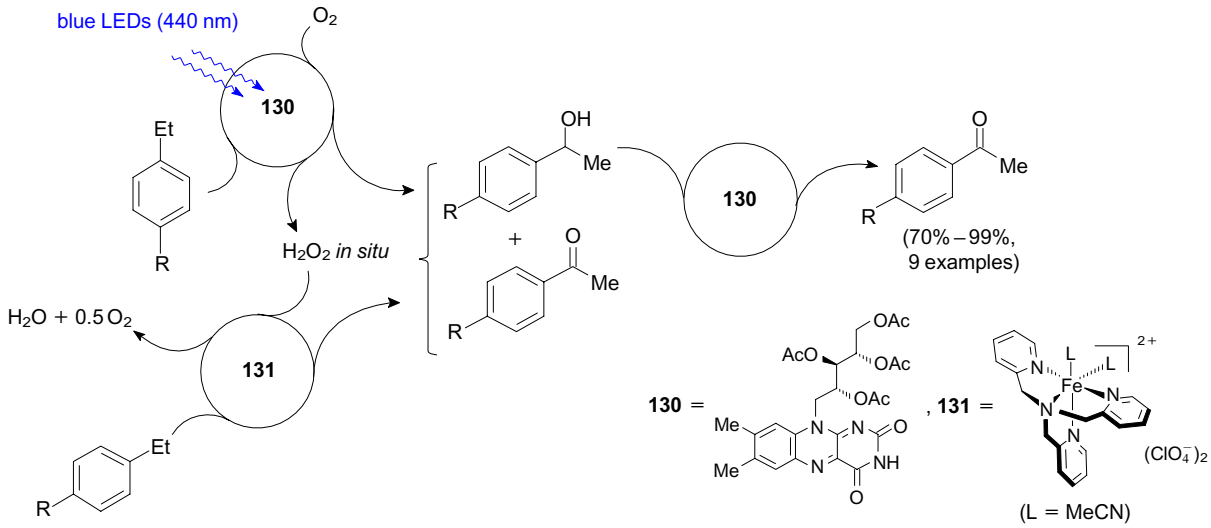
(*a*) O_2 (1 atm), $Ru(bpy)_3Cl_2 \cdot 6H_2O$ (1.5 mol.%), $Cu(MeCN)_4OTf$ (1.5 mol.%), MeCN, white LED, 25 °C;
R^1 = H, CO_2Me, $C(O)NMe_2$; R^2 = H, CHO, Ac, NHAc, NO_2, F, Br, I, Ph; R^3 = H, Br, Bu^t

substrate by hydrogen peroxide and disproportionation of H_2O_2. The method was tested with a small number of substrates. Aryl ketones were obtained in yields from 70% to 99%.

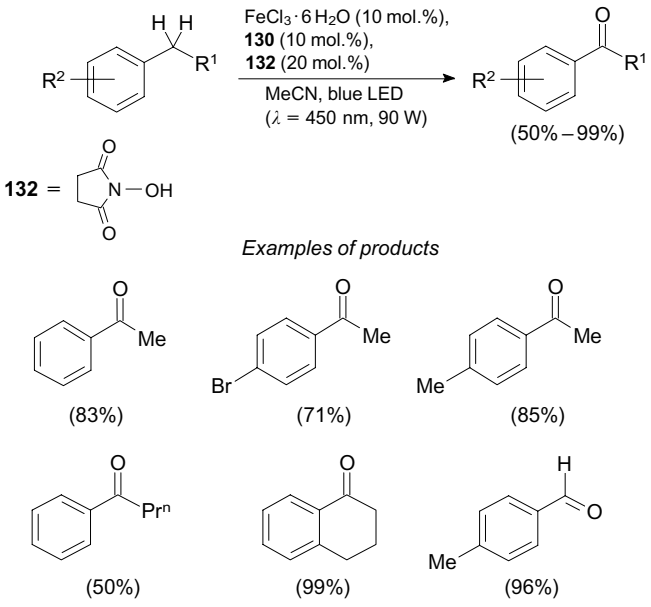
Subsequently, Sun and co-workers[240] improved the method for photooxidation of benzylic methylene groups in the presence of riboflavin by using *N*-hydroxysuccinimide (**132**) in the presence of iron(III) chloride instead of scandium triflate[234] or biomimetic iron complex **131**.[236] This method proved to be applicable to a wide range of substrates, providing high yields of ketones (Scheme 82).

A method was developed for the photochemical aerobic oxidation of alkylbenzenes in the presence of iron(III) chloride and lithium bromide in acetonitrile at room temperature (Scheme 83).[239] This method has significant advantages over methods for the photooxidation proposed previously, providing product yields and selectivity comparable to those of similar methods, which utilize complexes based on platinum metals and organic additives. It was

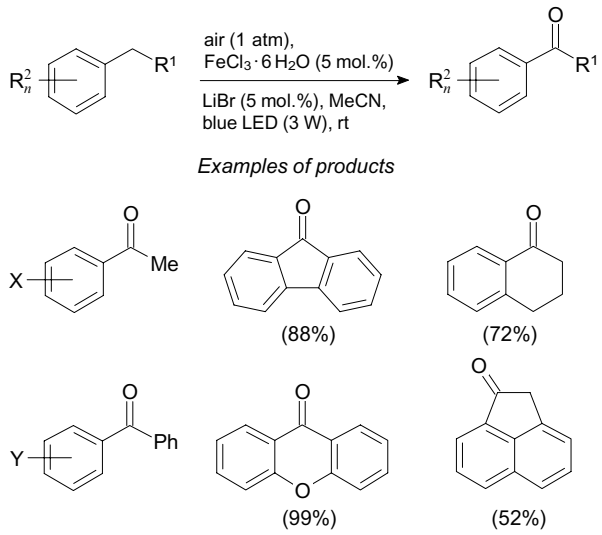
Scheme 81



Scheme 82



Scheme 83

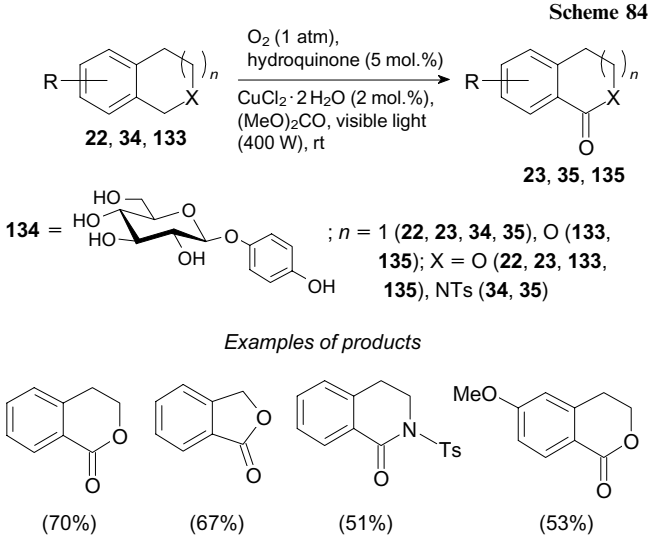


X = H (93%), 4-Cl (71%), 4-Br (67%), 3-Br (78%), 2-Br (79%), 4-Et (68%), 4-OMe (74%), 3-CN (35%); Y = H (76%), 4-Cl (79%), 4-NO_2 (54%)

assumed that tetrahaloferrate(III) generated in the system is transferred to an excited state under visible light irradiation and oxidizes the substrate *via* a single-electron transfer.

Moody and co-workers [241] performed visible light-mediated aerobic oxidation of methylene groups of cyclic benzyl ethers **22** (X = O, n = 1) and **133** (X = O, n = 0) and benzyltosylamines **34** (X = NTs, n = 1) in the presence of 1,4-hydroquinone [which can be generated *in situ* from natural β-D-glucopyranoside arbutin (**134**)] and copper(II) chloride as an electron-transfer mediator in dimethyl carbonate (Scheme 84). Advantages of this method are the use of available arbutin as an oxidant precursor and the utilization of a simple electron-transfer mediator and environmentally benign dimethyl carbonate as the solvent. The investigation of the reaction mechanism suggested that the oxidation occurs through a hydrogen atom abstraction from the substrate by benzoquinone in the photoexcited triplet state to form the benzylic radical, which reacts with molecular oxygen. Apart from cyclic products **23**, **35** and **135**, xanthone (**58**) and methyl 4-methoxybenzoate were

Scheme 84



obtained under similar conditions in 87% and 64% yields, respectively.

Photocatalytic methods have shown great promise for the selective oxidative C–H activation of organic compounds. Extensive literature on the visible light-mediated photocatalytic aerobic oxidation have appeared in the past decade. The main drawback of this approach is low selectivity of C–H oxidation of substrates containing different functional groups. Attempts to perform direct aerobic hydroxylation of methylene groups under photoredox catalysis failed.

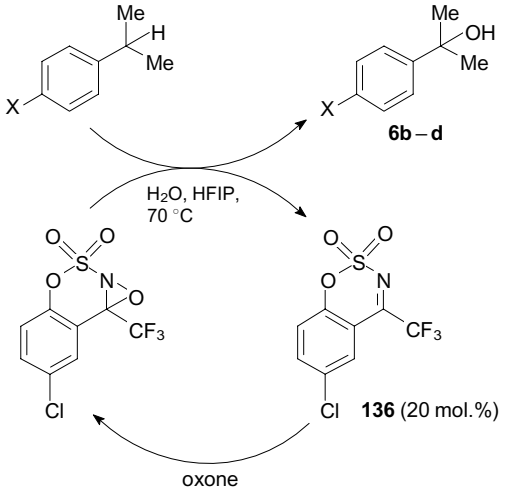
3. Oxidation of arylalkanes to benzylic alcohols

A large number of benzylic C–H hydroxylation reactions were published in the literature. Achieving high selectivity towards the major product formation in benzylic C–H hydroxylation is a more difficult problem compared to the C–H oxidation of benzylic derivatives to carbonyl compounds, which is attributable to a number of factors. The hydroxylation of methylene groups affords secondary alcohols containing an activated (weaker) C–H bond compared to the starting substrate and, hence, it is susceptible to further oxidation giving ketones. On the other hand, intermediates can undergo rearrangements to form carbonyl compounds *via* oxidation of tertiary C–H groups. Sections 3.1 and 3.2 deal with oxidation reactions of arylalkanes producing benzylic alcohols in the absence or in the presence of transition metal compounds, respectively.

3.1. Transition metal-free hydroxylation of arylalkanes

This Section considers C–H-hydroxylation reactions that occur under transition metal-free conditions. Peracids, dioxiranes and fluorinated oxaziridines can serve as stoichiometric oxidants in these processes. For instance, Du Bois and co-workers [136, 242] described the catalytic hydroxylation of cumene analogues with oxone at the tertiary and benzylic C–H positions of hexafluoroisopropanol in the presence of benzoxathiazine **136** as the catalyst giving alcohols **6b–d** (Scheme 85).

Scheme 85



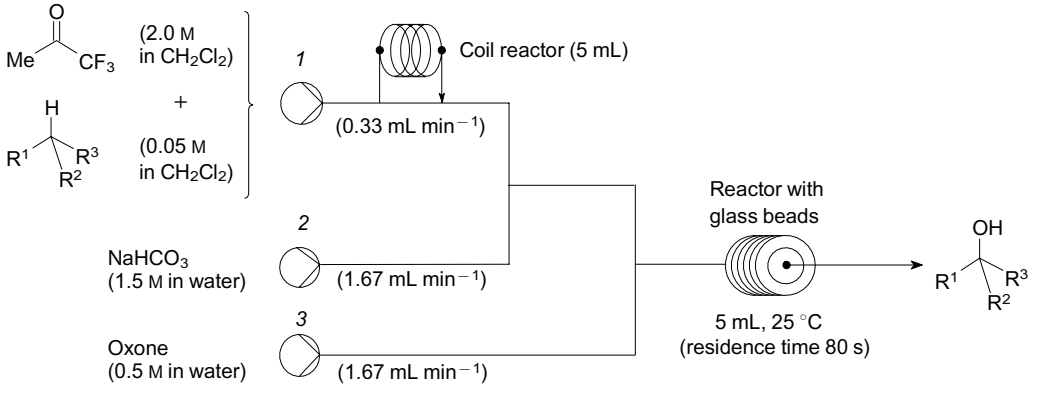
X = OSO_2Me (**b**, 55%), NO_2 (**c**, 50%), CN (**d**, 43%)

In 2019, Pasau and co-workers [243] proposed a method for the C(sp^3)–H oxidation by *in situ* generated TFDO using the flow chemistry technology. Methyl(trifluoromethyl)dioxirane was prepared by the reaction of trifluoroacetone with $NaHCO_3$ and oxone (Scheme 86; *1–3* are vessels). This method was employed to oxidize gram amounts of adamantane (96% yield) and other compounds containing the benzylic tertiary C–H group (yields from 27% to 56%).

3.2. Benzylic hydroxylation in the presence of transition metal complexes

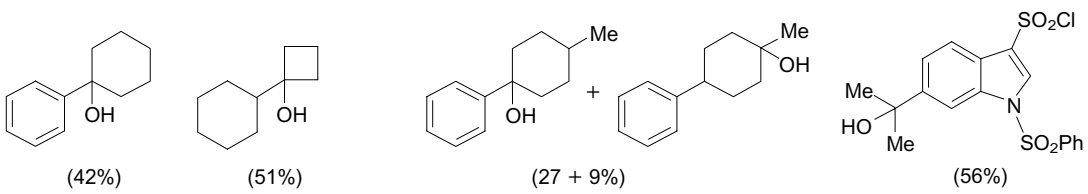
The development of a strategy for the regio- and stereoselective C–H-oxidation is an ambitious and challenging goal in synthetic chemistry. In biological systems, these processes are efficiently catalyzed by enzymes, such as cytochrome P450 and methane monooxygenase (MMO). In recent years, great attention has been paid to biomimetic porphyrin, salen and aminopyridine (in particular, chiral)

Scheme 86



1–3 are vessels

Examples of products

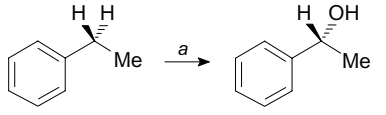


complexes of transition metals capable of catalyzing enantioselective hydroxylation.[244] Apart from iron complexes, manganese and ruthenium complexes are extensively examined as catalysts for the C – H oxidation. In these processes, NaClO and PhIO are most commonly employed as oxidants. However, recent years have witnessed increasing use of green oxidants such as hydrogen peroxide and molecular oxygen.[245] Generally, the oxidation in the presence of biomimetic complexes occurs in a manner similar to the oxidation in the presence of cytochrome P450, in which reactive metal oxygen species interacts with a C – H group *via* an oxygen-rebound mechanism (see Scheme 31).

3.2.1. Benzylic hydroxylation in the presence of iron complexes

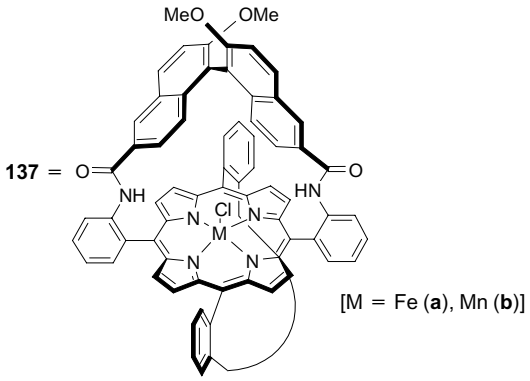
The first example of the non-enzymatic catalytic asymmetric benzylic C – H hydroxylation was reported in 1990 by Groves and Viski,[246] who synthesized iron complex **137a** containing a porphyrin ligand and chiral binaphthyl moieties (Scheme 87). The oxidation of ethylbenzene by PhIO occurred with an enantioselectivity of 40% (the product yield was 40%, alcohol : ketone = 2.3). Under these conditions, the highest selectivity towards alcohol formation (alcohol : ketone = 20.2) was achieved in the oxidation of tetralin (47% yield, 72% *ee*). The authors suggested that the formation of ketone occurs *via* the decomposition of a radical intermediate rather than through the further oxidation of the resulting alcohol. The reaction catalyzed by manganese complex **137b** afforded alcohol in higher yield but the selectivity towards the alcohol formation was lower (alcohol : ketone = 1.3 – 4.5).

Scheme 87



(40%, 40% *ee*)

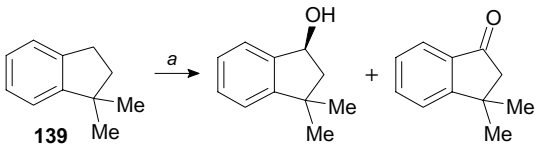
(*a*) PhIO, **137a**, CH_2Cl_2, 0 °C (**137a** : PhIO : substrate = 1 : 100 : 1000);



[M = Fe (**a**), Mn (**b**)]

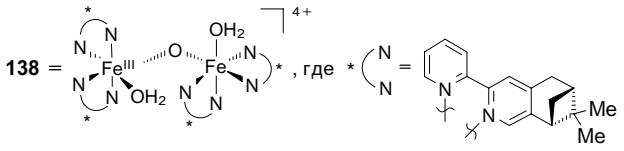
In 2000 Ménage and co-workers[247] reported the first example of utilization of non-haem (non-porphyrin) iron complexes as catalysts for the stereoselective hydroxylation of alkanes with hydrogen peroxide. The benzylic C – H hydroxylation was performed in the presence of binuclear iron μ-oxo complex **138** with the 4,5-(–)-pinene-2,2′-bipyridine ligand, which mimics the active site motif of soluble methane monooxygenase (Scheme 88). The enantioselectivity of this process was low: 7% for the oxidation of ethylbenzene and 15% in the case of 2,2-dimethylindane (**139**) (alcohol : ketone = 1.8 : 1.5).

Scheme 88



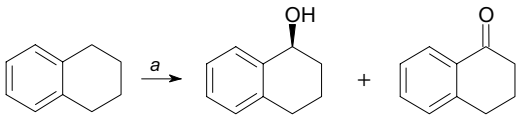
(48%, 15% *ee*)

(*a*) H_2O_2, **138**, MeCN, argon, rt (**138** : H_2O_2 : substrate = 1 : 10 : 1100);



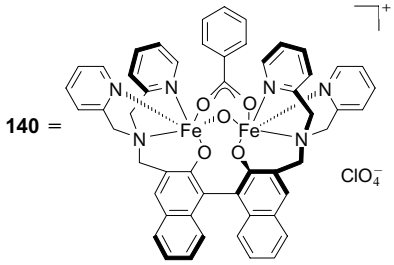
Itoh and co-workers[248] evaluated the catalytic activity of binuclear iron(III) complex **140** with chiral binaphthol ligands (Scheme 89) using mCPBA as the oxidant. The enantioselectivity of benzylic hydroxylation of tetralin (**59**) was lower than 10%.

Scheme 89



59 (*S*)-**61** (TON 88) (9.9% *ee*) **60** (TON 10)

(*a*) mCPBA, **140**, CH_2Cl_2, MeCN, rt, 15 min (**140** : mCPBA : substrate = 1 : 27 : 75);

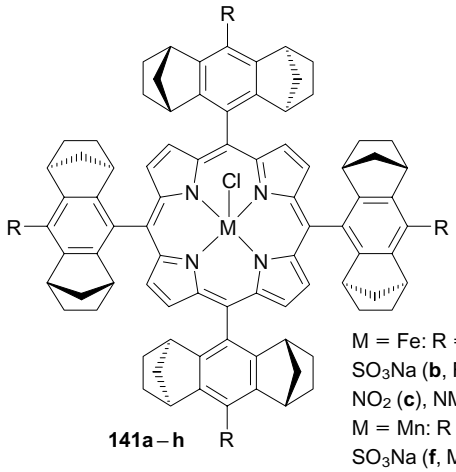


In 2012, Simonneaux and co-workers[249] prepared iron complexes **141a**,**b** with Halterman porphyrins, in particular with the porphyrin modified by SO_3Na groups, thereby rendering the complex water soluble, and used them as catalysts for the enantioselective benzylic C – H oxidation of arylalkanes by $PhI(OAc)_2$ in a aqueous methanol solution.

Ethylbenzene was transformed into (*S*)-1-phenylethanol in 46% yield (alcohol : ketone = 91 : 9) with moderate enantioselectivity (75% *ee*) (Scheme 90). Similar results were obtained in the hydroxylation of tetralin (**59**) (alcohol : ketone = 96 : 4). The oxidation by hydrogen peroxide instead of $PhI(OAc)_2$ gave the product in much lower yields with lower selectivity (5% and 15% *ee*, respectively, in the oxidation of ethylbenzene).

In 2014, this research group[250] described a method for the regioselective nitration of Halterman porphyrin with

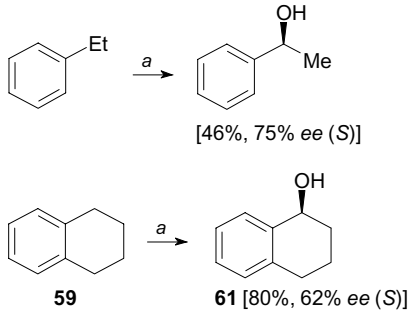
Structures 141



141a – h

M = Fe: R = H (**a**, FeHaltCl), SO_3Na (**b**, FeHaltSCl), NO_2 (**c**), NMe_2 (**d**);
M = Mn: R = H (**e**, MnHaltCl), SO_3Na (**f**, MnHaltSCl), NO_2 (**g**), NMe_2 (**h**)

Scheme 90

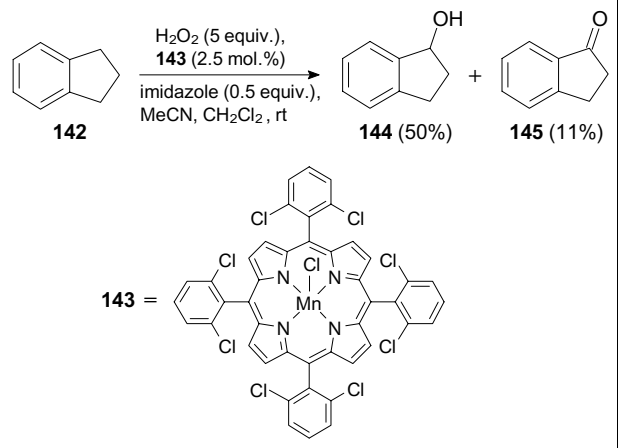


(*a*) $PhI(OAc)_2$, **141b**, imidazole, $MeOH-H_2O$ (5 : 1), argon (**141b** : imidazole : $PhI(OAc)_2$: substrate = 1 : 10 : 100 : 1000)

$NaNO_2$ in trifluoroacetic acid. The nitrated porphyrin can be reduced and methylated to prepare a NMe_2 derivative. These ligands can be used to synthesize iron complexes (**141c**,**d**) and manganese complexes (**141e – h**), which can be employed for the catalytic hydroxylation in a $CH_2Cl_2-MeOH-H_2O$ mixture. The iron complexes showed good outcomes in reactions using $PhI(OAc)_2$, whereas the product yield and enantioselectivity in the oxidation by hydrogen peroxide were lower. Complex **141a** displayed higher conversion and enantioselectivity in the oxidation of ethylbenzene (41%, alcohol : ketone = 83 : 17, 68% *ee*, *R* isomer) and indane (**142**) compared to the complexes with NO_2 and NMe_2 substituents. On the contrary, manganese(III) porphyrin complexes exhibited better catalytic properties when using hydrogen peroxide as the oxidant. Ethylbenzene and indane (**142**) were hydroxylated to form secondary alcohols with an enantioselectivity of up to 38% but with very low conversion (2% – 15%) and regioselectivity towards alcohol formation.

Examples of the use of iron aminopyridine complexes as catalysts for enantioselectivity benzylic C – H hydroxylation were reported; low enantioselective, conversion and selectivity of alcohol formation were observed in these processes.[136, 251 – 254]

Scheme 91



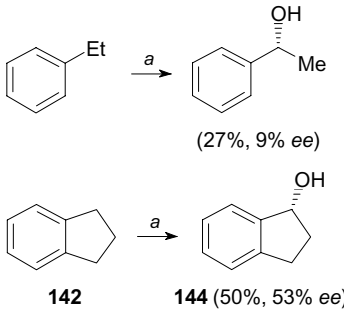
3.2.2. Benzylic hydroxylation in the presence of manganese complexes

In 1988, Mansuy and co-workers[255] reported the catalytic benzylic C – H oxidation of arylalkanes by hydrogen peroxide in the presence of manganese porphyrin complex **143** (Scheme 91). In the oxidation of ethylbenzene, the conversion of the substrate was 66%, the selectivity of alcohol formation being low (alcohol : ketone = 28 : 38). In the oxidation of indane (**142**), the conversion increased to 80% and the alcohol **144** : ketone **145** ratio was 50 : 11. In the reaction with tetralin (**59**), a high conversion was retained, and the alcohol **61** : ketone **60** ratio changed to 52 : 20.

Two years later, Groves and Viski[246] reported the enantioselective oxidation of arylalkanes by PhIO in the presence of chiral manganese(III) binaphthyl porphyrin complex **137b** (see Scheme 87). The yields of the alcohols (46% – 98%) were higher than those obtained in the reactions in the presence of related iron complexes. However, the latter displayed a higher selectivity in the oxidation. Thus, the oxidation of tetralin (**59**) in the presence of iron complex **137a** occurs with a selectivity of 72% *ee*, whereas the selectivity in the reaction using Mn complex **137b** was low (12% *ee*).

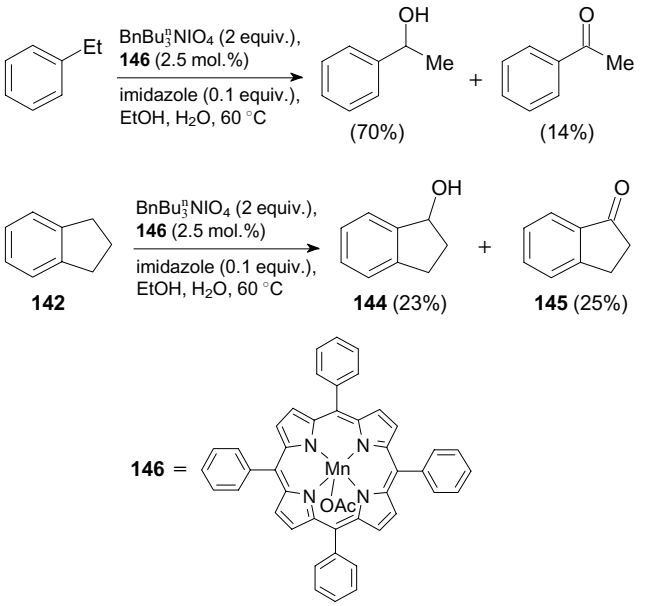
In 1997, Halterman *et al.*[256] demonstrated that chiral D_4-symmetric Mn^{III} porphyrin complex **141e** can act as a catalyst for the enantioselective benzylic oxidation of arylalkanes (Scheme 92). However, the oxidation of ethylbenzene by PhIO afforded alcohol as an equimolar mixture with ketone with a low *ee* value, whereas the reaction with indane (**142**) taken in excess gave 1-indanol (**144**) as the major product (alcohol : ketone = 5) with a moderate enantioselectivity.

Scheme 92



(*a*) PhIO, **141e**, 4-Bu^t-Py, CH_2Cl_2, rt (**141e** : 4-Bu^t-Py : PhIO : substrate = 1 : 20 : 100 : 1000)

Scheme 93



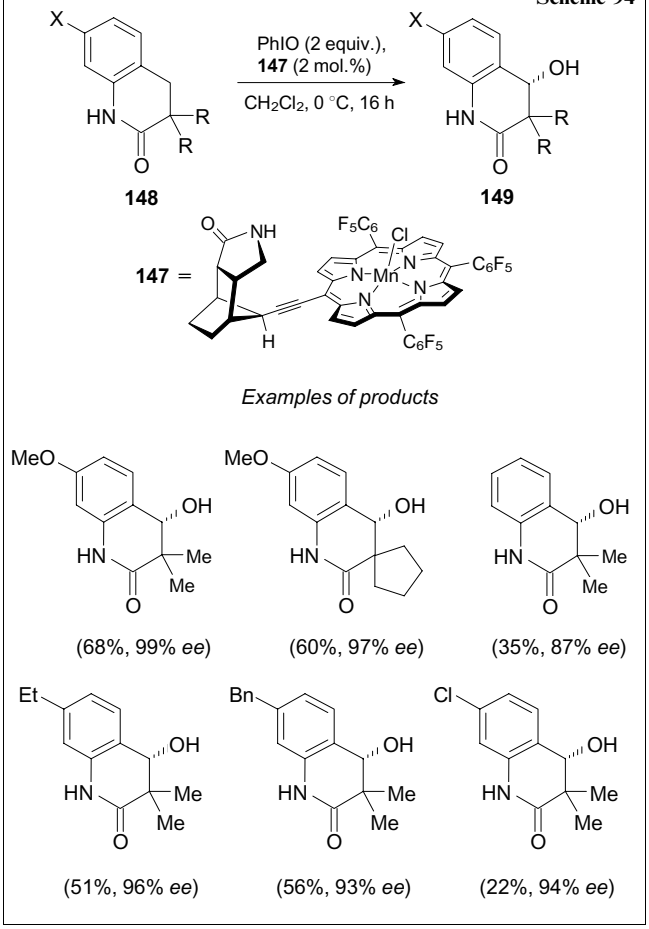
Jafarpour and co-workers[257] synthesized benzyltri-n-butylammonium periodate, which was used as the oxidant for the benzylic oxidation of arylalkanes in an EtOH – H_2O mixture in the presence of the manganese *meso*-tetraphenylporphyrin complex Mn(TPP)OAc (**146**) and imidazole (Scheme 93). The conversion of ethylbenzene was 84%; the conversion of indane was 48%; the reaction gave a mixture of the corresponding alcohol and ketone in 21% – 84% yield.

The first example of the enantioselective benzylic hydroxylation of arylalkanes with hydrogen peroxide in the presence of a manganese porphyrin complex was reported by Simonneaux and co-workers[258] in 2012. The reaction using complex **141f** with addition of imidazole in an aqueous methanol solution gave alcohols with an enantioselectivity of 32% – 57%. The substrate conversion was 100%, the alcohol : ketone ratio being varied in a wide range. Thus, the oxidation of 4-ethyltoluene to (*S*)-*p*-tolylethanol occurs at a conversion of 97% with an enantioselectivity of 57% *ee* (alcohol : ketone = 93 : 7); in the oxidation of ethylbenzene giving (*S*)-1-phenylethanol, the conversion and enantioselectivity were 88% (alcohol : ketone = 57 : 43) and 38% *ee*, respectively. The replacement of SO_3Na groups of the ligand by H, NMe_2 or NO_2 led to a significant decrease in the chemo- and stereoselectivity of oxidation.

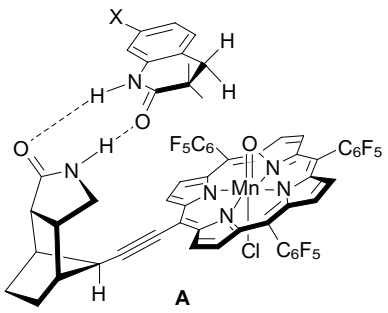
In 2018, Bach and co-workers[259] investigated the selective oxidation of the methylene group by means of molecular recognition and synthesized manganese porphyrin complex **147**, which can catalyze the enantioselective oxidation of 3,4-dihydroquinolones **148** by iodosobenzene (Scheme 94).

The conversion of the substrate was 29% – 97%, the yields of alcohols **149** were 19% – 68%, and the enantioselectivity was 87% – 99%. In the authors' opinion, high selectivity in the oxidation is provided by two-point hydrogen bonding of the substrate to the manganese(V) oxo porphyrin complex (structure **A**). This facilitates the abstraction of a hydrogen atom on the porphyrin side. The oxidation of *N*-methylated derivative **148a**, which cannot form two hydrogen bonds, gave product **149a** in almost racemic form (5% *ee*) in low yield (Scheme 95).

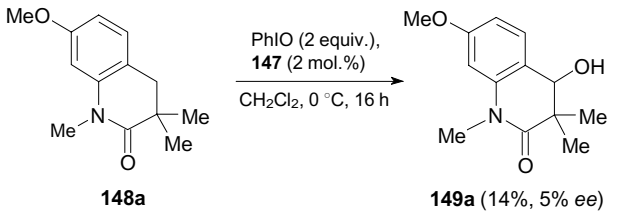
Scheme 94



Structure A

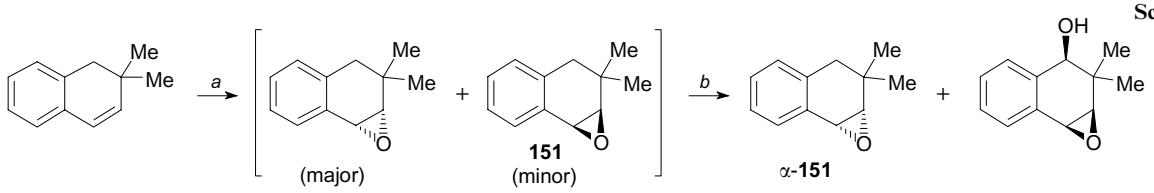


Scheme 95

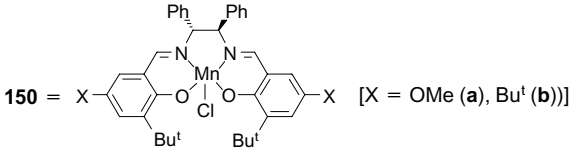


Apart from manganese porphyrin complexes, chiral manganese salen complexes were found to be efficient catalysts for the benzylic hydroxylation in an enantioselective manner. In 1994, Larrow and Jacobsen[260] performed the kinetic resolution of racemic 3,4-dihydronaphthalene epoxide **151** in the presence of manganese salen complexes **150a**,**b** *via* stereoselective benzylic C – H oxidation by

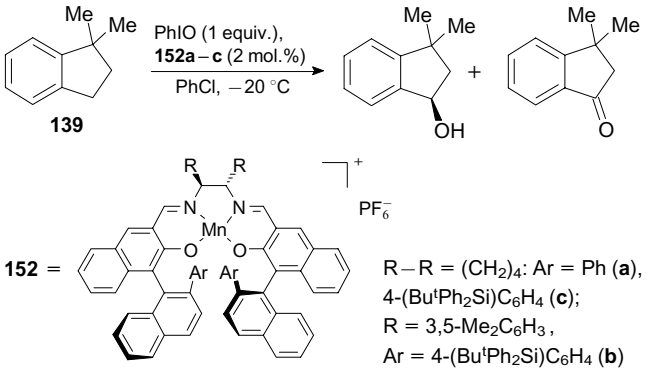
Scheme 96



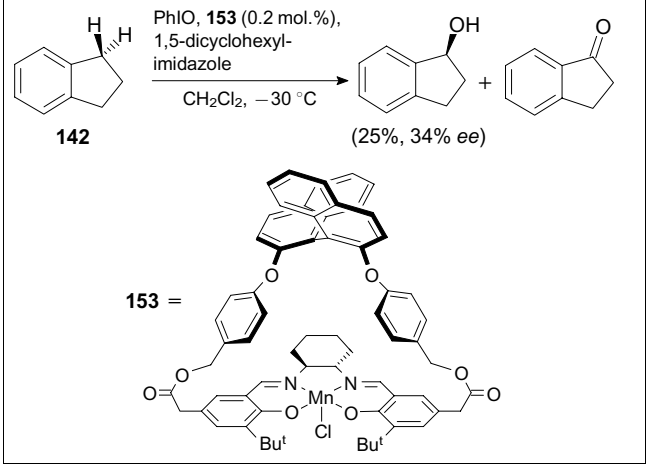
(*a*) NaOCl (2 equiv.), **150a**,**b**, PhCl, 0 – 5 °C; (*b*) NaOCl (2 equiv.), **150a**,**b**, 4-phenylpyridine *N*-oxide, PhCl, 0 – 5 °C;



Scheme 97



Scheme 98



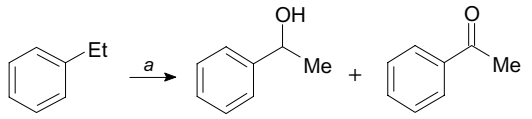
sodium hypochlorite [the relative rate constant (k_{rel}) = 28] (Scheme 96).

The first example of the enantioselective benzylic hydroxylation of arylalkanes in the presence of manganese(III) salen complexes **152a** – **c** (Scheme 97) was reported in 1996 by Katsuki and co-workers.[261, 262] The oxidation of 1,1-dimethylindane (**139**) by PhIO in chlorobenzene at – 20 °C in the presence of catalytic amounts (2 mol.%) of complexes **152a** – **c** for 10 min afforded (*R*)-3,3-dimethylindan-1-ol (56% – 84% *ee*) in a very low yield (1.5% – 4.8%, the yields of the ketone by-product were not higher than 0.2%). An increase in the reaction time to 20 h led to an increase in the enantioselectivity to 81% – 90% due to oxidative kinetic resolution of the resulting alcohol (the yields of alcohols were 16.6% – 24.5% and those of ketones were 10.2% – 11.9%). It was assumed that the mechanism of C – H-hydroxylation in the presence of salen complexes is similar to that in the presence of porphyrin complexes and involves the formation of short-lived C-centred radical intermediates in a solvent cage.

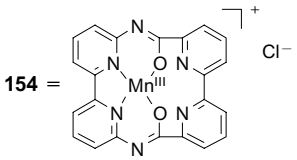
Murahashi *et al.*[263] used chiral manganese complex **153** with a salen ligand bearing the binaphthyl moiety (Scheme 98) and achieved 34% *ee* in the oxidation of indane (**142**) by iodosobenzene. It was found that the addition of 1,5-dicyclohexylimidazole increases the enantioselectivity of oxidation from 5% *ee* (in the absence of additives) or 8% (in the presence of unsubstituted imidazole) to 34%. The alcohol : ketone ratio was 4.1.

Apart from manganese porphyrin and salen complexes, manganese complexes with chelating *N*- and *O*-donor ligands were examined. In 2007, Ogawa and co-workers[264] employed Mn^{III} complex **154** with a *N*,*O*-donor macrocyclic ligand to oxidize ethylbenzene by hydrogen peroxide to form 1-phenylethanol (20% yield with respect H_2O_2) and acetophenone (15% yield based on H_2O_2) (Scheme 99).

Scheme 99



(*a*) H_2O_2, **154**, CH_2Cl_2, MeCN (**154** : H_2O_2 : substrate = 1 : 20 : 1000);



Srinivas and co-workers[265] performed the benzylic oxidation by hydrogen peroxide in the presence of a complex generated *in situ* from $MnSO_4$ and 1,4,7-trimethyl-1,4,7-triazacyclonane in oxalate or citrate buffer. The oxidation of ethylbenzene gave 1-phenylethanol (19.4% yield, TON 48.5) and acetophenone (40.8%, TON 102) at a substrate conversion of 69%.

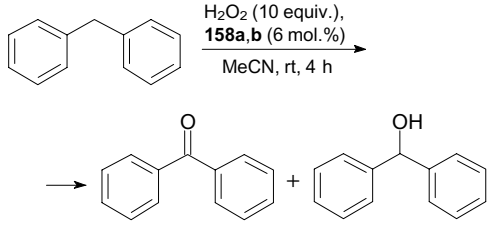
Currently, attention is being focused on the design of stereoselective catalysts based on bis(amino)bis(pyridine) and related manganese complexes for the enantioselective C – H-hydroxylation reactions.[266, 267] Main advantages of this type of catalysts are high stability under catalytic reaction conditions and, as a consequence, high perform-

ance (high TON), as well as the high oxidant efficiency. Generally, the benzylic C – H oxidation in the presence of manganese aminopyridine complexes requires very low catalyst loadings (0.1 mol.% – 0.5 mol.%) compared to related iron complexes (up to 15 mol.%) and a relatively small excess of hydrogen peroxide (1.3 – 3.0 equiv. with respect to the substrate).[136]

The first example of the highly efficient regioselective oxidation of aliphatic C – H groups by hydrogen peroxide in the presence of manganese aminopyridine complexes was reported in 2012 by Bryliakov and co-workers.[268] Chiral manganese complexes **155** – **157** showed a high efficiency and selectivity in the oxidation of various secondary and tertiary alkanes by H_2O_2 in the presence of acetic acid (TON up to 970).

Golchoubian and Ghasemi[269] investigated the oxidation of diphenylmethane by hydrogen peroxide in the presence of manganese aminopyridine complexes **158a**,**b** (Scheme 100) and found that the reaction gave diphenylmethanol rather than benzophenone as the major oxidation product (the alcohol selectivity was up to 68%).

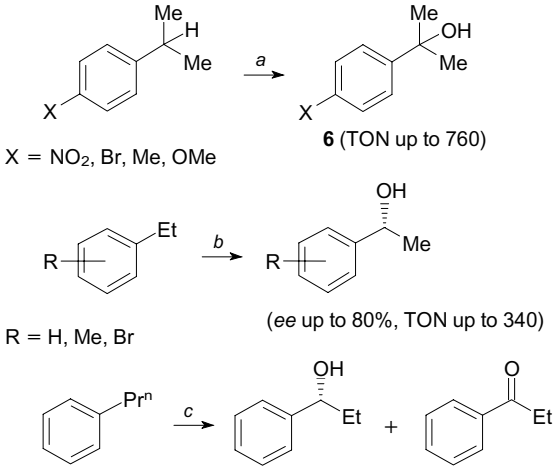
Scheme 100



Catalyst	Conversion (%)	Yield of alcohol (%)	Yield of ketone (%)
158a	19	8	11
158b	47	32	15

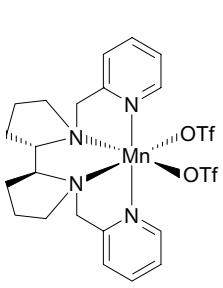
In 2015, Bryliakov and co-workers[270] synthesized chiral manganese bis(amino)bis(pyridine) complexes **159** and **160** with strong electron-donating substituents (OMe and NMe_2), which showed higher performance (TON up to 760) compared to complex **155** in the oxidation of substituted cumenes by hydrogen peroxide to form cumyl alcohols (Scheme 101).[270] Acetophenone was obtained as the major oxidation product of ethylbenzene (TON up to 470,

Scheme 101

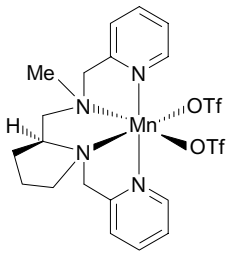


(*a*) H_2O_2 (1.3 equiv.), **159** or **160** (0.1 mol.%), AcOH (6 equiv.), MeCN, 0 °C; (*b*) H_2O_2, **161**, *N*-Boc-L-proline, MeCN, 0 °C (**161** : *N*-Boc-L-proline : H_2O_2 : substrate = 0.1 : 30 : 70 : 200);
(*c*) H_2O_2 (0.5 equiv.), **162** (1 mol.%), EHA (2 equiv.), TFE;
EHA is 2-ethylhexanoic acid, TFE is 2,2,2-trifluoroethanol

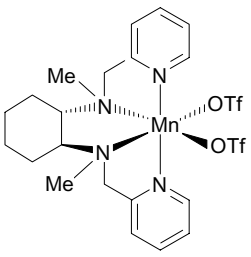
Structures 155 – 164



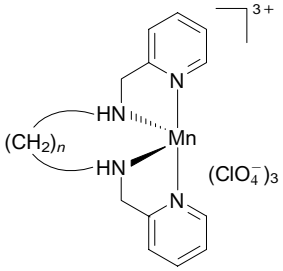
155



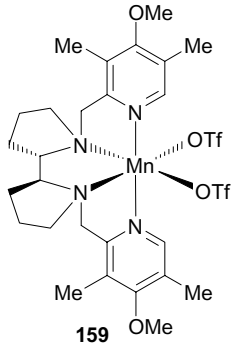
156



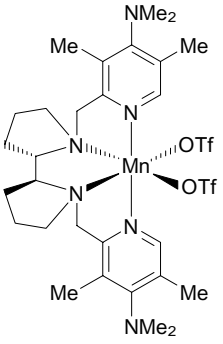
157



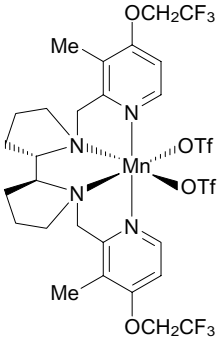
158a,b
n = 2 (**a**), 3 (**b**)



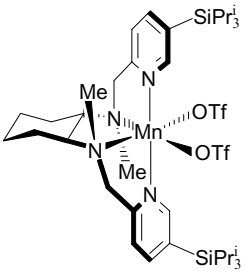
159



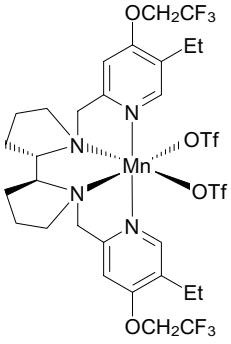
160



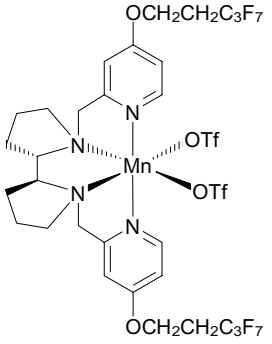
161



162



163



164

ketone : alcohol = 41 : 5). The mechanism of C – H oxidation in the presence of manganese bis(amino)bis(pyridine) complexes was investigated. The reaction was found to occur *via* an oxygen-rebound mechanism.

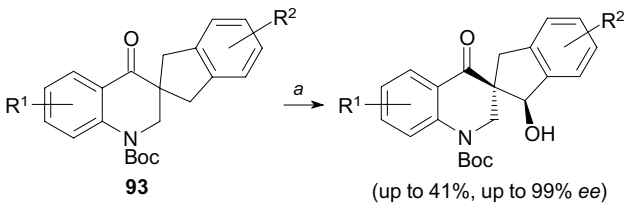
In 2017, chiral manganese bis(amino)bis(pyridine) complexes were used for the first time as the catalysts for the asymmetric C – H hydroxylation with hydrogen peroxide. Thus, manganese complex **161** proved to be an efficient catalyst for the enantioselective hydroxylation of ethylbenzene and its derivatives with hydrogen peroxide with a turnover number of up to 340 (see Scheme 101).[271] The oxidation of ethylbenzene in the presence of racemic 2-ethylhexanoic acid as an additive resulted in an enantiomeric excess of 41%; in the presence of *N*-Boc-protected proline as a chiral additive, the enantiomeric excess reached 76%. The stereoconvergent kinetic resolution of the resulting 1-arylethanol, which simultaneously decreases the yield of the latter product, contributes to the observed enantiomeric excess. To avoid the further oxidation of alcohols to ketones, it is necessary to use an excess of the substrate and stop the reaction at low conversion values (~10%).

Costas and co-workers[272] demonstrated that the catalytic hydroxylation of alkanes with hydrogen peroxide in β-polyfluorinated alcohols (2,2,2-trifluoroethanol, hexafluoroisopropanol) leads to an increase in the selectivity of alcohol formation due to suppression of its further oxidation to ketone. This significantly increases the yield of the alcohol. Thus, the oxidation of propylbenzene by hydrogen peroxide (substrate : H_2O_2 : EHA = 1 : 0.5 : 2) in TFE in the presence of 1 mol.% complex **162** (see Scheme 101) gave 1-phenylpropanol in a yield of up to 44% (based on H_2O_2) along with ketone (7%) with an enantioselectivity of up to 60%.

Recently, Bryliakov and co-workers[273] investigated the benzylic hydroxylation of arylalkanes with hydrogen peroxide in the presence of catalyst **161** in β-polyfluorinated ethanols. In this reaction, chiral alcohols can be prepared in yields of up to 45%. The highest enantioselectivity was observed in 2,2-difluoroethanol (up to 89% *ee*). Structurally similar catalysts **163** and **164** provide lower yields and enantioselectivity of alcohol formation compared to complex **161**.

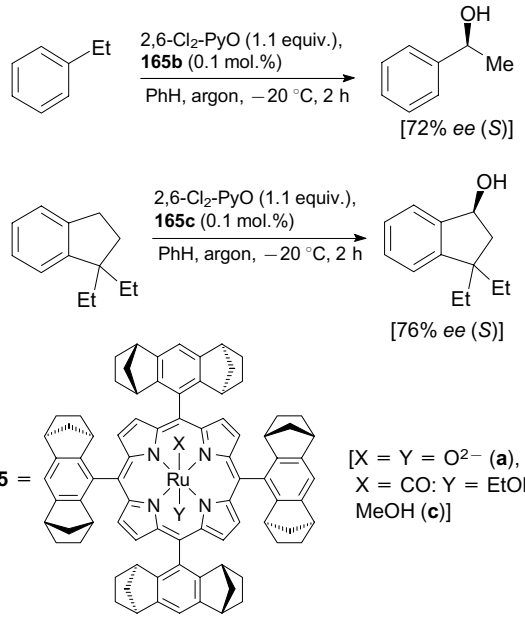
In 2019, Sun and co-workers[160] examined the oxidative desymmetrization (through ketonization of the methylene group) of spirocyclic oxindoles **92** and dihydroquinolinones **93** in the presence of the Mn catalyst [(*S*)-PEB]Mn(OTf)$_2$ (**88b**) and reported the asymmetric hydroxylation of dihydroquinolines **93** at a conversion of up to 63%. The enantioselectivity of this reaction reached 70% – 99%, the yields of the alcohols being in the range of 22% – 41% (Scheme 102).

Scheme 102



(*a*) 30% H_2O_2 (2 equiv.), **88b** (2 mol.%), 2,2-dimethylbutanoic acid (14 equiv.), CH_2Cl_2 – MeCN (1 : 1), argon, –20 °C, 2 h

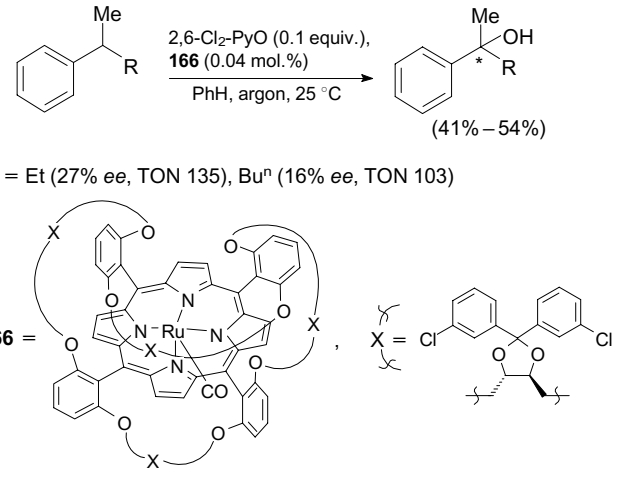
Scheme 103



3.2.3. Benzylic hydroxylation in the presence of ruthenium complexes

The first example of the enantioselective benzylic C – H hydroxylation in the presence of ruthenium complexes was reported in 1999 by Che and co-workers,[274] who demonstrated that the chiral ruthenium(VI) dioxo complex with Halterman porphyrin [$Ru^{VI}HaltO_2$] (**165a**) can act as a stoichiometric oxidant of arylalkanes (Scheme 103). The reaction affords optically active alcohols having an (*S*) configuration (up to 58% *ee*) and ketones. Chiral complexes **165a** and [$Ru^{II}Halt(CO)(EtOH)$] (**165b**) were found to act as catalysts for the hydroxylation of substrates with 2,6-dichloropyridine *N*-oxide (2,6-Cl_2-PyO, 1.1 equiv.). In the latter case, the enantioselectivity of the oxidation was up to 76%, but the substrate conversion was low (*e.g.*, 14% for ethylbenzene; ketone : alcohol = 62 : 37). Under these conditions, the 1,1-diethylindane conversion in the presence of similar complex **165c** was 36% (ketone : alcohol = 70 : 30). For other arylalkanes, the conversion of the substrate in the presence of complexes **160a** – **c** as catalysts varied in the range of 5% – 54%.

Scheme 104

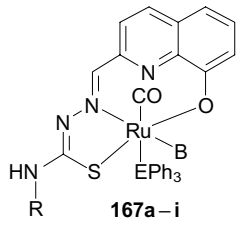


In 1999, Gross and Ini[275] synthesized ruthenium porphyrin complex **166** (Scheme 104), which catalyzes the oxidative kinetic resolution of aryl-substituted secondary alkanes. 2,6-Dichloropyridine *N*-oxide in 48% HBr was used as the oxidant. Tertiary alcohols were obtained with an optical purity of 16% – 38% *ee*, the enantiomeric enrichment of the unreacted substrate being observed (8% *ee* after the formation of alcohol in 35% yield). The low optical purity of the resulting alcohol is attributed to partial racemization due to the ability of the C-centred radical intermediate to undergo a rapid inversion.

It was shown that the hydroxylation of cumene and its derivatives can be accomplished using the $RuCl_3-PyH-KBrO_3$ (27% – 37% yields) and [(tmtacn)$RuCl_3$] – CAN systems (65% – 75% yields).[136]

In 2014, Viswanathamurthi and co-workers[276] synthesized ruthenium(II) complexes **167a – i** with hydroxyquino-

Structures 167

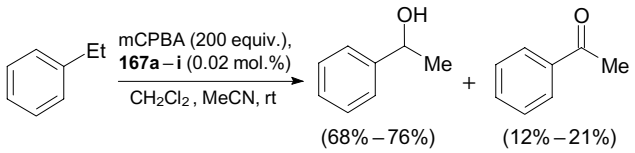


167a – i

R = Me: E = P, B = PPh_3 (**a**); E = P, B = PyH (**b**); E = As, B = $AsPh_3$ (**c**); R = H: E = P, B = PPh_3 (**d**); E = P, B = PyH (**e**); E = As, B = $AsPh_3$ (**f**); R = Ph: E = P, B = PPh_3 (**g**); E = P, B = PyH (**h**); E = As, B = $AsPh_3$ (**i**)

line-thiosemicarbazone ligands. These complexes were found to catalyze the oxidation of cyclohexane and ethylbenzene with *m*-chloroperoxybenzoic acid. The yields of racemic 1-phenylethanol were 68% – 76%, the alcohol : ketone ratio varied from 3.4 to 5.7 (Scheme 105).

Scheme 105



4. Conclusion

As can be seen from the analysis of the literature data, significant progress was made in the discussed area in the past four decades. Various strategies and efficient synthetic methods were developed for the selective benzylic oxofunctionalization of organic compounds, most of which utilize catalysts based on transition metal complexes. The focus is being shifted from catalysts based on platinum group metal complexes (Ru, Rh, Ir) to more available compounds of the first-raw transition metals (Mn, Fe, Cu). Besides, inexpensive and environmentally benign oxidants (H_2O_2 and O_2),[245, 277, 278] as well as electrochemical and photocatalytic methods are increasingly used in these processes.

The most efficient methods for the selective benzylic C – H functionalization allow the synthesis of the target products in high yields with high selectivity (in the case of oxidation to ketones), utilize environmentally benign oxidants, enable the selective activation of one of different C – H groups in complex organic molecules and conduct the oxidation in enantioselective fashion. In some cases, a particular C – H group can be subjected to oxidation due to non-covalent interactions between the catalyst and substrate, like in the highly selective processes mediated by natural metalloenzymes. The most significant recent advances are related to the design of biomimetic catalysts based on manganese complexes,[266, 267] which use H_2O_2 as the oxidant, ensure high selectivity (up to 99%) and allow the stereoselective C – H oxidation.

Considerable progress was made in understanding the mechanisms of benzylic C – H oxidation. Despite the fact that in most cases, key intermediates of the reaction cannot be detected by available experimental methods, indirect methods (kinetic, isotopic) often allow reliable conclusions about the overall mechanism of the process to be drawn.

However, most of the known methods for the selective C – H oxidation do not satisfy the requirements necessary for practical applications. Significant drawbacks are large overconsumption (by a large factor) of the oxidant, the use of difficult-to-handle and expensive metal complexes (Ru, Rh, Ir) and a small turnover number of the catalyst. If the oxidation occurs *via* a free-radical mechanism, the process is accompanied by side reactions, thereby decreasing the selectivity to the target product. In most studies, the oxidation was investigated for a rather narrow range of substrates and the reactions were not scaled up. Achieving high C – H hydroxylation selectivity of methylene groups has been a challenge because the initially formed secondary alcohol contains an activated (weaker) C – H bond compared to the starting substrate and, hence, it is susceptible to further oxidation giving ketone. Examples of the simultaneous activation of the most attractive oxidant (triplet dioxygen) *via* a heterolytic mechanism and the selective C – H oxidation of the substrate by the resulting transition metal oxo complex in the catalytic cycle are unknown.

The solution of the above-mentioned practical problems and the development of feasible, inexpensive, environmentally benign, highly efficient and versatile methods for the selective benzylic C – H oxidation may revolutionize synthetic approaches to functionalized complex molecules in fine organic synthesis, including the preparation of biologically active compounds and pharmaceuticals. An analysis of the current trends shows that efforts are made to address technical problems. Hence, a breakthrough in this field could be expected in a medium-term perspective.

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