Selectivity enhancement in functionalization of C–H bonds: A review

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The selectivity is an extremely important characteristic of a chemical reaction. This review deals mainly with supramolecular and nano-chemical approaches to the problem of selectivity enhancement in various functionalizations of C–H compounds. Enzyme mimics is a very fruitful method to achieve the predominant formation of desirable products and isomers. By obstructing the approach of certain C–H bonds of a substrate to the active catalytic centre we simultaneously increase the relative reactivity of other fragments. This can be done by creating steric hindrance around the active centre. Spatial restrictions can be made if we place the catalyst into a nano-cavity. We can achieve discrimination in reactivity of different C–H bonds if we allow certain fragments to approach closely the active centre. In order to do this chemists use coordination of the catalyst to some groups of the substrate with the participation of relatively strong binding (chelate control) or relatively weak forces (molecular recognition).

1 Introduction

More than 30 years ago the distinguished Russian expert in chemical kinetics and oxidation reactions Prof. Emanuel' wrote in his review "The problems of the selectivity of chemical reactions":[1a] "The high selectivity and rate of a chemical reaction have become the main criteria of the practical usefulness of a chemical process". Indeed, non-selective reactions that give rise to the formation of a variety of undesirable products are unlikely to be used in chemical practice. The selective conversion of various C–H compounds[1b–t] and especially inert alkanes (which are the "noble gases of organic chemistry"[1h,i]) constitutes a very intriguing goal of contemporary catalytic chemistry. Usually a reaction gives a few products and only one of them is a target compound. Oxidation of alkanes leads to the formation of target products (TP: alkyl hydroperoxides, alcohols, ketones and carboxylic acids) which are in many cases not less (usually even more) reactive than the parent alkane, RH. It means that when the concentration of the target product approaches the concentration of the remaining alkane, the target product will be involved in a substantial over-oxidation to produce undesirable compounds:

$$\mathrm{RH} \xrightarrow[k_1]{\text{oxidant}} \mathrm{TP} \xrightarrow[k_2]{\text{oxidant}} \text{over-oxidation products} \qquad (1.1)$$

The maximum attained yield of TP can be calculated[1j] using eqn (1.2):

$$\frac{[\mathrm{TP}]_{\max}}{[\mathrm{RH}]_0} = (k_2/k_1)^{\frac{k_2/k_1}{1-(k_2/k_1)}} \qquad (1.2)$$

It can be concluded[1j] that maximum yield of TP at $k_2/k_1 = 1$ will be 37%, and only at $k_2/k_1 = 0.01$ (which is practically improbable for the case of the alkane oxidation) will the yield attain 95% (see also a work by Labinger[1f]).

Eqn (1.1) represents the case when we are interested in the yield of the target product relative to the total yield of all products including over-oxidation products which are formed at the second stage of the process. However, the first stage of a reaction can give more than one product. The products can belong to different classes of organic compounds, for example, alcohols and ketones can be formed simultaneously. We shall consider here only the reactions affording *isomeric* products of the same class. Electronic[2a,b] and/or steric[2c,d] factors govern the formation of the predominant isomer. For example, the Pd-catalyzed annulation reaction (eqn (1.3))[2e] of pyrrole **1.1** proceeds at the C2 position when R is the relatively small toluene-4-sulfonyl (Ts) group. This route leads to the "expected" isomer **1.2**. If Ts is replaced by the bulky triisopropylsilyl (TIPS) group the annulation reaction forms the cycle at the C4 position affording product **1.3**. Thus, the switch in selectivity can be attributed to the sterically demanding nature of the TIPS group that shields the C2 position.

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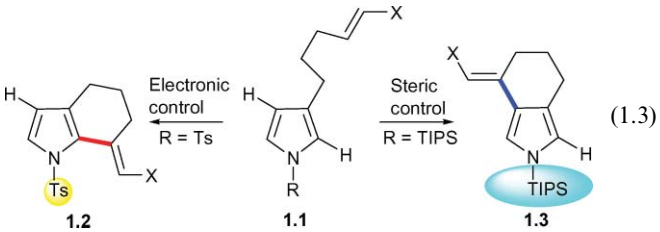


(1.3)

It is interesting that Pd-catalyzed regioselective *meso*-β-coupling of bromoporphyrins proceeds through formal direct C–H functionalization of porphyrin at the most hindered β-position.[2f] For other examples of regioselective reactions (*i.e.* when the substitution occurs at a certain position or region of the molecule) of aromatic compounds, see very recent reviews.[3a,b] Martin, Milstein and their co-workers[3c] reported the selective sp^3-C–H activation of alkyl ketones at the β position. A difference between 2-butanone and 3-pentanone has been found which is due to the fact that the α hydrogen is less sterically hindered in 2-butanone. DFT calculations showed that in the case of 2-pentanone, steric preference for β activation also plays a role.

The "selectivity" is a polysemantic term. We considered above the positional (regio-) selectivity. An oxidizing species which attacks the substrate can discriminate between primary, secondary and tertiary C–H bonds, usually giving preference in the following order: *tert* > *sec* > *primary* (or 3° > 2° > 1°). In this case, we deal with bond-selectivity. Various oxidizing systems are able to replace *tert*-hydrogens in *cis*- and *trans*-isomers of decalin with retention of configuration when the resting *tert*-hydrogen atom and the entering hydroxyl substituent in the products (*cis*-decalol-9 and *trans*-decalol-9) are situated in the same mutual orientation as in the parent hydrocarbon.[3d,e] Such reactions are stereoselective. If a reagent discriminates between two diastereotopic C–H bonds we can talk about diastereoselective reaction.[3f] Finally, if a reaction with a C–H compound gives rise to products with a predominance of one enantiomer we deal with enantioselectivity.[3f] Reactions with 100% degree of selectivity are specific ones (regiospecific, stereospecific *etc.*). In this review, we shall restrict our discussion mainly to the problems of regioselectivity in reactions of C–H compounds.

How could we enhance the regioselectivity, in other words, how can we obtain in the reaction predominantly one isomer of a functionalized C–H compound containing the substituent at a certain (desirable) position? First of all it is necessary to mention that "traditional" organic chemistry uses mainly rather non-selective methods for the functionalization of C–H compounds. Reactions of monosubstituted benzenes under electronic control often occur with the selectivity *ortho* ≈ *meta* ≈ *para*. In compounds containing saturated C–H bonds usually methyl groups are less reactive than methylene groups and tertiary hydrogen are the most reactive. Eqn (1.3) demonstrates that by introducing bulky substituents into the substrate molecule and thus creating steric hindrance we can dramatically change the regioselectivity. Creating voluminous catalytic reaction centres which could approach only less sterically hindered fragments of the substrate seems to be a more universal and productive method (Fig. 1b). Obviously, we can only functionalize sterically non-hindered C–H bonds by this method. This review is devoted predominantly to the regioselectivity enhancement by creating spatial restrictions around reaction centres. Alternatively, in order

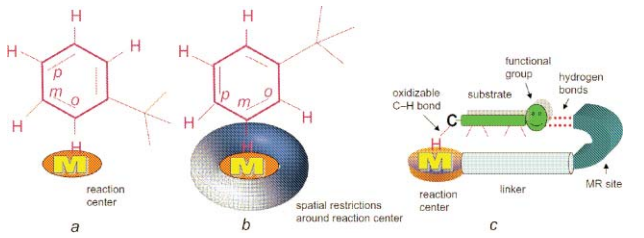


Fig. 1 *ortho*-Substitution is possible in the case of a small reaction centre (*a*). Creating the bulky environment around the metal(M)-containing reaction centre allows us to exclude substitution at the *ortho*-position of a monosubstituted benzene (*b*). Using principles of molecular recognition (MR) it is possible to oxidize only certain C–H bonds in a substrate containing a functional group (*c*).

to enhance the selectivity we can allow the C–H bond which we want to functionalize to approach closely to the reaction centre. It is possible to hold the C–H close to the reaction centre involving hydrogen bonds or other weak bonds between special functional groups in the substrate and the catalyst (molecular recognition, MR; see Fig. 1c). An excellent Feature Article by Das, Brudvig and Crabtree[4a] has been devoted mainly to MR and due to this we shall discuss this field only briefly in Section 2.2. "The term 'molecular recognition' is usually limited to cases where a number of attractive non-covalent interactions cooperate to achieve binding of a substrate molecule."[4a] Cyclodextrins bound to the catalyst molecule can act as hydrophobic binding sites which fix the substrate molecule in the correct position.[4b] The reaction centre oxidizes only closely situated C–H bonds. Molecular recognition strategy allows us to functionalize remote C–H bonds; however, it is clear that the MR method with the participation of functional groups is not applicable to reactions of unsubstituted alkanes. Employing the 'chelate effect' we can easily functionalize C–H bonds that are situated closer to the directing group (often this is an amino nitrogen atom). Section 2 is devoted to this type of functionalization of remote and 'close' C–H bonds. In both cases, transformations of hydrocarbon derivatives and not unsubstituted hydrocarbons are possible. We shall begin with a brief discussion of functionalization of C–H in molecules which contain functional 'directing' groups.

Enzymes "achieve astonishing selectivities and catalytic efficiencies"[4b] using both principles of supramolecular chemistry[4c-e] mentioned above: a hydrophobic pocket around the reaction centre and molecular recognition. Section 4 is devoted to selectivity in enzymatic C–H functionalization. Section 5 describes in detail examples of chemical methods employing these approaches.

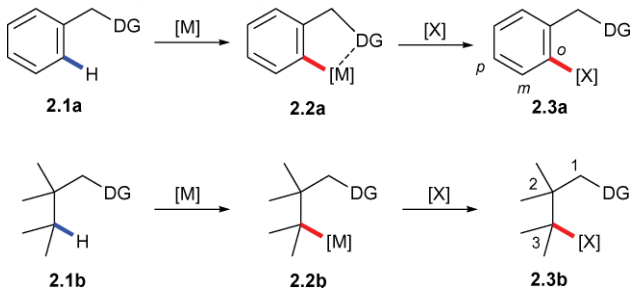
2 Functionalization of C–H bonds in molecules containing 'directing groups'

Some functional groups in organic substrates can facilitate the spatial approach of certain C–H bonds of the substrate to the catalytic metal-containing reaction centre. Binding interactions between the substrate and the catalyst, like in enzymatic catalysis, decrease the activation energy of the reaction.[4b]

2.1 Cyclometallation (chelate control)

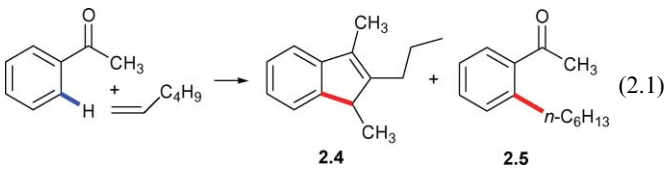
Metal ions which are coordinated to certain functional directing groups DG in a molecule of compound **2.1** easily cleave the

C–H bond to afford a chelated organometallic derivative **2.2** if the chelating cycle consists of 5 or 6 members (cyclometalation).[5a] Both aromatic (**2.1a**) and sp^3-C–H bonds (**2.1b**) can be cleaved in such processes. If the intermediate organometallic compound is involved further in a reaction with reagent [X], the functionalization of **2.1** occurs to produce in a catalytic cycle compound **2.3**. Obviously, the overall process will be regiospecific and compound **2.3** will contain substituent X either at the *ortho*-position of the benzene ring or at position 3 (or 4) of the alkane chain (Scheme 1).



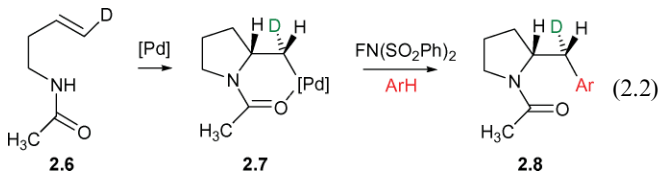
Scheme 1 Schematic representation of regioselective C–H functionalization *via* cyclometalation.

Ketone functionality can play the role of directing group. Thus, ruthenium complexes catalyze the coupling reaction of acetophenone and 1-hexene involving C–H bond activation in the methyl group of acetophenone and chelate-assisted insertion in the *ortho*-C–H bond of the benzene ring (eqn (2.1)).[5b] The product ratio strongly depends on the nature of the catalyst: catalyst $RuCl_2(PPh_3)_3$ leads to the formation of only **2.4** whereas the reaction catalysed by $RuH_2(CO)(PPh_3)_3$ affords only **2.5**.



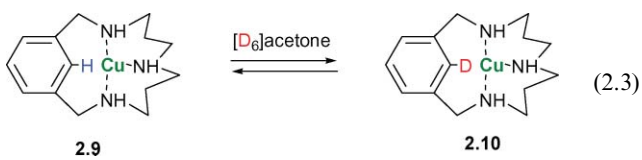
(2.1)

The regioselective aminopalladation of compound **2.6** gives chelated product **2.7** which in turn reacts with an arene to give regioselectively and with retention of stereochemistry the arylated compound **2.8** (eqn (2.2)).[5c]



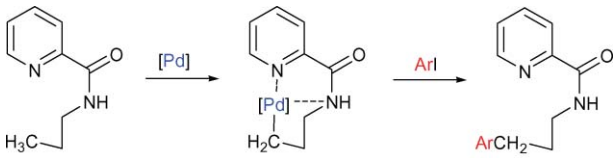
(2.2)

Arylation of benzoic acids at the *ortho*-position occurs *via* the formation of *ortho*-palladated derivative which reacts with aryl iodide.[5d] Analogously, the group $-CH_2NH_2$ in benzene derivatives directs the aryl substituent to the *ortho*-position.[5e] Directing groups containing a nitrogen atom are often used in coupling reactions[5f,g] and other processes. Regiospecific reversible H/D exchange **2.9** ⇄ **2.10** is promoted by Cu(I) complexes (eqn (2.3)).[5h]



(2.3)

Daugulis and co-workers[6a] described highly regioselective Pd-catalyzed arylation of sp^3-C–H bonds. In the transformation of amine **2.11** into **2.13**, pyridine played the role of a directing group and the reaction proceeds *via* palladacycle **2.12** (eqn (2.4)).



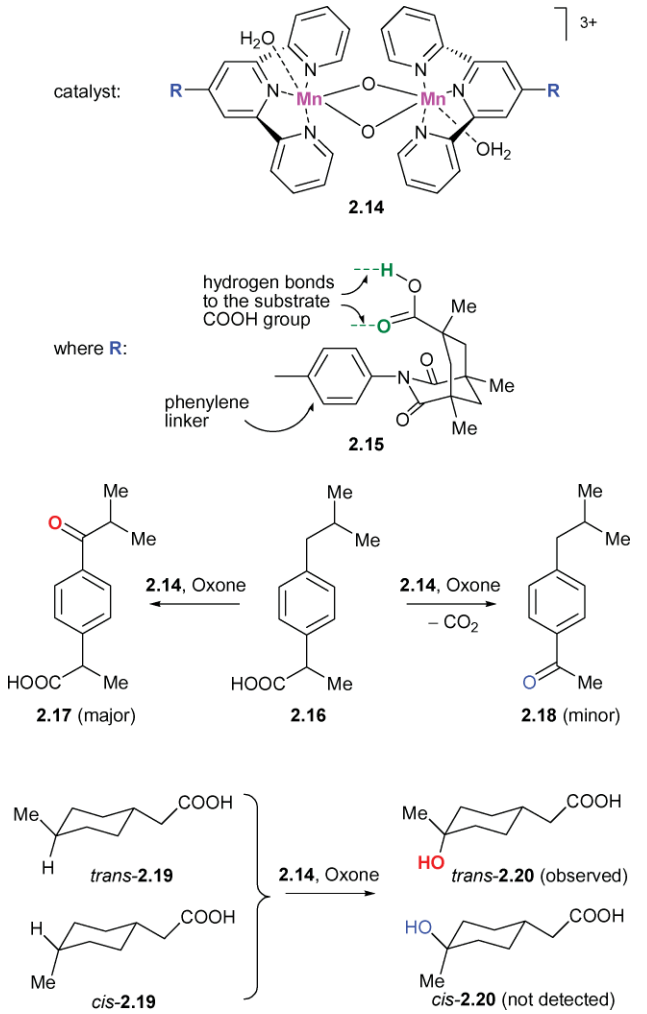
(2.4)

Sanford,[6b-d] Dixneuf,[6e,f] Ackermann,[6g] Cheng,[6h] Li,[6i] Wu[6j] and their co-workers used pyridine and similar directing groups in various regioselective metal-catalyzed C–H functionalizations. Sames and co-workers[6k] reported an interesting regio- and stereoselective transformations of amino acids under the action of platinum catalysts. Legzdins and co-workers[6l] found that thermolysis of the bis(neopentyl) complex $Cp^*W(NO)(CH_2CMe_3)_2$ in various substituted benzenes, C_6H_5X, affords the corresponding $Cp^*W(NO)(CH_2CMe_3)(o\text{-}C_6H_4X)$ complexes. The *ortho*-selectivity is diminishing as the steric demands of the substituents increase: X = F > OMe > Cl > Br > C≡CPh. The *ortho*-directing ability of these groups without coordination to the metal centre is unique. Indeed, the *ortho*-C–H activation generates the species in which there are no interactions between the W centres and the Lewis-basic benzene substituents. It was proposed that the Lewis-acidic tungsten centres are involved in agostic interactions with the methylene C–H bonds of the neopentyl ligands.

2.2 Functionalization of remote C–H bonds (molecular recognition)

A possible method to enhance the regioselectivity is to bring C–H bonds which we wish to functionalize close to the reaction centre. Close approach of selected C–H bonds to the active centre facilitates the reaction. In Section 2.1 we considered the reactions occurring *via* cyclometalated intermediates. The driving force of such processes is the formation of strong 5- or 6-membered cycles. Obviously, this method does not allow us to introduce into the reaction C–H bonds which are situated far from a directing group. The simplest way is to connect a substrate and the active centre with a chain of covalent bonds. In 1987, Groves and Neumann reported the epoxidation by PhIO of steroid fragments covalently linked to iron porphyrin.[7a] In this case only the double bonds of the side chains were epoxidized, while in the reaction catalyzed by the non-linked porphyrin the double bonds in the steroid nucleus were considerably more reactive. Later Grieco and co-workers[7b] used a similar system in which steroid substrates were covalently linked to manganese(III) salen active centre. Preferential oxidation with PhIO of only one of C–H bonds in the steroid was detected.

In recent years, Brudvig, Crabtree and co-workers[4a,7c-f] designed and thoroughly studied interesting systems for regioselective oxidation of remote C–H bonds using the MR approach (see Fig. 1c). The system consists of catalyst **2.14**, oxidant Oxone (peroxomonosulfate) and a substrate containing different types of C–H bonds (Scheme 2). The active centre of the catalyst contains two manganese ions and is bound to two MR fragments R (**2.15**). The carboxylic groups of these fragments can coordinate *via* hydrogen bonds to carboxylic bonds of the substrates:



Scheme 2 Oxidation of ibuprofen (**2.16**) and 4-methylcyclohexane acetic acid (**2.19**) by the Brudvig–Crabtree MR system.

anti-inflammatory drug ibuprofen (**2.16**) or 4-methylcyclohexane acetic acid (**2.19**). In accordance with the MR principle (see Fig. 1c), the Brudvig–Crabtree system oxidizes predominantly the CH_2 group of ibuprofen (which is situated in proximity to the active centre of catalyst **2.14**) to afford regioselective product **2.17** (98.5%) rather than alternative product **2.18** (1.5%). The oxidation of 4-methylcyclohexane acetic acid (a 5 : 4 mixture of *cis* and *trans* isomers) gave only a single product, *trans*-**2.20** (>99%). The amount of *cis*-**2.20** was <1%.

Breslow and co-workers in pioneering works on biomimetic oxidations of steroid compounds (see recent references[7g-j]) used two methods in order to link a steroid fragment to the catalytic centre (manganese porphyrinate). In the first strategy, pyridine recognition fragments were present in the catalyst which due to this was able to bind the substrate containing also pyridine groups. Selected C–H bonds from the steroid were in proximity to the active centre due to coordinating metals such as copper(II) ions (Fig. 2a). In the second method, for fixing selected C–H bonds from the steroid, manganese porphyrin was connected with β-cyclodextrin (CD) which is able to bind hydrophobic species in its central space (Fig. 2b).

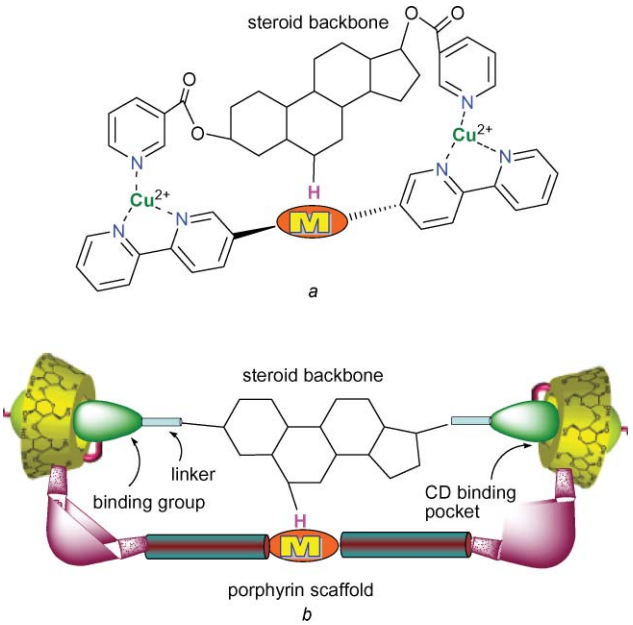
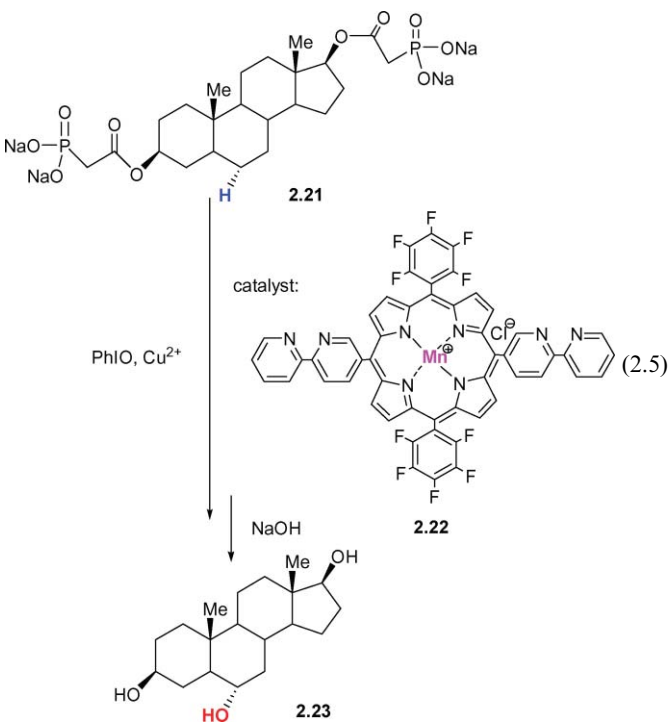


Fig. 2 Schematic representation of principles of regioselective steroid oxidation used in works by Breslow and co-workers.

A derivative of androstane-3,17-diol **2.21** was, under the action of PhIO and catalyst **2.22**, hydroxylated very regioselectively (90% of the product **2.23**) at the 6α position (eqn (2.5)).[7j] Reaction of steroid derivative **2.24** with PhIO in the presence of catalyst **2.25** afforded derivative **2.26** of androstane tetrol (eqn (2.6)).[7g] A similar catalyst has been also synthesized[7h] in which a manganese-containing active centre is linked to four hydrophobic cyclophane binding groups instead of CD fragments. It is important that in such systems saturated carbons of the substrates are hydroxylated in the presence of double bonds and secondary carbinol groups, which are not attacked for geometric reasons.



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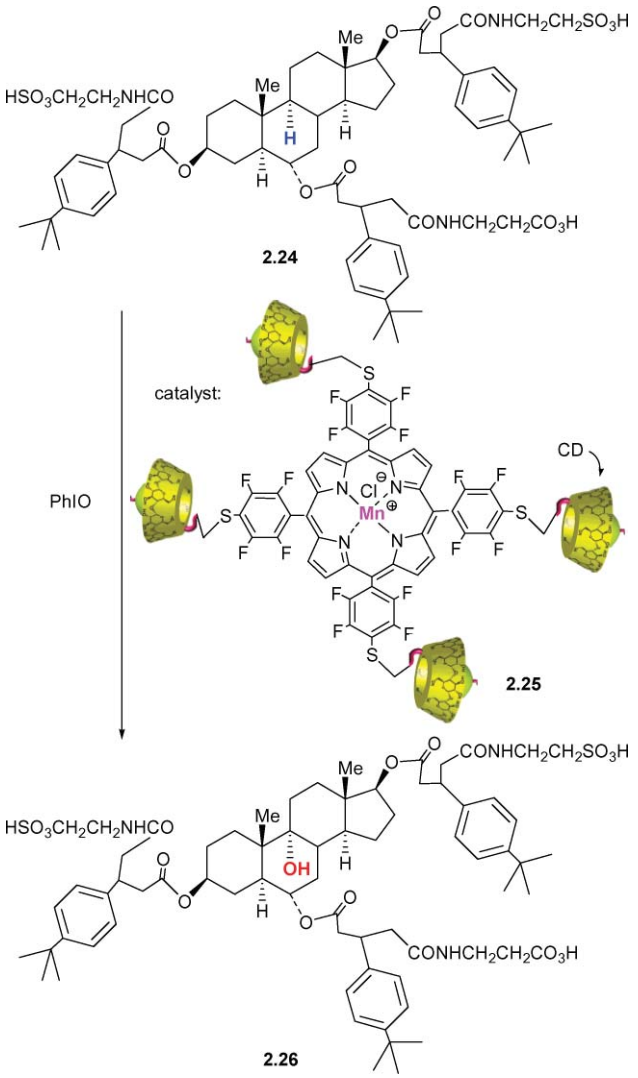


(2.6)

3 Steric hindrance in organometallic C–H activation

In the early eighties we discovered that the reaction of hexachloroplatinic acid with arenes in aqueous CF_3COOH or CH_3COOH affords stable σ-aryl complexes of platinum(IV) which can be isolated in the form of adducts with ammonia after chromatography on silica gel containing ammonia.[8a-d] The reaction can be induced not only thermally but also by the irradiation at low temperature with light[8d,e] or γ-quanta.[8d] Prolonged heating of the reaction solution at 70–97 °C leads to the decomposition of the σ-aryl complex with the formation of the corresponding biaryl as well as chlorinated arene. The reaction exhibits a few remarkable peculiarities (eqn (3.1)). Thus, the thermally induced process affords in the case of monosubstituted benzenes a mixture of the *meta*- (*m*-**3.1**) and *para*-metalated (*p*-**3.1**) isomers; the formation of the isomers is accompanied by the *meta–para*-isomerization leading to the statistical distribution *meta* : *para* ≈ 2 : 1 (Fig. 3, curve at 90 °C). In contrast, the light-induced process occurs only in the case of monosubstituted benzenes containing electron-releasing groups (OH, OCH_3, CH_3) and affords solely *para*-metalated products (for example, *p*-**3.1**, R = OCH_3; Fig. 4). The effective activation energy

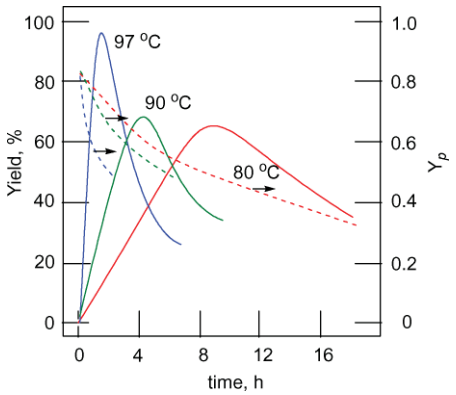


Fig. 3 Accumulation and decomposition with time of complex [σ-tolyl-$PtCl_4NH_3$]NH_4 (**3.1**, R = CH_3; a sum of *para* and *meta* isomers) in the thermal reaction of H_2PtCl_6 with toluene in CH_3COOH/H_2O at different temperatures. Dashed curves correspond to the relative content of the *para* isomer Yp = [*p*-tolyl–Pt]/([*p*-tolyl–Pt] + [*m*-tolyl–Pt]).

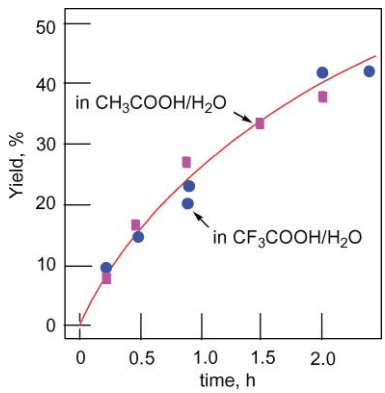
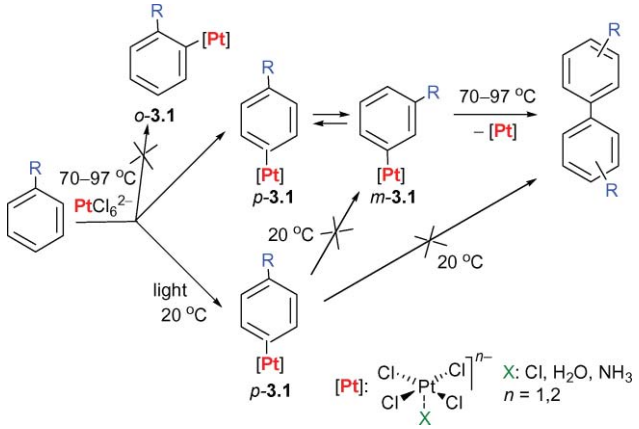


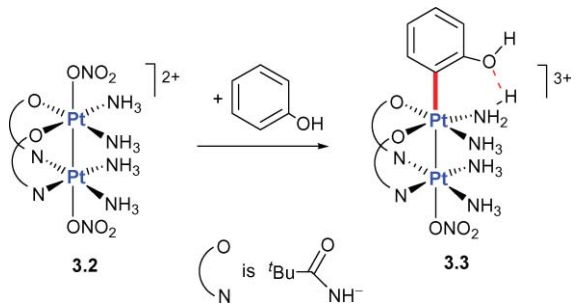
Fig. 4 Accumulation of complex [*p*-$CH_3OC_6H_4PtCl_4NH_3$]NH_4 (*p*-**3.1**, R = OCH_3) in the reaction of H_2PtCl_6 with toluene in CH_3COOH/H_2O (90 : 1) and CF_3COOH/H_2O (4 : 1) under light (320–485 nm) irradiation at 22 °C.

of the product formation in the photo-induced reaction is 5 kcal mol^{-1} and the activation energy of *para–meta* isomerization is 25 kcal mol^{-1}. This is the reason why the *para*-isomer exclusively formed in the photo-reaction at room temperature is not involved in simultaneous *para–meta* isomerization. It is interesting that the photoinduced reaction also proceeds in methylene chloride as a solvent.



(3.1)

The substituent in the reaction of arenes with H_2PtCl_6 does not enter the *ortho* position of toluene (as well as the α position in naphthalene) for steric reasons because the octahedral $PtCl_5(H_2O)^-$ fragment which can attack the arene is very large (Fig. 5a). Matsumoto and co-authors[8f] found that the thermal reaction of the pivalamidate-bridged Pt(III) dinuclear complex HH-$[Pt^{III}_2(NH_3)_4(^tBuCONH)_2(NO_3)_2](NO_3)_2{\cdot}2H_2O$ (**3.2**) (HH is head to head) with phenol proceeds *via* regio-selective C–H activation of the *ortho* position of the phenol molecule (eqn (3.2)). The *ortho*-metalated product **3.3** contains a hydrogen bonding between the phenolic oxygen and the NH_3 ligand. The authors assumed that "the steric hindrance is not so critical in the present reaction with phenol compared to Shul'pin's reaction".[8f] The hydrogen bonding between the oxygen atom and a proton of the equatorial ammonia ligand can act as an anchor to regioselectively activate the *ortho* C–H bond of phenol (Fig. 5b).



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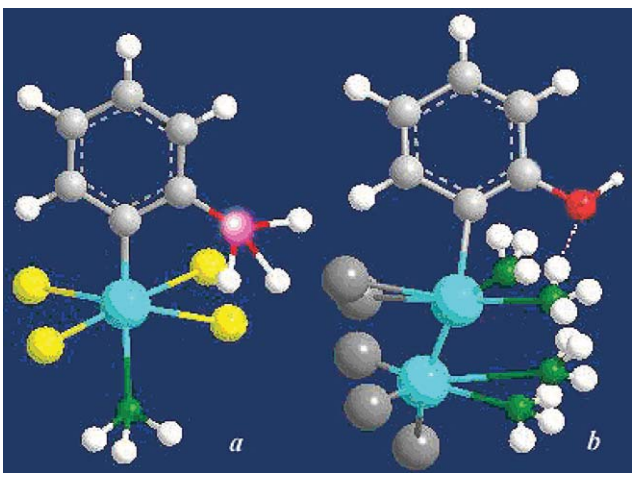


Fig. 5 Isomer *o*-**3.1**, R = CH_3 does not exist due to spatial restrictions (*a*). Complex **3.3** exists (*b*).

The thermal decomposition of isomers of the σ-tolyl complex formed in our reaction with H_2PtCl_6 in the initial period affords bitolyls which do not contain methyl groups at the *ortho* positions (Fig. 6).[8g] It is, however, noteworthy that after some induction period 2,3′- and 2,4′ isomers are formed, and after 8 h they are the predominant products. Similarly, the reaction with anisole affords 2,4′-dimethoxybiphenyl after the induction period (Fig. 7).[8h] Biaryls containing substituents in the *ortho* position are apparently produced on interaction of *meta* and *para* isomers of the σ-aryl complex with the free arene present in the solution. It is interesting that the reaction of Na_2PtBr_6 with toluene produces rapidly isomeric bitolyls: 3,3′, 3,4′ and 4,4′ (in the ratio 2.5 : 28 : 70), and *ortho*-substituted bitolyls have not been detected.[8i]

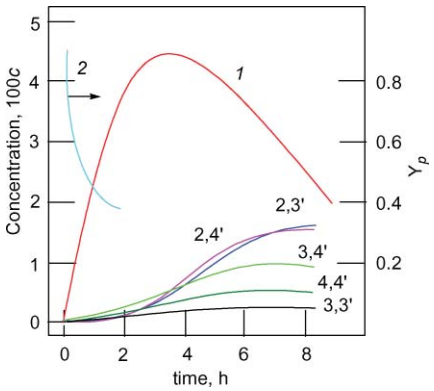


Fig. 6 Formation and decomposition of the σ-tolyl complex of platinum(IV) **3.1**, R = CH_3 (curve *1*), its *meta–para* isomerization (*2*) and accumulation of isomeric bitolyls with time (the reaction in CF_3COOH/H_2O at 90 °C).[8g]

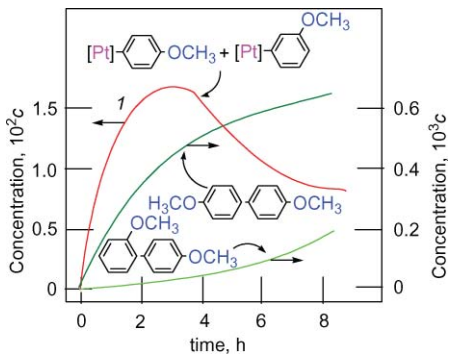
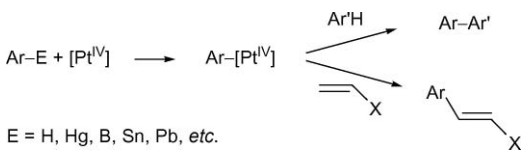


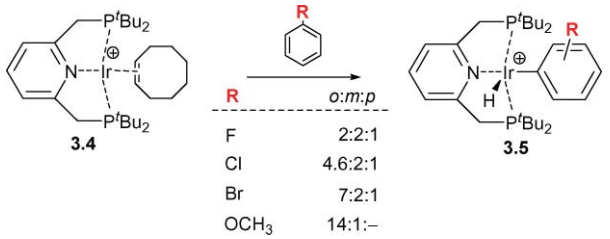
Fig. 7 Accumulation of the σ-methoxyphenyl complex of platinum(IV) (*para*+*meta*) and its decomposition (curve *1*) to produce two isomeric dimethoxybiphenyls (the reaction in CF_3COOH/H_2O at 85 °C).[8h]

Our reaction of $PtCl_6^{2-}$ with aromatic compounds is similar to well-known organometallic electrophilic reactions of arenes with ions Hg(II), Tl(III), Pb(IV), Au(III) and Pd(II).[8d] Palladium(II) derivatives which are used in numerous catalytic coupling reactions of aromatic and unsaturated compounds typically form unstable σ-aryl derivatives. Our platinum(IV) complexes can be considered as models of both metalation and coupling reactions. σ-Aryl complexes of platinum(IV) are easily obtained *via* splitting of Aryl–*E* bonds where *E* = H, Hg, B, Sn, Pb, Bi, Sb, in the reaction with H_2PtCl_6. These relatively stable complexes (isolated or prepared *in situ*) react with free arenes (see above) or olefins (eqn (3.3)).[8j] In contrast to Pt(IV) chlorides, derivatives of non-transition and transition metals active in metalation mentioned above including palladium(II) have noticeably less sterically large molecules. Due to this the coupling reactions with platinum are more regioselective. For example, complexes of Au(III)[8k] and Pd(II)[8l,m] easily metalate monosubstituted benzenes at the *ortho* position. In contrast, the electrophilic metalation of anisole, toluene and chlorobenzene by the very bulky (octaethylporhyrinato)rhodium(III) chloride molecule occurs exclusively at the *para* position.[8n]



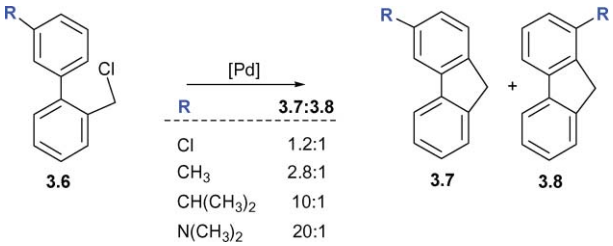
(3.3)

In an interesting work, Milstein, Martin and co-workers[9a] found that complex (PNP)Ir(COE)$^+$ (PNP = 2,6-bis(di-*tert*-butylphosphinomethyl)pyridine; COE = cyclooctene) **3.4** containing bulky substituents at the reactive centre exhibited in the reaction with fluorobenzene no preference for the *ortho* C–H bond (eqn (3.4)). In contrast, *ortho* selectivity was observed with chlorobenzene, bromobenzene and anisole. The authors assumed that this selectivity is due to the *o*-C–H activation assisted by coordination to chlorine, bromine and oxygen atoms (see Section 2.1).



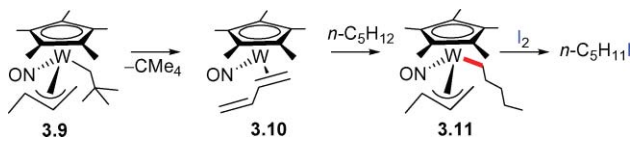
(3.4)

It should be noted that in some cases when bulky substituents in arene rings are present, the steric influence of substituents on the regioselectivity can be seen. Thus, in the Pd-catalyzed synthesis of fluorene derivatives from compounds **3.6** according to eqn (3.5)[9b] steric factors are more dominant for regiocontrol than electronic effects. On going from less bulky groups to more voluminous substituents the **3.7** : **3.8** ratio increases.



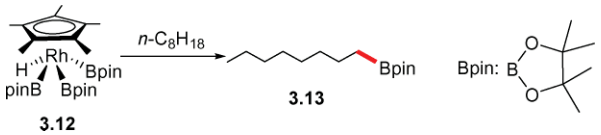
(3.5)

Legzdins and co-workers[9c,d] described very interesting functionalizations of various hydrocarbons exclusively at their terminal carbons. For example, thermolysis of complex **3.9** leads to the formation of the intermediate **3.10** which, in the presence of a linear alkane, affords *n*-alkyl derivative **3.11** (eqn (3.6)). These complexes produce alkyl iodides, **3.11**.[9c] The reaction of a triruthenium complex [Cp*Ru(μ-H)]$_3$(μ$_3$-H)$_2$ with *n*-pentane gave a *closo*-ruthenacyclopentadiene complex [Cp*Ru]$_2$[Cp*Ru(μ$_3$-CMe=CHCH=CH–)](μ-H).[9e] Six C–H bonds including that of one of the methyls are cleaved in this process.



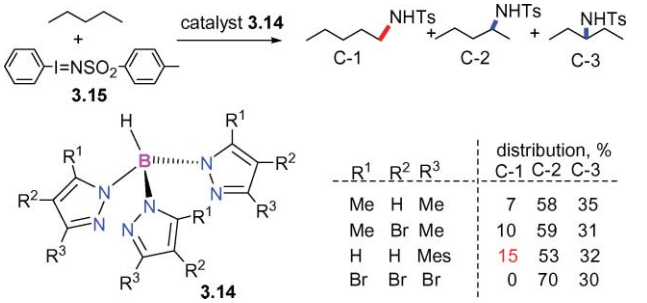
(3.6)

Hartwig and co-workers developed a very efficient method for remarkable regiospecific functionalization of C–H bonds in linear alkanes.[10a-c] Thus, the reaction of complex **3.12** with *n*-octane gives exclusively *n*-octylboronate ester **3.13** in 72% yield (eqn (3.7)).[10a]



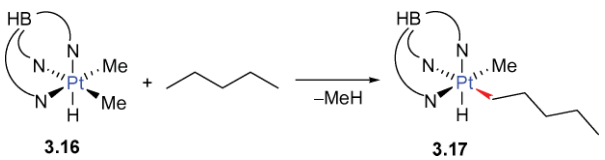
(3.7)

Metal-catalyzed reactions of carbene and nitrene insertion into C–H bonds[10d-g] can proceed regioselectively if sterically encumbered catalysts are used.[10h-k] Thus, Pérez and co-workers found that complexes Tp^{x}Ag (Tp^x is hydrotris(pyrazolyl)borate ligand) **3.14** catalyze insertion of a nitrene unit from PhI=NTs (**3.15**) into the C–H bond of the alkane (eqn (3.8)). Catalyst **3.14** (R^1 = R^2 = H, R^3 = Mesityl) provided the highest value of the primary site activation product C-1 (15%). The authors proposed that "this may be interpreted as a consequence of the steric pressure of the mesityl substituents, which reduces the size of the catalytic pocket, disfavoring activation of the more sterically demanding sites".[10i] Dias and co-workers[10l,m] studied silver scorpionate mediated insertion of carbenes into C–H bonds and demonstrated that the carbene insertion into primary C–H bonds increases in the following order of tris(pyrazolyl)boratosilver(I) catalysts: [MeB(3-(CF$_3$)Pz)$_3$]Ag(C$_2$H$_4$) < [MeB(3-(C$_2$F$_5$)Pz)$_3$]Ag(C$_2$H$_4$) < [HB(3,5-(CF$_3$)$_2$Pz)$_3$]Ag(C$_2$H$_4$).



(3.8)

Templeton and co-workers used the platinum scorpionate complex Tp′PtMe$_2$H where Tp′ = hydridotris(3,5-dimethylpyrazolyl)borate (**3.16**) in activation of C–H bonds in alkanes.[10n,o] The reaction of **3.16** with *n*-pentane (eqn (3.9)) gave Tp′Pt(1-pentyl)(Me)H (**3.17**). Products of activation of positions 2 and 3 in *n*-pentane were not detected.



(3.9)

4 Selectivity of biological oxidation

Enzymes (cytochrome P450,[11a-e] methane monooxygenase, MMO, alkane hydroxylase[11f]) catalyze the selective oxidation of alkanes and other C–H compounds to the corresponding alcohols.[11g-i] Normal alkanes are often oxygenated to produce selectively 1-alkanols, whereas carboxylic acids give products of ω hydroxylation.[11j-m] However, soluble MMO oxidizes *n*-heptane to 100% 2-heptanol and *n*-pentane to 2-pentanol (73%) and 1-pentanol (27%).[11n] Oxidation of some acids by cyctochrome P450 BM3 (CYP102) from *Bacillus megaterium* demonstrated a significant preference for oxidation at the ω-2 methylene.[11o] Toluene was oxidized with some predominance of *p*-cresol by toluene *o*-xylene monooxygenase from *Escherichia coli* cells.[11p]

The hydroxylation of substrates occurs in a hydrophobic pocket around the active site.[12a,b] It has been shown that in the regioselective oxygenation of a functionalized C–H compound (cineole) in cytochrome P450cin from *Citrobacter braakii*, substrate–protein

hydrogen bonding plays the critical role.[12c] Urlacher, Pleiss and co-workers studied anchoring effects in a wide binding pocket of cytochrome P450 in the oxidation of (–)-α-pinene.[12d] They demonstrated that a widely open binding site does not necessarily result in low regioselectivity. A single residue can induce selectivity by stabilizing the nonpolar substrate in defined binding conformations.

Different mutants of cyctochrome P450 afford different distribution of hydroxylated regio-isomers. Thus, wild-type P450 BM3 oxidizes saturated fatty acids producing a mixture of ω-1, ω-2 and ω-3 hydroxylated products. Some mutants were able to oxidize lauric acid in addition to these isomers not only at ω-7 position, but they also gave ω-8 and ω-9 oxygenated products.[12e] The oxidation of linear alkanes by cytochrome P450 is especially interesting for us here. Arnold and co-workers studied the hydroxylation of *n*-octane by cytochrome P450 BM3 mutants.[12f] It can be seen in Fig. 8 that mutant 77-9H hydroxylates *n*-octane not very selectively at the terminal position. Mutant 53-5H more selectively oxidizes C–H bonds at position 2. It is noteworthy that both mutants hydroxylate predominantly position 2 in alkanes which are shorter or longer than *n*-octane.

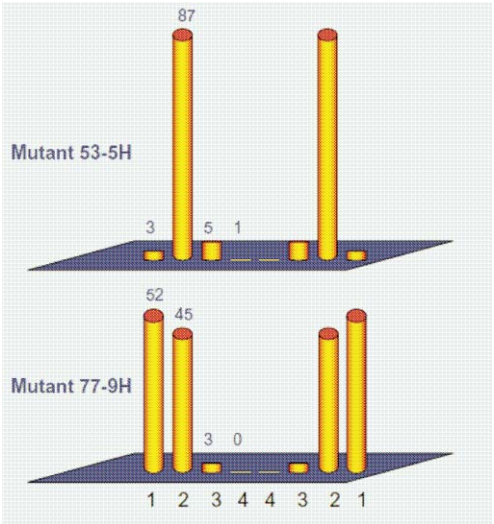


Fig. 8 Distribution (ratio of a specific alcohol isomer to the total amount of alcohols,%) of regio-isomers in *n*-octane oxidation by two mutants of cytochrome P450 BM3.

5 Creating spatial restrictions around the reaction centre using bulky substituents

Certain metal complexes can be considered as models of the cytochrome P450 active centre. Such complexes catalyze the oxygenation of C–H bonds of various substrates by molecular oxygen as well as peroxo or oxo compounds. A remarkable peculiarity of some forms of cytochrome P450 is preferable hydroxylation of the ω and ω-1 positions of linear alkanes (see Section 4). To model this unusual regioselectivity is a challenging goal of homogeneous biomimetic catalysis.

Metalloporphyrins[13a] are the closest models of the cytochrome P450 active centre. Shilov and Shteinman,[13b] Suslick[13c] and Mansuy[13d-f] and their co-workers were the first to use sterically hindered metalloporphyrins in order to increase the relative amount of the ω-oxidized *n*-alkanes; Collman's "picket fence" concept (Fig. 9)[13g] was employed. For example, in the case of the *n*-hexane oxidation with PhIO catalyzed by non-hindered tetraphenylporphyrinatoiron the normalized (that is, calculated taking into account the number of hydrogen atoms at each carbon) regioselectivity parameter C(1) : C(2) : C(3) was 1 : 100 : 100. However, catalysis by hindered tetra(*o*-nitrophenyl)porphyrinatoiron gave much higher relative concentrations of the ω and ω-1 isomers: C(1) : C(2) : C(3) = 1.0 : 12.5 : 3.1.[13b] In another example, the moderately hindered (5,10,15,20-tetrakis(2′,4′,6′-trimethoxyphenyl)porphyrinato)manganese(III) acetate showed little selectivity toward terminal methyl hydroxylation.[13c] Thus, the oxidation of *n*-heptane gave the 1-, 2-, 3-, and 4-hydroxylated products in yields of 3, 49, 33, and 15%, respectively. The primary selectivity (the ratio of the total primary alcohol to total secondary alcohols normalized for the relative number of hydrogen atoms) was only 0.052. The catalysis by the very sterically hindered (5,10,15,20-tetrakis(2′,4′,6′-triphenylphenyl)porphyrinato)manganese(III) acetate showed good regioselectivity: yields of isomers were 14, 55, 21, and 10%; primary selectivity was 0.24. It is noteworthy that *t*-butyl hydroperoxide (TBHP) showed no primary carbon selectivity, and reaction product ratios were independent of the metalloporphyrin catalyst.

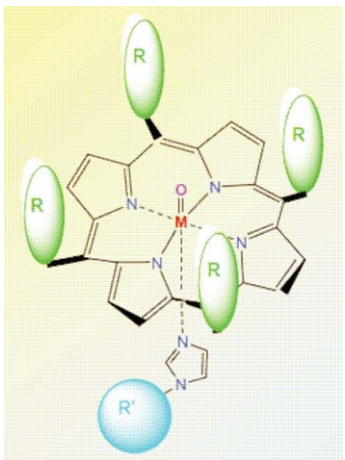
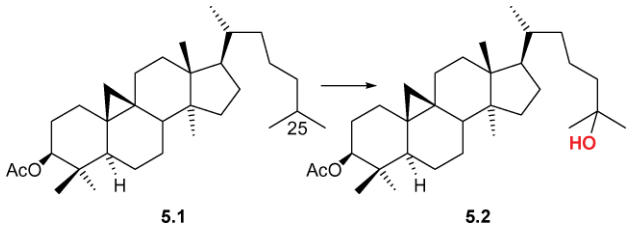


Fig. 9 Collman's "picket fence" concept. Bulky substituents R inhibit bimolecular reactions, allowing contact between the metal centre and the linear hydrocarbon only *via* the terminal CH_3 group whereas bulky R′ disfavors coordination of the base on the picket fence side.

The oxidation of cycloartanyl acetate (**5.1**) with TBHP catalyzed by *meso*-5,10,15,20-tetramesitylporphyrinate osmium(II) carbonyl complex gave the sole product 25-hydroxycycloartanyl acetate (**5.2**) in 50% isolated yield.[13h] In this reaction the oxidant with voluminous substituents preferentially attacks a sterically less hindered carbon C-25.

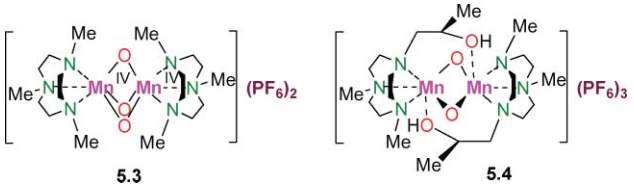
In metalloporphyrin-catalyzed oxidations of hydrocarbons the steric hindrance around the reactive centre can be created by using cyclodextrin (CD). The *n*-hexane hydroxylation with PhIO catalyzed by the substituted ironporphyrin in water gave 1-, 2-, and 3-hexanols in 3, 62, and 35% yield, respectively.[13i] Shilov, Shteinman and their co-workers showed[13i] that in the presence of CD the relative amount of primary alcohol dramatically increased:



5.1 5.2 (5.1)

26, 50, and 24%. Suslick *et al.*[13j] created porous solids using various polyfunctionalized porphyrins with pores which are comparable with those of zeolites. Unfortunately, no shape selectivity was observed in studies of catalytic oxidation of *n*-alkanes. Recently, Mahy and co-workers[13k] described the non-covalent insertion of a cationic iron-porphyrin–estradiol cofactor into an *anti*-estradiol antibody using the "Trojan horse" strategy. The authors assumed that artificial metalloenzymes generated by this valuable method can act as catalysts for selective alkene epoxidation and alkane hydroxylation.

In 1998, we discovered that in the presence of a carboxylic (acetic, oxalic *etc.*) acid dinuclear manganese(IV) complex **5.3** catalyzes the efficient oxidation of alkanes (as well as other organic compounds) with peroxides.[14a,b] The oxidation of linear alkanes with H_2O_2 in acetonitrile gave an even distribution of isomeric alkyl hydroperoxides (which were quantitatively reduced by PPh_3 to the corresponding alcohols): the selectivity parameters C(1) : C(2) : C(3) : C(4) were 1 : 42 : 37 : 34 in the case of *n*-heptane[3d] and 1 : 29 : 25 : 24 in the *n*-octane oxidation.[14c] It should be noted that the calculations were based on the concentrations of only corresponding alcohols after reduction of the reaction samples with triphenylphosphine. These concentrations were equal to the concentration of the isomeric alkyl hydroperoxides (major products) plus concentration of the alcohol (minor products). It turned out that the oxidation in aqueous solution gave unusual distribution of regio-isomers (Fig. 10).[14d] We assumed that the oxidation occurs in a hydrophobic cleft[14e] of an active catalyst form generated from precatalyst **5.3**. *n*-Heptane exists in water in the compact "bull's head conformation" (terminal methyls are modeled by bull's horns) and position 4 of the alkane is in the closest contact with the oxidizing centre.[14d]



In the oxidation of *n*-octane catalyzed by complex **5.4** containing a very hindered active centre both by H_2O_2 and TBHP marked predominance of isomers 2 and 3 over isomer 4 has been found (Fig. 11).[14f] Similar isomer distribution has been obtained in the oxidation of *n*-octane with TBHP catalyzed by sterically hindered tetracopper(II) triethanolaminate complex [O ⊂ $Cu_4\{N(CH_2CH_2O)_3\}_4(BOH)_4][BF_4]_2$: C(1) : C(2) : C(3) : C(4) = 1 : 65 : 32 : 30.[14g] In the oxidation of methylcyclohexane by this system, the reactivity of C–H bonds at the position 2 of the cyclohexane ring relative to the methyl group is about nine

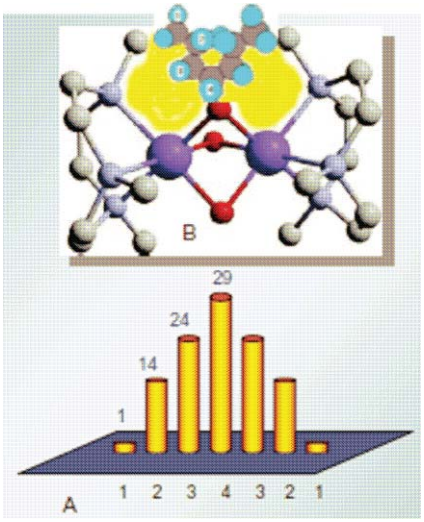


Fig. 10 A: Isomer distribution (alcohols, after reduction with PPh_3; normalized) in the *n*-heptane oxidation with H_2O_2/**5.3**/oxalic acid in H_2O. B: A schematic representation of the *n*-heptane oxidation in the catalyst **5.3** cleft (yellow cavity).[14d]

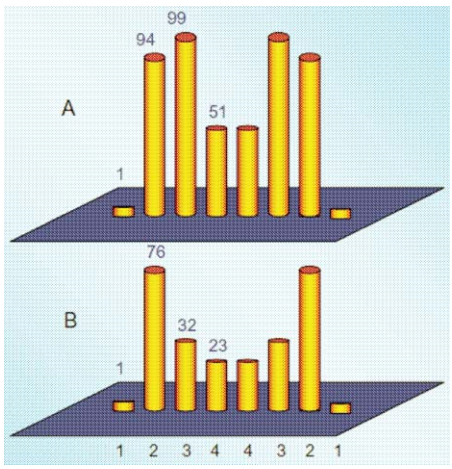


Fig. 11 Isomer distribution (alcohols, after reduction with PPh_3; normalized) in *n*-octane oxidation with H_2O_2/**5.4**/oxalic acid (A) and TBHP/**5.4**/oxalic acid (B) in MeCN.

and three times lower in comparison with the reactivities of C–H bonds at the positions 3 and 4, respectively, and this indicates significant steric hindrance. It has been similarly shown that hydrogen abstraction by photoexcited decatungstate from methylcyclohexane occurs from positions 1/2/3/4 in the ratio ~0 : ~0 : 1.2 : 1 which results from steric hindrance.[14h] Mizuno and co-workers[14i] very recently described efficient stereo- and regioselective alkane hydroxylation with hydrogen peroxide catalyzed by the bulky divanadium-substituted phosphotungstate $[\gamma\text{-}H_2PV_2W_{10}O_{40}]^{3-}$. For example, in the oxidations of *cis*- and *trans*-decalins and *trans*-1,2-dimethylcyclohexane, stereospecific oxygenation of tertiary C–H bonds was observed. The reaction with *n*-hexane gave 1-, 2- and 3-hexanols in a 2 : 66 : 26 ratio.

6 Reactions within constrained inorganic nano pores

If we place metal ions or complexes into constrained environments, the selectivity of the reaction may be changed in comparison with the selectivity observed in the cases when homogeneous catalysts are used.[15] The simplest example is when the catalyst is anchored to a concave surface. Thus, changes in the selectivity have been noticed in the oxidation of 2-methylhexane with H_2O_2 catalyzed by a maltolato vanadium complex covalently bonded to silica gel and pyrazine-2-carboxylic acid.[16a] Immobilization of anionic iron(III) porphyrins into three-dimensionally macroporous layered double hydroxide led to enhancement of the selectivity relative terminal methyl groups in the oxidation of *n*-heptane with PhIO.[16b] The authors noted that "the particular structure of the support with channel and micro-environments can create a suitable structure for the access of the terminal position of the substrate for this family of biomimetic catalysts in the case of the selective oxidation in position C-1 of the linear alkane". Pombeiro and co-workers[16c] studied alkane oxidations with TBHP catalyzed by homogeneous Mn(salen) complexes as well as by analogous complexes immobilized on a polydimethylsiloxane (PDMS) based membrane. No products of oxygenation at the terminal CH_3 groups were detected. When the immobilized catalyst was used, the hydrogens at the position 2 in *n*-heptane and *n*-octane were more accessible in view of the presence of the bulky hydrophobic PDMS chains and thus were preferably oxygenated. In many cases, however, mesoporous catalysts give rise to the even distribution of isomers in the oxygenation of linear alkanes and the reactions proceed non-stereoselectively (see, for example, oxidations with H_2O_2 catalyzed by Ti-MMM-2[16d]). It is interesting that the oxidation[16e] with H_2O_2 catalyzed by montmorillonite K-10 exhibits some stereoselectivity: predominant formation of the alcohol with *cis*-orientation of the methyl groups (the *trans*/*cis* ratio is 0.6) is noticed in the case of oxidation of *cis*-1,2-dimethylcyclohexane. The oxidation of *trans*-1,2-dimethylcyclohexane gave rise to the prevalence of the alcohol with mutual *trans*-orientation of methyl groups (the *trans*/*cis* ratio is 1.5). Iron ions in low concentration within the montmorillonite interlayer space are apparently responsible for the catalysis.[16e]

Herron and Tolman in their pioneering works on "completely inorganic mimics of cytochrome P450 and alkane ω-hydroxylases",[17a,b] demonstrated, that, for example, if Fe on zeolite ZSM-5 is used as a catalyst, *n*-octane can be oxidized with H_2O_2 with unusual regioselectivity: the distribution of the oxygenates along the chain was 45, 23, 19, and 13%. It was noted that the substrate selectivity is defined by the simple diameter of the pores. Thomas, Raja and co-workers[17c] used in aerobic oxyfunctionalization of linear alkanes microporous aluminophosphates with narrow pores (AlPO-18 with pore aperture 0.38 nm) and with more wide pores (AlPO-36: 0.65 × 0.75 nm). Small quantities of metal ions (Co^{III}) within the pores played the role of catalytically active centres. Oxyfunctionalization catalyzed by CoAlPO-18 is favored at the terminal methyl group because only an end-on approach of the alkane to the active site is allowed. The larger pore dimensions of AlPO-36 lead to functionalization predominantly at the 3 and 4 positions (Fig. 12). Ciuffi and co-workers[17d] found that oxidation of *n*-heptane with PhIO catalyzed by cobalt aluminium silicate complexes prepared by the non-hydrolytic sol–gel route affords exclusively 2-heptanol.

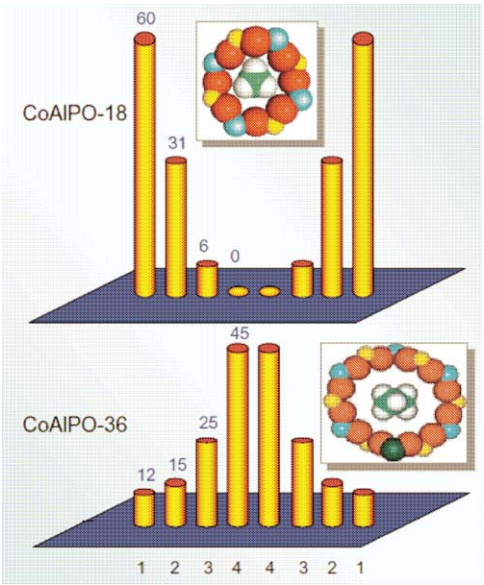


Fig. 12 Distribution of regio-isomers (mol%; the total of alcohols, ketones, aldehydes and acids at a given position) in aerobic oxidation of *n*-octane.

It has been shown by Tatsumi and co-workers[17e] that in the phenol hydroxylation with H_2O_2 catalyzed by microporous titanosilicalite TS-1, addition of benzene or cyclohexane enhances *para*-selectivity. The authors assumed that the coexistent molecules "impose the steric restriction for the transition state of phenol hydroxylation, resulting in the enhancement of the shape-selectivity". We have found[17f,g] that TS-1 catalyzes oxidation of *n*-hexane and *n*-heptane with H_2O_2 without any solvent to produce predominantly 3-isomers of alcohols and ketones (Fig. 13A). The analysis of the products by GC before and after reduction with PPh_3 demonstrated that alkyl hydroperoxides are not formed in this reaction. Addition of 3-hexanol leads to a substantial improvement of the selectivity (Fig. 13B). *n*-Octane gave predominantly 2-oxygenates, however, when 3-hexanol was added the amount of 2-octanol and 2-octanone became negligible and 3-oxygenates considerably prevailed. We assumed that the oxidation proceeds in the narrow channels of TS-1 and *n*-heptane adopts a "hairpin conformation". When acetonitrile was used as a solvent and some amount of NaOH was added[17h] the reaction mechanism was cardinally changed. Concentrations of alkyl hydroperoxides formed in this reaction were measured by a simple method developed by us earlier (for this method, see[1h-j,17i]). Comparison of concentrations of alcohols and ketones obtained before and after reduction of the reaction samples with PPh_3 indicated that alkyl hydroperoxides were the main products. The oxidation of linear alkanes led to "usual" distribution of isomers. The reaction proceeds apparently not in narrow channels of the TS-1 solid but on its surface and hydroxyl radicals are the oxidizing species in this case.

The material discussed in this review allows us to say in conclusion after Nobel Laureate Prof. N. N. Semenov: "by applying the ideas of biochemistry, chemical science may solve the energy crisis, make industrial production infinitely more efficient, and provide mankind with wings".

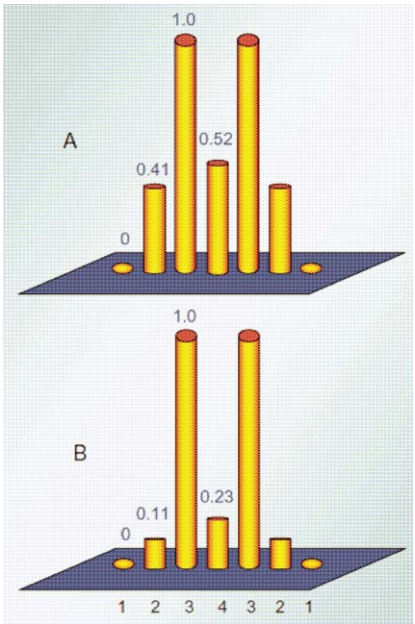


Fig. 13 A: Isomer distribution (total of all products: alcohols plus ketones; normalized) in the *n*-heptane oxidation with H_2O_2 catalyzed by TS-1. B: The same, but in the presence of 3-hexanol.

References

1 (*a*) N. M. Emanuel', *Russ. Chem. Rev.*, 1978, **47**, 705–741; (*b*) A. E. Shilov and G. B. Shul'pin, *Chem. Rev.*, 1997, **97**, 2879–2932; (*c*) A. E. Shilov and G. B. Shul'pin, "*Activation and Catalytic Reactions of Saturated Hydrocarbons in the Presence of Metal Complexes*", Kluwer Academic Publishers, Dordrecht/Boston/London, 2000; (*d*) G. B. Shul'pin, "Oxidations of C–H Compounds Catalyzed by Metal Complexes", in M. Beller, C. Bolm, (ed.), *Transition Metals for Organic Synthesis*, Wiley–VCH, Weinheim/New York, vol. 2 (chapter 2.2), 2nd edition, 2004, pp. 215-242; (*e*) R. A. Periana, G. Bhalla, W. J. Tenn, III, K. J. H. Young, X. Y. Liu, O. Mironov, C. J. Jones and V. R. Ziatdinov, *J. Mol. Catal. A: Chem.*, 2004, **220**, 7–25; (*f*) J. A. Labinger, *J. Mol. Catal. A: Chem.*, 2004, **220**, 27–35; (*g*) R. H. Crabtree, *J. Organomet. Chem.*, 2004, **689**, 4083–4091; (*h*) G. B. Shul'pin, *Mini-Rev. Org. Chem.*, 2009, **6**, 95–104; (*i*) G. B. Shul'pin, *J. Mol. Catal. A: Chem.*, 2002, **189**, 39–66; (*j*) G. B. Shul'pin, Y. N. Kozlov, L. S. Shul'pina, A. R. Kudinov and D. Mandelli, *Inorg. Chem.*, 2009, **48**, 10480–10482; (*k*) A. Ishikawa, Y. Nakao, H. Sato and S. Sakaki, *Dalton Trans.*, 2010, **39**, 3279–3289; (*l*) K. R. Sawyer, J. F. Cahoon, J. E. Shanoski, E. A. Glascoe, M. F. Kling, J. P. Schlegel, M. C. Zoerb, M. Hapke, J. F. Hartwig, C. E. Webster and C. B. Harris, *J. Am. Chem. Soc.*, 2010, **132**, 1848–1859; (*m*) J. M. Villalobos, A. J. Hickman and M. S. Sanford, *Organometallics*, 2010, **29**, 257–262; (*n*) S. M. Bischof, D. H. Ess, S. K. Meier, J. Oxgaard, R. J. Nielsen, G. Bhalla, W. A. Goddard, III and R. A. Periana, *Organometallics*, 2010, **29**, 742–756; (*o*) L. I. Matienko, L. A. Mosolova and G. E. Zaikov, *Russ. Chem. Rev.*, 2009, **78**, 211–230; (*p*) W. H. Bernskoetter, S. K. Hanson, S. K. Buzak, Z. Davis, P. S. White, R. Swartz, K. I. Goldberg and M. Brookhart, *J. Am. Chem. Soc.*, 2009, **131**, 8603–8613; (*q*) Z. Huang, E. Rolfe, E. C. Carson, M. Brookhart, A. S. Goldman, S. H. El-Khalafy and A. H. Roy MacArthur, *Adv. Synth. Catal.*, 2010, **352**, 125–135; (*r*) B. C. Bailey, R. R. Schrock, S. Kundu, A. S. Goldman, Z. Huang and M. Brookhart, *Organometallics*, 2009, **28**, 355–360; (*s*) J. Roithova and D. Schröder, *Chem. Rev.*, 2010, **110**, 1170–1211; (*t*) Z. Fang, C. Fu and S. Ma, *Chemistry – Eur. J*, 2010, **16**, 3910–3913.

2 (*a*) L. V. Desai, K. J. Stowers and M. S. Sanford, *J. Am. Chem. Soc.*, 2008, **130**, 13285–13293; (*b*) H.-Q. Do and O. Daugulis, *Chem. Commun.*, 2009, 6433–6435; (*c*) M. S. Chen and M. C. White, *Science*, 2007, **318**, 783–787; (*d*) L. Li, W. W. Brennessel and W. D. Jones, *Organometallics*, 2009, **28**, 3492–3500; (*e*) E. M. Beck, N. P. Grimster, R. Hartley and M. J. Gaunt, *J. Am. Chem. Soc.*, 2006, **128**, 2528–2529; (*f*) S. Tokuji, T. Yurino, N. Aratani, H. Shinokubo and A. Osuka, *Chem.–Eur. J.*, 2009, **15**, 12208–12211.

3 (*a*) J. Roger, A. L. Gottumukkala and H. Doucet, *ChemCatChem*, 2010, **2**, 20–40; (*b*) J.-W. Park and C.-H. Jun, *ChemCatChem*, 2009, **1**, 69–71; (*c*) M. Feller, A. Karton, G. Leitus, J. M. L. Martin and D. Milstein, *J. Am. Chem. Soc.*, 2006, **128**, 12400–124001; (*d*) G. B. Shul'pin, G. Süss-Fink and J. R. Lindsay Smith, *Tetrahedron*, 1999, **55**, 5345–5358; (*e*) B. H. Brodsky and J. Du Bois, *J. Am. Chem. Soc.*, 2005, **127**, 15391–15393; (*f*) R. Giri, B.-F. Shi, K. M. Engle, N. Maugel and J.-Q. Yu, *Chem. Soc. Rev.*, 2009, **38**, 3242–3272.

4 (*a*) S. Das, G. W. Brudvig and R. H. Crabtree, *Chem. Commun.*, 2008, 413–424; (*b*) J. K. M. Sanders, *Chem.–Eur. J.*, 1998, **4**, 1378–1383; (*c*) M. J. Wilkinson, P. W. N. M. van Leeuwen and J. N. H. Reek, *Org. Biomol. Chem.*, 2005, **3**, 2371–2383; (*d*) A. B. Descalzo, R. Martínez-Máñez, F. Sancenón, K. Hoffmann and K. Rurack, *Angew. Chem., Int. Ed.*, 2006, **45**, 5924–5948; (*e*) H.-J. Schneider and A. K. Yatsimirsky, *Chem. Soc. Rev.*, 2008, **37**, 263–277.

5 (*a*) M. Albrecht, *Chem. Rev.*, 2010, **110**, 576–623; (*b*) C. S. Yi and D. W. Lee, *Organometallics*, 2009, **28**, 4266–4268; (*c*) P. A. Sibbald, C. F. Rosewall, R. D. Swartz and F. E. Michael, *J. Am. Chem. Soc.*, 2009, **131**, 15945–15951; (*d*) H. A. Chiong, Q.-N. Pham and O. Daugulis, *J. Am. Chem. Soc.*, 2007, **129**, 9879–9884; (*e*) A. Lazareva and O. Daugulis, *Org. Lett.*, 2006, **8**, 5211–5213; (*f*) X. Chen, K. M. Engle, D.-H. Wang and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2009, **48**, 5094–5115; (*g*) C.-L. Sun, B.-J. Li and Z.-J. Shi, *Chem. Commun.*, 2010, **46**, 677–685; (*h*) X. Ribas, R. Xifra, T. Parella, A. Poater, M. Solà and A. Llobet, *Angew. Chem., Int. Ed.*, 2006, **45**, 2941–2944.

6 (*a*) V. G. Zaitsev, D. Shabashov and O. Daugulis, *J. Am. Chem. Soc.*, 2005, **127**, 13154–13155; (*b*) K. L. Hull, E. L. Lanni and M. S. Sanford, *J. Am. Chem. Soc.*, 2006, **128**, 14047–14049; (*c*) K. L. Hull and M. S. Sanford, *J. Am. Chem. Soc.*, 2007, **129**, 11904–11905; (*d*) K. J. Stowers and M. S. Sanford, *Org. Lett.*, 2009, **11**, 4584–4587; (*e*) I. Özdemir, S. Demir, B. Çetinkaya, C. Gourlaouen, F. Maseras, C. Bruneau and P. Dixneuf, *J. Am. Chem. Soc.*, 2008, **130**, 1156–1157; (*f*) P. Arockiam, V. Poirier, C. Fischmeister, C. Bruneau and P. Dixneuf, *Green Chem.*, 2009, **11**, 1871–1875; (*g*) L. Ackermann, P. Novák, R. Vicente and N. Hofmann, *Angew. Chem., Int. Ed.*, 2009, **48**, 6045–6048; (*h*) X. Jia, D. Yang, S. Zhang and J. Cheng, *Org. Lett.*, 2009, **11**, 4716–4719; (*i*) S. Chen, G. Song and X. Li, *Tetrahedron Lett.*, 2008, **49**, 6929–6932; (*j*) F. Yang, Y. Wu, Y. Li, B. Wang and J. Zhang, *Tetrahedron*, 2009, **65**, 914–919; (*k*) B. D. Dangel, J. A. Johnson and D. Sames, *J. Am. Chem. Soc.*, 2001, **123**, 8149–8150; (*l*) J. Y. K. Tsang, M. S. A. Buschhaus, P. Legzdins and B. O. Patrick, *Organometallics*, 2006, **25**, 4215–4225.

7 (*a*) J. T. Groves and R. Neumann, *J. Am. Chem. Soc.*, 1987, **109**, 5045–5047; (*b*) M. D. Kaufman, P. A. Grieco and D. W. Bougie, *J. Am. Chem. Soc.*, 1993, **115**, 11648–11649; (*c*) R. H. Crabtree, *Dalton Trans.*, 2003, 3985–3990; (*d*) S. Das, G. W. Brudvig and R. H. Crabtree, *J. Am. Chem. Soc.*, 2008, **130**, 1628–1637; (*e*) D. Balcells, P. Moles, J. D. Blakemore, C. Raynaud, G. W. Brudvig, R. H. Crabtree and O. Eisenstein, *Dalton Trans.*, 2009, 5989–6000; (*f*) S. Das, G. W. Brudvig and R. H. Crabtree, *Inorg. Chim. Acta*, 2009, **362**, 1229–1233; (*g*) R. Breslow, J. Yang and J. Yan, *Tetrahedron*, 2002, **58**, 653–659; (*h*) R. Breslow and Z. Fang, *Tetrahedron Lett.*, 2002, **43**, 5197–5200; (*i*) J. Yang, B. Gabriele, S. Belvedere, Y. Huang and D. Breslow, *J. Org. Chem.*, 2002, **67**, 5057–5067; (*j*) Z. Fang and R. Breslow, *Org. Lett.*, 2006, **8**, 251–254.

8 (*a*) G. B. Shul'pin, *J. Gen. Chem. USSR*, 1981, **51**, 1808–1818; (*b*) G. B. Shul'pin, A. E. Shilov, A. N. Kitaigorodskii and J. V. Zeile Krevor, *J. Organomet. Chem.*, 1980, **201**, 319–325; (*c*) G. B. Shul'pin, *J. Organomet. Chem.*, 1981, **212**, 267–274; (*d*) G. B. Shul'pin, G. V. Nizova and A. T. Nikitaev, *J. Organomet. Chem.*, 1984, **276**, 115–153; (*e*) G. B. Shul'pin, G. V. Nizova and A. E. Shilov, *J. Chem. Soc., Chem. Commun.*, 1983, 671–672; (*f*) M. Ochiai, K. Fukui, S. Iwatsuki, K. Ishihara and K. Matsumoto, *Organometallics*, 2005, **24**, 5528–5536; (*g*) G. B. Shul'pin, A. E. Shilov, G. V. Nizova, A. K. Yatsimirskii, S. A. Deiko and P. Lederer, *Bull. Acad. Sci. USSR,Div. Chem. Sci. (Engl. Transl.)*, 1986, **35**, 2177–2179; (*h*) G. B. Shul'pin, S. Y. Skripnik, S. A. Deiko and A. K. Yatsimirskii, *Metalloorg. Khim*, 1989, **2**, 1301–1304(in Russian); (*i*) G. B. Shul'pin, S. A. Deiko and A. K. Yatsimirskii, *J. Gen. Chem. USSR*, 1991, **61**, 742–744; (*j*) G. B. Shul'pin and G. V. Nizova, *J. Organomet. Chem.*, 1984, **276**, 109–114; (*k*) Y. Fuchita, Y. Utsunomiya and M. Yasutake, *J. Chem. Soc., Dalton Trans.*, 2001, 2330–2334; (*l*) Y. Rong, R. Li and W. Lu, *Organometallics*, 2007, **26**, 4376–4378; (*m*) M. Catellani, E. Motti and N. Della Ca', *Acc. Chem. Res.*, 2008, **41**, 1512–1522; (*n*) Y. Aoyama, T. Yoshida, K. Sakurai and H. Ogoshi, *Organometallics*, 1986, **5**, 168–173.

9 (*a*) E. Ben-Ari, R. Cohen, M. Gandelman, L. J. W. Shimon, J. M. L. Martin and D. Milstein, *Organometallics*, 2006, **25**, 3190–3210; (*b*) S. J. Hwang, H. J. Kim and S. Chang, *Org. Lett.*, 2009, **11**, 4588–4591; (*c*) J. Y. K. Tsang, M. S. A. Buschhaus, P. M. Graham, C. J. Semiao, S. P. Semproni, S. J. Kim and P. Legzdins, *J. Am. Chem. Soc.*, 2008, **130**, 3652–3663; (*d*) S. P. Semproni, P. M. Graham, M. S. A. Buschhaus, B. O. Patrick and P. Legzdins, *Organometallics*, 2009, **28**, 4480–4490; (*e*) T. Takao, M. Moriya and H. Suzuki, *Organometallics*, 2008, **27**, 18–20.

10 (*a*) J. F. Hartwig, K. S. Cook, M. Hapke, C. D. Incarvito, Y. Fan, C. E. Webster and M. B. Hall, *J. Am. Chem. Soc.*, 2005, **127**, 2538–2552; (*b*) J. M. Murphy, J. D. Lawrence, K. Kawamura, C. Incarvito and J. F. Hartwig, *J. Am. Chem. Soc.*, 2006, **128**, 13684–13685; (*c*) J. F. Hartwig, *Nature*, 2008, **455**, 314–322; (*d*) H. M. L. Davis and R. E. J. Beckwith, *Chem. Rev.*, 2003, **103**, 2861–2903; (*e*) M. M. Díaz-Requejo, T. R. Belderraín, M. C. Nicasio and P. J. Pérez, *Dalton Trans.*, 2006, 5559–5566; (*f*) H. M. L. Davis and J. R. Manning, *Nature*, 2008, **451**, 417–424; (*g*) M. P. Doyle, R. Duffy, M. Ratnikov and L. Zhou, *Chem. Rev.*, 2010, **110**, 704–724; (*h*) H.-Y. Thu, G. S.-M. Tong, J.-S. Huang, S. L.-F. Chan, Q.-H. Deng and C.-M. Che, *Angew. Chem., Int. Ed.*, 2008, **47**, 9747–9751; (*i*) B. P. Gómez-Emeterio, J. Urbano, M. M Díaz-Requejo and P. J. Pérez, *Organometallics*, 2008, **27**, 4126–4130; (*j*) E. Despagnet-Ayoub, K. Jacob, L. Vendier, M. Etienne, E. Álvarez, A. Caballero, M. M. Díaz-Requejo and P. J. Pérez, *Organometallics*, 2008, **27**, 4779–4787; (*k*) C. Martín, T. R. Belderraín and P. J. Pérez, *Org. Biomol. Chem.*, 2009, **7**, 4777–4781; (*l*) H. V. R. Dias, R. G. Browning, A. A. Richey and C. J. Lovely, *Organometallics*, 2004, **23**, 1200–1202; (*m*) K. Rangan, M. Fianchini, S. Singh and H. V. R. Dias, *Inorg. Chim. Acta*, 2009, **362**, 4347–4352; (*n*) C. N. Kostelansky, M. G. MacDonald, P. S. White and J. L. Templeton, *Organometallics*, 2006, **25**, 2993–2999; (*o*) N. M. West and J. L. Templeton, *Can. J. Chem.*, 2009, **87**, 288–296.

11 (*a*) Y. Y. Jiang, X. He and P. R. Ortiz de Montellano, *Biochemistry*, 2006, **45**, 533–542; (*b*) R. Bernhardt, *J. Biotechnol.*, 2006, **124**, 128–145; (*c*) F. H. Arnold and J. C. Lewis, *Chimia*, 2009, **63**, 309–312; (*d*) P. R. Ortiz de Montellano, *Chem. Rev.*, 2010, **110**, 932–948; (*e*) S. Shaik, S. Cohen, Y. Wang, H. Chen, D. Kumar and W. Thiel, *Chem. Rev.*, 2010, **110**, 949–1017; (*f*) A. A. Shteinman, *Russ. Chem. Rev.*, 2008, **77**, 945–966; (*g*) M. Ayala and E. Torres, *Appl. Catal., A*, 2004, **272**, 1–13; (*h*) Z. Li and D. Chang, *Curr. Org. Chem.*, 2004, **8**, 1647–1658; (*i*) M. Schittmayer, Z. Liu, H. Bingfang, W. Ping, Z. Hua, O. Pingkai, D. Rozzell and A. Glieder, *J. Mol. Catal. B: Enzym.*, 2009, **57**, 72–77; (*j*) D. A. Rock, B. N. S. Perkins, J. Wahlstrom and J. P. Jones, *Arch. Biochem. Biophys.*, 2003, **416**, 9–16; (*k*) M. J. Coon, *Biochem. Biophys. Res. Commun.*, 2005, **338**, 378–385; (*l*) E. G. Funhoff, J. Salzmann, U. Bauer, B. Witholt and J. B. van Beilen, *Enzyme Microb. Technol.*, 2007, **40**, 806–812; (*m*) D. J. Koch, M. M. Chen, J. B. van Beilen and F. H. Arnold, *Appl. Environ. Microbiol.*, 2009, **75**, 337–344; (*n*) J. Green and H. Dalton, *J. Biol. Chem*, 1989, **264**, 17698–17703; (*o*) M. J. Cryle, R. D. Espinoza, S. J. Smith, N. J. Matovic and J. J. De Voss, *Chem. Commun.*, 2006, 2353–2355; (*p*) V. Cafaro, E. Notomista, P. Capasso and A. Di Donato, *Appl. Environ. Microbiol.*, 2005, **71**, 4736–4743.

12 (*a*) W.-C. Huang, A. C. G. Westlake, J.-D. Maréchal, M. G. Joyce, P. C. E. Moody and G. C. K. Roberts, *J. Mol. Biol.*, 2007, **373**, 633–651; (*b*) K.-Y. Ng, L.-C. Tu, Y.-S. Wang, S. I. Chan and S. S.-F. Yu, *ChemBioChem*, 2008, **9**, 1116–1123; (*c*) Y. T. Meharenna, K. E. Slessor, S. M. Cavignac, T. L. Poulos and J. J. De Voss, *J. Biol. Chem.*, 2008, **283**, 10804–10812; (*d*) R. J. F. Branco, A. Seifert, M. Budde, V. B. Urlacher, M. J. Ramos and J. Pleiss, *Proteins: Struct., Funct., Bioinf.*, 2008, **73**, 597–607; (*e*) M. Dietrich, T. A. Do, R. D. Schmid, J. Pleiss and V. B. Urlacher, *J. Biotechnol.*, 2009, **139**, 115–117; (*f*) P. Meinhold, M. W. Peters, A. Hartwick, A. R. Hernandez and F. H. Arnold, *Adv. Synth. Catal.*, 2006, **348**, 763–772.

13 (*a*) I. Beletskaya, V. S. Tyurin, A. Y. Tsivadze, R. Guilard and C. Stern, *Chem. Rev.*, 2009, **109**, 1659–1713; (*b*) A. Khenkin, O. Koifman, A. Semeikin, A. Shilov and A. Shteinman, *Tetrahedron Lett.*, 1985, **26**, 4247–4248; (*c*) B. R. Cook, T. J. Reinert and K. S. Suslick, *J. Am. Chem. Soc.*, 1986, **108**, 7281–7286; (*d*) J.-P. Mahy, G. Bedi, P. Battioni and D. Mansuy, *New J. Chem*, 1989, **13**, 651–657; (*e*) D. Mansuy, *Pure Appl. Chem.*, 1990, **62**, 741–746; (*f*) J. F. Bartoli, O. Brigaud, P. Battioni and D. Mansuy, *J. Chem. Soc., Chem. Commun.*, 1991, 440–442; (*g*) J. P. Collman, R. R. Gagne, C. A. Reed, T. R. Halbert, G. Lang and W. T. Robinson, *J. Am. Chem. Soc.*, 1975, **97**, 1427–1439; (*h*) S. Ogawa, Y. Wakatsuki, M. Makino, Y. Fujimoto, K. Yasukawa, T. Kikuchi, M. Ukiya, T. Akihisa and T. Iida, *Chem. Phys. Lipids*, 2010, **163**, 165–171; (*i*) A. B. Sorokin, A. M. Khenkin, S. A. Marakushev, A. E. Shilov and A. A. Shteinman, *Dokl. AN SSSR*, 1984, **279**, 939–941(in Russian); (*j*) K. S. Suslick, P. Bhyrappa, J.-H. Chou, M. E. Kosal, S. Nakagaki, D. W. Smithenry and S. R. Wilson, *Acc. Chem. Res.*, 2005, **38**, 283–291; (*k*) Q. Raffy, R. Ricoux, E. Sansiaume, S. Pethe and J.-P. Mahy, *J. Mol. Catal. A: Chem.*, 2010, **317**, 19–26.

14 (*a*) G. B. Shul'pin and J. R. Lindsay Smith, *Russ. Chem. Bull.*, 1998, **47**, 2379–2386; (*b*) J. R. Lindsay Smith and G. B. Shul'pin, *Tetrahedron Lett.*, 1998, **39**, 4909–4912; (*c*) G. B. Shul'pin, G. Süss-Fink and L. S. Shul'pina, *J. Mol. Catal. A: Chem.*, 2001, **170**, 17–34; (*d*) G. B. Shul'pin, G. V. Nizova, Y. N. Kozlov, V. S. Arutyunov, A. C. M. dos Santos, A. C. T. Ferreira and D. Mandelli, *J. Organomet. Chem.*, 2005, **690**, 4498–4504; (*e*) A. Mukherjee, M. Martinho, E. L. Bominaar, E. Münck and L. Que, Jr., *Angew. Chem., Int. Ed.*, 2009, **48**, 1780–1783; (*f*) V. B. Romakh, B. Therrien, G. Süss-Fink and G. B. Shul'pin, *Inorg. Chem.*, 2007, **46**, 1315–1331; (*g*) M. V. Kirillova, A. M. Kirillov, D. Mandelli, W. A. Carvalho, A. J. L. Pombeiro and G. B. Shul'pin, *J. Catal.*, 2010, **272**, 9–17; (*h*) D. Dondi, D. Ravelli, M. Fagnoni, M. Mella, A. Molinari, A. Maldotti and A. Albini, *Chem.–Eur. J.*, 2009, **15**, 7949–7957; (*i*) K. Kamata, K. Yonehara, Y. Nakagawa, K. Uehara and N. Mizuno, *Nat. Chem.*, 2010, **2**, 478–483.

15 (*a*) R. A. Sheldon, I. W. C. E. Arends and H. E. B. Lempers, *Catal. Today*, 1998, **41**, 387–407; (*b*) J. M. Thomas and R. Raja, *J. Organomet. Chem.*, 2004, **689**, 4110–4124; (*c*) J. H. Clark, D. J. Macquarrie and S. J. Tavener, *Dalton Trans.*, 2006, 4297–4309; (*d*) M. Tada and Y. Iwasawa, *Chem. Commun.*, 2006, 2833–2844; (*e*) C. E. Song, D. H. Kim and D. S. Choi, *Eur. J. Inorg. Chem.*, 2006, 2927–2935; (*f*) J. Wei, C. A. Floudas and C. E. Gounaris, *Catal. Lett.*, 2009, **133**, 234–241; (*g*) K. Smith, M. D. Ajarim and G. A. El-Hiti, *Catal. Lett.*, 2010, **134**, 270–278; (*h*) N. Danilina, E. L. Payrer and J. A. van Bokhoven, *Chem. Commun.*, 2010, **46**, 1509–1510.

16 (*a*) G. B. Shul'pin, G. S. Mishra, L. S. Shul'pina, T. V. Strelkova and A. J. L. Pombeiro, *Catal. Commun.*, 2007, **8**, 1516–1520; (*b*) M. Halma, K. A. D. de Freitas Castro, V. Prévot, C. Forano, F. Wypych and S. Nakagaki, *J. Mol. Catal. A: Chem.*, 2009, **310**, 42–50; (*c*) T. C. O. Mac Leod, M. V. Kirillova, A. J. L. Pombeiro, M. A. Schiavon and M. D. Asis, *Appl. Catal., A*, 2010, **372**, 191–198; (*d*) A. J. Bonon, D. Mandelli, O. A. Kholdeeva, M. V. Barmatova, Y. N. Kozlov and G. B. Shul'pin, *Appl. Catal., A*, 2009, **365**, 96–104; (*e*) D. Mandelli, A. C. N. do Amaral, Y. N. Kozlov, L. S. Shul'pina, A. J. Bonon, W. A. Carvalho and G. B. Shul'pin, *Catal. Lett.*, 2009, **132**, 235–243.

17 (*a*) N. Herron and C. A. Tolman, *J. Am. Chem. Soc.*, 1987, **109**, 2837–2839; (*b*) N. Herron, *New J. Chem*, 1989, **13**, 761–766; (*c*) J. M. Thomas, R. Raja, G. Sankar and R. G. Bell, *Acc. Chem. Res.*, 2001, **34**, 191–200; (*d*) B. L. Caetano, L. A. Rocha, E. Molina, Z. N. Rocha, G. Ricci, P. S. Calefi, O. J. de Lima, C. Mello, E. J. Nassar and K. J. Ciuffi, *Appl. Catal., A*, 2006, **311**, 122–134; (*e*) T. Yokoi, P. Wu and T. Tatsumi, *Catal. Commun.*, 2003, **4**, 11–15; (*f*) G. B. Shul'pin, T. Sooknoi, V. B. Romakh, G. Süss-Fink and L. S. Shul'pina, *Tetrahedron Lett.*, 2006, **47**, 3071–3075; (*g*) G. B. Shul'pin, T. Sooknoi and L. S. Shul'pina, *Petr. Chem*, 2008, **48**, 36–39; (*h*) G. B. Shul'pin, M. V. Kirillova, T. Sooknoi and A. J. L. Pombeiro, *Catal.Lett.*, 2008, **123**, 135–141; (*i*) G. B. Shul'pin, Y. N. Kozlov, L. S. Shul'pina and P. V. Petrovskiy, *Appl. Organomet. Chem*, 2010, **24**, 464–472.

