2546 *Chem. Rev.* **2007,** *107,* 2546–2562

Reactions of C–H Bonds in Water

Clara I. Herrerías, Xiaoquan Yao, Zhiping Li, and Chao-Jun Li*

Department of Chemistry, McGill University, 801 Sherbrooke Street West, Montreal, Quebec H3A 2K6, Canada

Received June 12, 2006

Contents

1. Introduction 2546
2. Formation of C–X Bonds 2546
  2.1. Formation of C–O Bonds 2546
    2.1.1. Transition-Metal-Catalyzed Oxidations 2546
    2.1.2. Biomimetic Oxidations 2550
    2.1.3. Metal-Free Functionalizations 2551
  2.2. Formation of C–Halogen Bonds 2551
3. Formation of C–C Bonds 2552
  3.1. Activation of sp C–H Bonds 2552
    3.1.1. Alkyne Dimerization 2552
    3.1.2. Reaction of Alkynes with Organic Halides 2552
    3.1.3. Reaction with Imines 2553
    3.1.4. Reaction of Alkynes with Carbonyl Compounds 2554
    3.1.5. Conjugate Addition 2555
  3.2. Activation of sp^2 C–H Bonds 2555
    3.2.1. Oxidative Homocoupling of Benzene Ring 2555
    3.2.2. Cyclocarbonylation 2555
    3.2.3. Oxidative Coupling of Aromatic Ring with Olefins 2556
    3.2.4. Isomerization of α-Arylpropargyl Alcohols to Indanones 2556
  3.3. Activation of sp^3 C–H Bonds 2557
    3.3.1. Carboxylation of Methane 2557
    3.3.2. Carbene Insertion into an Alkane C–H Bond 2557
    3.3.3. Aldol-type Reaction of Allylic Alcohols 2557
4. Multi-C–H Activations 2557
  4.1. CDC Reactions 2557
  4.2. Homocoupling Reactions 2558
5. Conclusion 2558
6. Acknowledgment 2560
7. References 2560

1. Introduction

The ideology of Green Chemistry calls for the development of new chemical reactivities and reaction conditions that can potentially provide benefits for chemical syntheses in terms of resource efficiency, energy efficiency, product selectivity, operational simplicity, and health and environmental safety.[1] One aspect of such reactivities is reactions that can directly transform the C−H bonds of organic molecules into the desired structures without extra chemical transformations.[2] Another aspect is the development of chemical reactions in water that can achieve the desired chemical transformations without the need for the protection−deprotection of reactive functional groups and generation of anhydrous conditions.[3] The combination of these two aspects is highly challenging and will provide even more benefits for chemical synthesis. Furthermore, the development of reactions of C−H bonds (generally having low reactivities) in the presence of various (more reactive) functional groups in (quite reactive) water raises fundamental questions and theoretical issues in chemical reactivity. This review will summarize the reported direct transformations of C−H bonds into other bonds in water (aqueous media). Although not all examples in this review can be called "Green Chemistry" in all situations, these examples, however, provide potential reactions (tools) for potential users (synthetic chemists) to design innovative syntheses with an eye toward Green Chemistry. Whether a reaction is green is highly subjective based upon the specific synthetic situations in a global context of a synthesis.

2. Formation of C–X Bonds

2.1. Formation of C–O Bonds

2.1.1. Transition-Metal-Catalyzed Oxidations

2.1.1.1. Platinum Complexes. While the selective catalytic functionalization of saturated hydrocarbons or C−H bonds at a remote position of reactive functional groups in organic compounds at reasonably low temperatures (and without affecting the reactive functional group) is of considerable scientific and economic importance, it also poses a significant challenge. Hydroxylation of linear alkanes or methane to generate terminal alcohols is very useful for the syntheses of chemicals and fuels.

In the 1970s Shilov et al. carried out the first examples of electrophilic activation of alkanes in aqueous solutions with platinum complexes.[4] In their system, chloride salts of Pt(II) catalyze the oxidation of alkanes to give alcohols (at 100−120 °C) along with chloroalkanes and ketones using Pt(IV) as the stoichiometric oxidant (eq 1).

$$\text{R-H} + \text{PtCl}_6^{2-} + \text{cat PtCl}_4^{2-} \xrightarrow[\text{100-120°C}]{\text{H}_2\text{O}} \underset{\text{(R-Cl)}}{\text{R-OH}} \qquad (1)$$

The mechanism for the reaction proposed by Shilov[5] and others[6] consists of three steps: (1) electrophilic activation of the alkane by a Pt(II) complex to yield an alkyl Pt(II) complex; (2) oxidation of this complex into a Pt(IV)−alkyl intermediate by [$PtCl_6^{2-}$] via electron transfer; and (3) the Pt(IV)−alkyl intermediate undergoes a reductive elimination to regenerate the Pt(II) catalyst and release the oxidized

---

* To whom correspondence should be addressed. Fax: 514-3983797. E-mail: cj.li@mcgill.ca.

10.1021/cr050980b CCC: $65.00

Clara I. Herrerías was born in Zaragoza, Spain, in 1976. She received her B.Sc. (1999), DEA (Advanced Studies Diploma) (2001), and Ph.D. (2005) degrees from the University of Zaragoza, working under the supervision of Professor J. A. Mayoral and Dr. J. M. Fraile. During her doctoral studies she spent a short period of time in the group of Professor O. Reiser (Regensburg University, Germany) as well as in the group of Professor S. V. Luis (University Jaume I, Spain). She received an extraordinary award for her thesis from the University of Zaragoza (2006). From 2005 to 2006 she was a postdoctoral fellow in the group of Professor Li at McGill University (Canada), where she was involved in the development of oxidation reactions promoted by organocatalysts and C–C bond formation reactions based on C–H activation using water as solvent. She also spent a period of time working with Professor Pericàs at the Institute of Chemical Research of Catalonia (ICIQ) (Tarragona, Spain). She has recently joined the University of Zaragoza as Assistant Professor in the research group of Professor Mayoral.

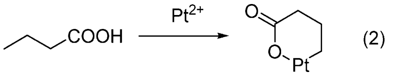
Xiaoquan Yao was born in 1973 in Nanjing, China. He received his B.S. degree from Nanjing Normal University in 1995 and Ph.D. degree from Dalian Institute of Chemical Physics, Chinese Academy of Sciences, in 2000 with Professor Huilin Chen. He spent 2001–2002 as a postdoctoral fellow in Professor Xiyan Lu's laboratory at Shanghai Institution of Organic Chemistry, CAS. This was then followed by another postdoctoral stint at McGill University in Canada with Professor Chao-Jun Li (2003–2006). Presently, he is working as a professor at Nanjing University of Aeronautics & Astronautics. His current research interests are focused on metal-mediated C–C bond formation reactions in water and organic materials research.

alkane (e.g., alkyl alcohols and organic halides). Typical reaction yields are low (less than 3% in the case of methane), the reaction rate is low, and the catalyst is short-lived due to poisoning. However, the system is highly attractive because it exhibits a unique selectivity[4b] and has mild reaction conditions. Linear alkanes are often functionalized at the terminal positions of stronger C−H bonds ($-CH_3$) rather than at the weaker, nonterminal secondary C−H bonds which are preferred by radical and electrophilic reagents such as superacids. Chemoselectivity is also observed since the oxidation products are relatively stable and immune to overoxidation.

Zhiping Li was born in Dalian, China, in 1971. He began his chemistry study at the Nanjing University of Science & Technology, China (B.A., 1993) and obtained his Ph.D. degree in Chemistry at the Dalian University of Technology, China (1999). After postdoctoral training with Professor Zhenfeng Xi at Peking University, China (2001), and with Professor Tamotsu Takahashi at Hokkaido University, Japan (2002), he became a Assistant Professor at Peking University (2002). From 2004 to 2006, he was at McGill University, Canada, as a postdoctoral fellow in Professor Chao-Jun Li's group. He joined the faculty at the Renmin University of China as an Associate Professor in March 2006. His current research interests involve developing iron-catalyzed new reactions in organic chemistry, C–C bond formation via the oxidative activation of C–H bonds, and synthesis of new antioxidants.

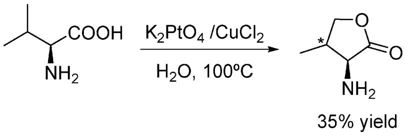
Chao-Jun Li (born in 1963) received his B.S. degree from Zhengzhou University (1983), M.S. degree from the Chinese Academy of Sciences in Beijing (1988), and Ph.D, degree at McGill University (1992) (with T. H. Chan and D. N. Harpp). He spent 1992–94 as a NSERC Postdoctoral Fellow with B. M. Trost at Stanford University. He was an Assistant Professor (1994), Associate Professor (1998), and Full Professor (2000–2003) at Tulane University and a visiting faculty (with Robert G. Bergman) at the University of California at Berkeley (2002). In 2003, he became a Canada Research Chair (Tier I) in Organic/Green Chemistry and a Professor of Chemistry at McGill University in Canada. His current research efforts are focused on developing innovative and fundamentally new organic reactions that will defy conventional reactivities and have high synthetic efficiency. His widely recognized research includes the development of Grignard-type reactions in water, transition-metal catalysis in air and water, alkyne–aldehyde–amine coupling (A^3-coupling), asymmetric alkyne–aldehyde–amine coupling (AA^3-coupling), and cross-dehydrogenative-coupling (CDC) reactions via C–H activations.

Several studies have been carried out to examine the scope and selectivity of the Shilov system. Sen et al. reported the oxidation of several substrates in an aqueous medium with platinum complexes. They utilized a K_2PtCl_6/K_2PtCl_4 system[7] for the oxidation of methane and ethane to give methanol and ethylene glycol, respectively.[7b] Catalytic hydroxylation of the nonactivated C−H bonds of aliphatic carboxylic acids was also achieved[7a,c] with moderate to high regioselectivity, resulting in a preference for γ-C−H bonds versus α, β, and even δ-C−H bonds (α-C−H $\ll$ β-C−H $<$ γ-C−H $\geq$ δ-C−H $\approx$ ϵ-C−H). This effect was explained by the formation of a more favorable strain-free six-membered metallacycle ("chelate effect") (eq 2).



The same results were obtained when aliphatic sulfonic acids and phosphonic acids were used.[7c] In addition, oxidation of aliphatic alcohols[7b,c] yields only diols without any overoxidation product. The reaction shows a similar reactivity order of α-C−H $\ll$ β-C−H $<$ γ-C−H $<$ δ-C−H. Analogous selectivity was obtained when the $PtCl_4^{2-}$ + Pt(0)/O_2 system was used to hydroxylate several light alkanes, alcohols, and ethers; however, in these cases, acids and hydroxyacids were also formed.[8] Bercaw et al. reported the selective oxidation of various aliphatic alcohols and acids[9,6b] such as *p*-toluenesulfonic acid and *p*-ethylbenzenesulfonic acid by aqueous solutions of K_2PtCl_6/K_2PtCl_4. Substantial oxidation occurs at the β position of the *p*-ethylbenzenesulfonic acid, indicating that benzylic activation is not required for these reactions. Under these conditions not only was hydroxylation observed, but overoxidation products (aldehydes only) were also detected.

The role of the Pt(IV) species in the catalytic system is to act as the oxidant to avoid the reduction of Pt(II) to Pt(0). The latter is known to promote the rapid oxidation of alcohols.[8] From a practical point of view, use of Pt(IV) as the stoichiometric oxidant is not economically viable. Several efforts have been made to replace Pt(IV) in the Shilov system, although this task is complicated because most primary oxidants tend to convert reactive Pt(II) to inactive Pt(IV). A system consisting of aqueous $PtCl_4^{2-}$ as catalyst and phosphomolybdic acid ($H_3PMo_{12}O_{40}$) as a redox mediator in an electrochemical cell containing a carbon cloth anode hydroxylates *p*-toluenesulfonic acid into the corresponding alcohol, *p*-$HO_3SC_6H_4CH_2OH$.[10] After six turnovers, overoxidation of the alcohol was observed, possibly due to formation of Pt(0). Recently, Sen et al. found that Shilov chemistry can be made catalytic with molecular oxygen as the ultimate oxidant using K_2PtO_4 as catalyst and $CuCl_2$ as cocatalyst in an aqueous medium.[11] Only one turnover was obtained in the absence of molecular oxygen. This study was also the first example of the direct use of molecular oxygen in the catalytic oxidation of nonactivated C−H bonds (in this case, aliphatic acids) under mild conditions without using a coreductant. The predominant reaction is hydroxylation of the remote methyl group. The same catalysts (K_2PtO_4/$CuCl_2$) have promoted the selective functionalization of α-amino acids in water,[12] which is an example of catalytic heteroatom-directed functionalization of remote alkyl groups. The aqueous medium avoided the need for protection of functional groups (eq 3).



Other authors have also succeeded in improving the original Shilov system; however, these studies are outside the scope of this review since the solvent used is, in most cases, a strong acid.[13]

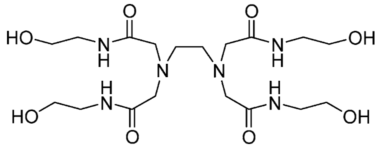
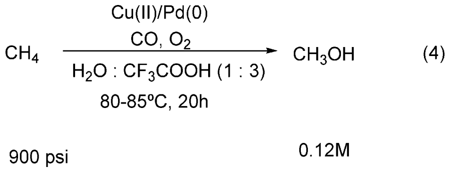


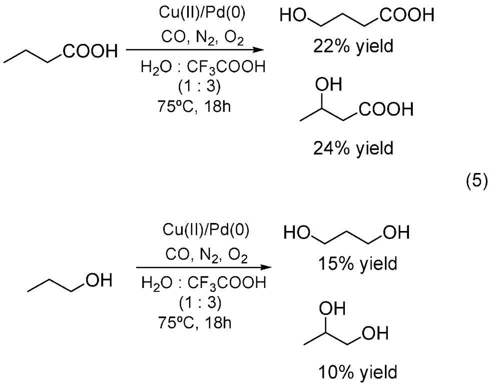
Figure 1.

2.1.1.2. Copper Complexes. For many years the combination of K_2PtCl_6/K_2PtCl_4 was the only example of metal-catalyzed hydroxylation of remote primary C−H bonds in aqueous media. Recently, Sen et al. reported a low-temperature, selective oxidation of methane to methanol in a mixture of trifluoroacetic acid and water using a combination of copper chloride and metallic palladium in the presence of molecular oxygen and carbon monoxide as coreductant (eq 4).[14]



$$\underset{900\ \text{psi}}{CH_4} \xrightarrow[\substack{H_2O : CF_3COOH\ (1:3) \\ 80\text{-}85°C,\ 20h}]{\substack{Cu(II)/Pd(0) \\ CO,\ O_2}} \underset{0.12M}{CH_3OH} \qquad (4)$$

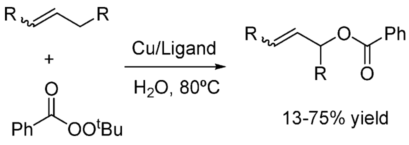
Oxidation of methane yields methanol as the only product. However, for ethane and *n*-butane, products derived from C−C cleavages competed with or dominated over those derived from C−H cleavage. In other words, methanol was also formed with these two higher alkanes. Several remote primary C−H bonds in acids, alcohols (eq 5), and aliphatic halides were hydroxylated by this method.[15]



The mechanism of the reaction in these conditions involves formation of hydrogen peroxide by Pd,[16] whereas the role of $CuCl_2$ is to effect the subsequent oxidation of the substrate by the formed hydrogen peroxide. Increasing the amount of $CuCl_2$ reduces products resulting from overoxidation and C−C cleavage.

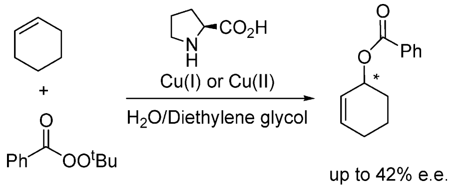
In 2002, Muzart et al. reported an efficient and recyclable water-soluble system to promote the allylic oxidation of olefins with organic peroxyesters, also known as the Kharasch−Sosnovsky reaction, in water.[17] The mixture of the hydrophilic N-donor ligand (Figure 1) with $Cu(MeCN)_4BF_4$ in water led to an efficient and reusable catalytic system for the allylic oxidation of olefins with *tert*-butyl perbenzoate (eq 6).

The aqueous phase recovered after extraction of the reaction products remained catalytically active, and oxidation of cyclohexene was repeated four times with the same



(6)

aqueous phase without a drop in the yield. The use of the water-soluble ligand avoided the loss of the copper complex into the organic phase, obtaining an effective recycling of the catalyst. Subsequently, the enantioselective variant of this reaction[18] was carried out in a biphasic medium (water + diethylene glycol) using a mixture of amino acids and copper complexes (eq 7).

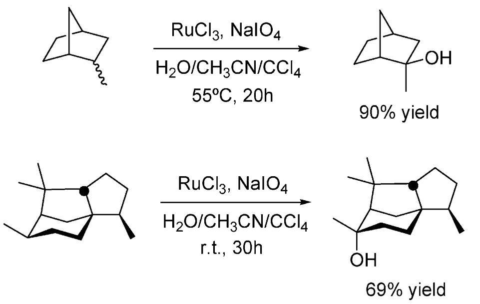


(7)

When the reaction was carried out under argon atmosphere, recycling of the catalyst was also possible. The enantiomeric excess decreased slightly from run to run, while the yields were not affected. Use of diethylene glycol was necessary to carry out the reaction at room temperature; no reaction occurred in its absence.

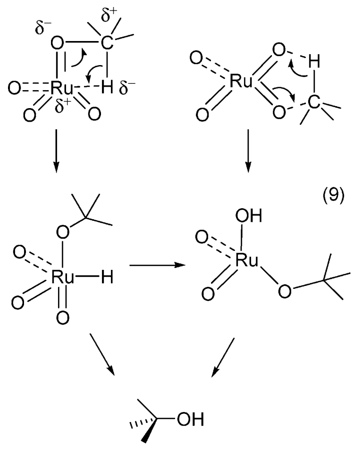
2.1.1.3. Other Transition Metals. Although platinum chemistry has been the leader in the oxidation of nonactivated C−H bonds of alkanes in aqueous media, other transition-metal complexes besides copper complexes have also promoted oxidation reactions in aqueous mixtures. One of these complexes is $RhCl_3$, which, together with NaCl and KI, promoted formation of methanol and acetic acid from methane, carbon monoxide, and oxygen in a mixture of perfluorobutyric acid and water at 80−85 °C.[19] When ethane was used, the reaction generated ethanol, acetic acid, and methanol (due to C−C cleavage). In both cases, the product alcohols were less reactive than the starting alkanes, which is consistent with the chemoselectivity observed with $[PtCl_4^{2-}]$. It is worth mentioning that it was possible to selectively form either methanol or acetic acid by a simple change in the solvent system, as was also reported by Chepaikin et al. later.[20] In a mixture of trifluoroacetic acid and water, the yield of reaction products is dependent upon the mole fraction of water in the solution: formation of methanol is optimized when the mole fraction of water is 0.61. However, as in the preceding case, a mixture of methanol, acetic acid, formic acid, and methyl trifluoroacetate is formed in all these cases. The mechanism was proposed to involve reaction of methane with various possible Rh−oxo compounds to form intermediate complexes with a five-coordinate carbon atom at high oxygen content. At low oxygen pressure, another mechanism was not excluded.

On the other hand, RuO_4, formed in situ from $RuCl_3$, promoted the catalytic hydroxylation of various bicyclic and tricyclic alkanes in a mixture of $H_2O/CH_3CN/CCl_4$ (3:2:2).[21] $NaIO_4$ is used as a reoxidizing reagent. The stereoselective oxidation occurred at the exo position of tertiary carbons for alkanes having the bicyclo[2.2.1]heptane skeleton (norbornanes) and with retention of configuration for cedrane derivatives (eq 8).



(8)

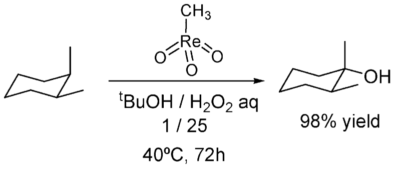
Although both involvement of a carbonium intermediate and a concerted mechanism have been postulated,[22] kinetic isotope experiments and model studies of this reaction[23] with RuO_4 led to the conclusion that the reaction proceeds via a concerted mechanism either through a five-membered-ring transition state (more likely) or alternatively via a polarized four-membered-ring transition state (eq 9).



(9)

Other ruthenium complexes have promoted the activation of various alkanes in biphasic water−organic phase systems using several primary oxidizing agents such as oxone ($KHSO_5$),[24] $NaIO_4$,[24] *tert*-butyl hydroperoxide (TBHP),[25] NaClO,[25a] H_2O_2,[26] or an O_2/ascorbic acid system.[27] Mixtures of alcohols and carbonyl compounds were obtained, although in some cases the reaction to form the carbonyl compounds is highly selective.[25b]

Methyltrioxorhenium (MTO) also catalyzed the C−H oxidation of various hydrocarbons by hydrogen peroxide.[28] The reactions proceeded with retention of configuration in the functionalized carbon to give the corresponding alcohol with good to excellent yields (eq 10). In the absence of the catalyst, no oxidation products were found. The catalytic monoperoxo− and diperoxo−rhenium(VII) species are formed when MTO reacts with H_2O_2.[29]



(10)

An example of using electro-organic synthesis for the direct oxidation of alkanes was reported by Yamanaka et al.[30] Electrocatalytic oxidation of cyclohexane, *n*-hexane, and adamantane with H_2O occurred using $Ir(acac)_3$ supported on a carbon fiber anode. Aqueous H_2SO_4 was found to be the best electrolyte. In this case, water is both the solvent and the reagent. A mixture of the corresponding alcohols and ketones (due to further oxidation) was obtained.

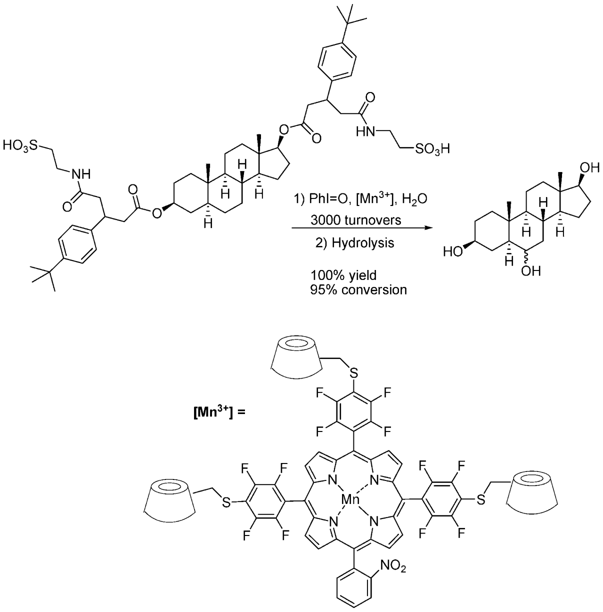
2.1.2. Biomimetic Oxidations

A variety of organic compounds can be oxidized easily by molecular oxygen or other oxygen donors in the cells of bacteria, fungi, plants, insect, fish, and mammals.[31] Oxidoreductases[32] are enzymes capable of promoting these biotransformations which, out of necessity, are carried out in aqueous environments under mild reaction conditions (ambient temperature and pressure). Biological catalysis is beyond the scope of the present review; however, it is worth noting the important analogies between chemical activations catalyzed by metal complexes and by biological enzymes which could lead to biomimetic approaches to such oxidations. Oxidoreductases consist of dehydrogenases[33] (enzymes that use water as an oxygen donor), oxidases[34] (enzymes that reduce molecular oxygen to H_2O_2 or water), peroxidases[35] (enzymes that use H_2O_2 or organic peroxides as electron acceptors), and oxygenases[36] (enzymes that introduce the oxygen atom from molecular oxygen into C−H bonds). The latter category includes several of the more intensively studied enzymes because of their physiological role in detoxification, biosynthesis of hormones, hydrocarbon biodegradation, etc. Some examples[37] are the heme-dependent cytochrome P450 monooxygenase which contains an iron porphyrin complex in the enzyme active site and the nonheme methane monooxygenase (MMO) which consists of a di-iron system with two bridging carboxylate groups and a bridging hydroxide. These enzymes are able to carry out highly selective catalytic oxidations of nonactivated C−H bonds of hydrocarbons by molecular oxygen with the loss of water (eq 11). Many efforts have been made to find chemical models to mimic this behavior.[38] Although most such oxidation reactions are carried out in acetonitrile and other organic solvents, some are performed in aqueous media.

$$RH + O_2 + 2e^- + 2H^+ \longrightarrow ROH + H_2O \qquad (11)$$

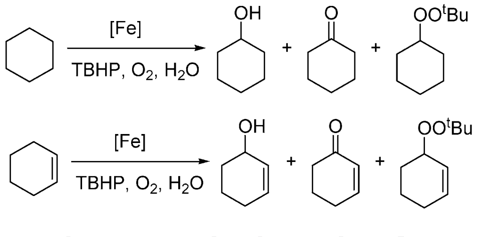
It is important to note that several oxidation reactions discussed earlier could also be included in this section since they used a metal−complex catalyst together with either molecular oxygen or oxygen-atom donors and therefore could be models of biological oxidation. However, we will dedicate this section to studies based on metals bearing more complex ligands which mimic the active-site structure of enzymes.

Oxygenation of nonactivated hydrocarbons by cytochrome P-450 has stimulated interest in metalloporphyrin oxidation catalysis. This is the case in manganese porphyrin systems. Several examples of the hydroxylation of alkanes and cycloalkanes in aqueous media promoted by manganese porphyrins have been reported. These systems use different kinds of oxygen-atom donors such as sodium hypohalites (NaClO or NaBrO),[39,40] sodium chlorite ($NaClO_2$),[40] potassium hydrogen persulfate or oxone ($KHSO_5$),[41,42] sodium periodate ($NaIO_4$),[43,44] O_2/ascorbic acid system,[43,44] H_2O_2,[45] and magnesium monoperoxyphthalate (MMPP).[46,47] In some cases, use of a phase-transfer catalyst was also required. Turnovers varied in each case; however, the reactions were not very selective, and a mixture of products was obtained in all cases (alcohols, ketones, halides, etc.). Only some examples show the selective hydroxylation of cholesterol at carbon 25 with membrane-spanning steroidal metalloporphyrins in aqueous media.[43,44] Breslow et al. reported the regioselective and stereoselective hydroxylation of several steroids in water using manganese porphyrins carrying β-cyclodextrins as catalysts with iodosobenzene as the oxidant (eq 12).[48] The β-cyclodextrins acted as templates to place the substrate directly over the metal. The geometry of the catalyst−substrate complex directed the site of the hydroxylation. With substrates that were not able to fit well into the catalyst, more than one hydroxylation product was formed and hydroxylation did not occur when the substrate did not bind to the catalyst. Subsequently,[48h] by attaching thiolate groups in the system, it was possible to use the more environmentally benign hydrogen peroxide as the oxidant.



(12)

In addition to porphyrin-based enzyme mimics, several non-porphyrin models of methane monooxygenase (MMO) have been reported to perform catalytic oxidations of nonactivated C−H bonds in water. The active site of the MMO has the following structure: $[Fe_2(\mu\text{-}OH)(\eta^1\text{-}H_2O)(L)_x]$. Fish et al. observed the oxidation of cyclohexane and cyclohexene with two MMO biomimetic complexes, $[Fe_2O(\eta^1\text{-}H_2O)(\eta^1\text{-}OAc)(TPA)_2]^{3+}$ (TPA = tris[(2-pyridyl)methyl]amine) and $[Fe_2O(\eta^1\text{-}H_2O)(\eta^1\text{-}OAc)(BPIA)_2]^{3+}$ (BPIA = bis[(2-pyridyl)methyl)][2-(1-methylimidazolyl)methyl]amine), in an aqueous micelle system using *tert*-butyl hydroperoxide (TBHP) as oxidant in the presence of O_2 (eq 13).[49] Use of a surfactant was necessary to create the micelles, and no reaction occurred in its absence. The reaction gave a mixture of cyclohexanol, cyclohexanone, and *tert*-butylperoxycyclohexane in the case of cyclohexane and 2-cyclohexen-1-ol and 2-cyclohexen-1-one and 3-(*tert*-butylperoxy)cyclohexene in the case of cyclohexene. The product ratio is dependent upon the amount of TBHP and starting material used. A radical mechanism, in which the favorable redox chemistry of the iron complexes in the aqueous micelle system provided t-BuO$^\cdot$ and t-BuOO$^\cdot$ radicals as initiators (Harber−Weiss process), was proposed.



(13)

In a subsequent study, the catalyst, $[Fe_2O(\eta^1\text{-}H_2O)(\eta^1\text{-}OAc)(TPA)_2]^{3+}$, was embedded in an amorphous silicate

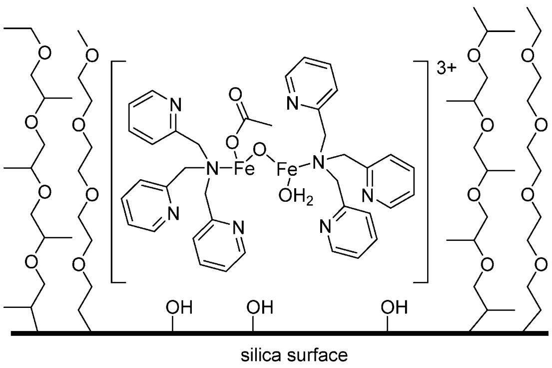


Figure 2.

surface modified by a combination of hydrophilic poly(ethylene oxide) and hydrophobic poly(propylene oxide)[50] (Figure 2). This catalytic assembly also allowed the functionalization of several alkanes with TBHP/O_2 in aqueous reaction medium and turned out to be more efficient in balancing the critical hydrophobic and hydrophilic parameters than the aqueous micelle system.

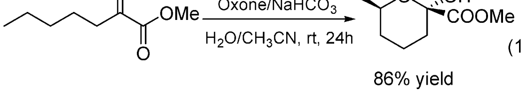
On the other hand, another model of the MMO system was reported by Shukla et al.[51] They carried out the hydroxylation of cyclohexane to cyclohexanol in a mixture of acetone and water (60:40 v/v) using only molecular oxygen as the oxidant. The ruthenium complex $[Ru_2O(Py)_6\text{-}\mu\text{-}(AcO)_2]\,(PF_6)_2$ was found to be an efficient catalyst for this oxidation under moderate conditions of pressure (5 atm) and temperature (30 °C) to give 57% conversion of cyclohexane. A nonradical (ionic) mechanism was proposed based on the kinetic experiments.

Despite this progress, all these systems are generally neither as efficient nor as selective as the natural ones. More efforts are needed to develop mimics of the biological catalysts.

2.1.3. Metal-Free Functionalizations

Although the most common way to activate C−H bonds is using metal complexes, other techniques such as photochemical oxidations, free-radical reactions, and carbene and superacid reactions are also used to carry out such functionalizations[52] (even on an industrial level).[53] When water was used as solvent in a biphasic system, bromide anions, which belonged to the quaternary ammonium salts used as the phase-transfer catalysts, could be precursors to the chain reaction initiator in the absence of metals. Under such conditions, alkylarenes were oxidized with molecular oxygen at 125−140 °C in aqueous media.[54] It was proposed that oxidation of *p*-xylene was initiated by formation of arylalkyl hydroperoxide.[55]

Dioxiranes,[56] efficient organic reagents for oxofunctionalization of C−H bonds, can also occur in water. Alkylketones and alkylketoesters could be regioselectively oxidized at the δ position of the aliphatic chain by dioxiranes generated in situ by oxone in a mixture of H_2O/MeCN (1/1.5 v/v) (eq 14).[57] The authors postulated a concerted nonradical mechanism in which oxidation of the C−H bond generates a δ-hydroxy ketone which cyclizes to give a hemiketal. This hemiketal prevents further oxidation at the δ site.



(14)

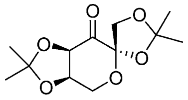
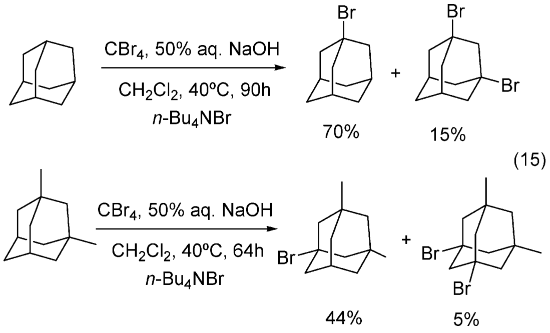


Figure 3.

Chiral α-hydroxy ketones (up to 69% ee) were also prepared using an optically active dioxirane generated in situ from the fructose-derived ketone (Shi's ketone) (Figure 3) and oxone in aqueous medium.[58] Other alkanes, such as the dimer of norbornadiene (binor-S), were regiospecifically oxidized by dimethyldioxirane in 98% yield in a mixture of CH_2Cl_2/acetone/H_2O.[59]

2.2. Formation of C–Halogen Bonds

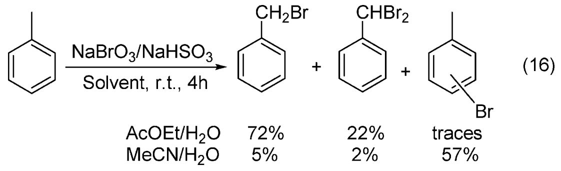
Formation of C−halogen bonds to produce haloalkanes is usually carried out via free-radical halogenations.[52b,c] On the other hand, water is an excellent solvent for radical reactions because of the exceptionally strong O−H bonds; therefore, hydrogen abstraction from the solvent is unlikely to occur. Schreiner et al. solved the lack of selectivity of halogenation reactions by means of phase-transfer catalysis in aqueous biphasic systems. They reported useful chlorinations, brominations, and iodinations of various alkanes.[60] The procedure involves a solution of the alkane in an inert organic solvent (or an excess of the alkane) over a highly concentrated basic aqueous solution. A quaternary ammonium salt serves as phase-transfer catalyst and CCl_4, CBr_4, or CHI_3 as sources of halides. Use of the phase-transfer system avoided the overfunctionalization of the products. In addition, the reaction is highly regioselective toward tertiary C−H bonds, and in the case of adamantane, the transformation takes place in the bridge head position even in the presence of methyl groups (eq 15).[61] A single-electron transfer was proposed to initiate the reaction to generate a trihalomethyl radical which abstracts a hydrogen atom from the alkane to produce an alkyl radical. The alkyl radical reacts again with tetrahalomethane to give the halogenated products.



(15)

Another example of free-radical halogenation is the photochemical bromination of several alkanes and alkylarenes with Br_2 in water.[62] Use of water provided a diluting medium where free radicals were uniformly distributed over the reaction volume. In these conditions, overbromination of the alkanes was reduced.

On the other hand, Ishii et al. reported the bromination of alkylarenes with a mixture of $NaBrO_3$/$NaHSO_3$ under mild conditions in aqueous media.[63] The regioselectivity of the reaction could be controlled by the reaction conditions. Different regioisomers were obtained when the solvent was a mixture of AcOEt/H_2O or MeCN/H_2O, which were proposed to involve different mechanisms. Free-radical bromination occurred in AcOEt by Br$^{\cdot}$, and ring bromination occurred in aqueous MeCN by Br^{+} (eq 16).



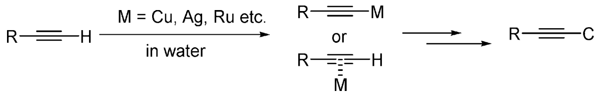
Although the main processes to carry out halogenations involve free radicals, chlorination of alkanes can also take place by other mechanisms. Chloroalkanes were obtained when aqueous Na_2PtCl_4 and Na_2PtCl_6 were used as catalysts in the hydroxylation reactions of nonactivated C−H bonds (see section 2.1.1.1.). Horváth et al. reported that the aqueous Na_2PtCl_4/Na_2PtCl_6 system could be used as catalyst for the homogeneous catalytic chlorination of methane with Cl_2 between 100 and 125 °C.[64] No formation of metallic platinum was detected.

3. Formation of C−C Bonds

3.1. Activation of sp C−H Bonds

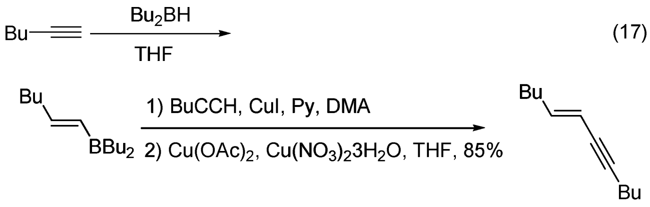
Compared to other C−H bonds, the sp C−H bonds in terminal alkynes are relatively more acidic and reactive, and can be activated readily by many transition-metal catalysts to form either metal acetylides or π complexes in water. Such complexes can react with other functional groups to form new C−C bonds (Scheme 1).

Scheme 1

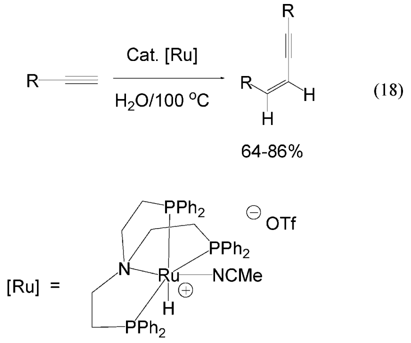


3.1.1. Alkyne Dimerization

The additive coupling of terminal alkynes catalyzed by copper is another classical reaction known as the Strauss coupling. Unfortunately, under classical conditions, a mixture of regioisomers was generally obtained.[65] Recently, a rhodium-catalyzed homopolymerization and oligomerization of alkynes has been reported.[66] A major development in overcoming this limitation was made by Trost, who found that using catalytic amounts of $Pd(OAc)_2$ and triphenylphosphine in dichloroethane resulted in a high yield of homocoupling of terminal alkynes.[67]



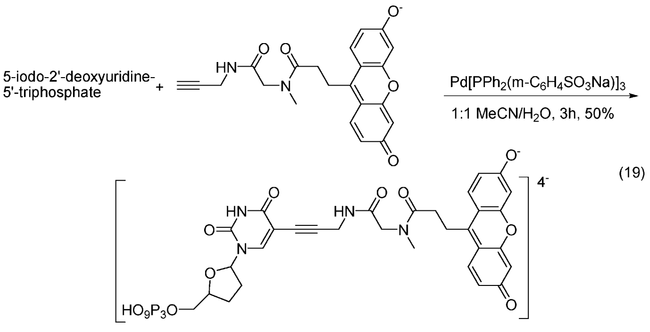
Alternatively, it is interesting to note that a copper(II)-mediated coupling reaction of alkenyldialkyl- or trialkylboranes with alkynylcopper compounds, generated in situ in the presence of various solvents and a small amount of water, gives (*E*)-1,3-enynes (or disubstituted alkynes) with various functional groups in reasonable yields (eq 17).[68] A ruthenium catalyst, $[RuH(CH_3CN)(NP_3)]OTf$, catalyzed the additive dimerization of both aliphatic and aromatic terminal alkynes effectively to give (*Z*)-enynes in high regio- and stereoselectivity in an aqueous medium (eq 18).[69]



3.1.2. Reaction of Alkynes with Organic Halides

The coupling of terminal alkynes with organic halides, known as the Castro−Stephens−Sonogashira reaction, has been widely utilized in synthesis. The most widely used method is the Sonogashira coupling using a combination of palladium and copper as the catalyst, in which formation of copper(I) acetylides and subsequent transmetalation to palladium species were proposed as the key steps.[70]

Recently, the reaction was investigated extensively in aqueous media with reactions that do not use copper as the cocatalyst. For example, when a water-soluble palladium complex is used as the catalyst, unprotected nucleosides, nucleotides, and amino acids undergo coupling with terminal acetylenes in aqueous acetonitrile.[71] Compound T-505, part of a family of chain-terminating nucleotide reagents used in DNA sequencing and labeling, was synthesized by this route in 50% yield (eq 19).



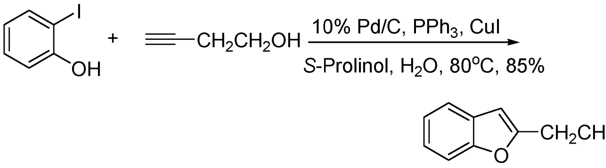
T-505

Another copper-free Sonogashira reaction of aryl iodides with terminal acetylenes in water under aerobic conditions was reported by Yang's group. Use of 1 mol % $PdCl_2$ in the presence of pyrrolidine allows the coupling reaction to proceed at room temperature or 50 °C with good to excellent yields.[72]

Genet,[73] Beletskaya,[74] and others[75] carried out more detailed studies of the aqueous Sonogashira reaction. A variety of aryl and vinyl iodides were coupled with terminal acetylenes in aqueous media with either a water-soluble catalyst or a non-water-soluble catalyst. The reaction can also be carried out without the use of a phosphine ligand in a water−alcohol emulsion in the presence of cetyltrimethylammonium bromide (CTAB) as an emulsifier.[76] Sterically demanding, water-soluble alkylphosphines such as *t*-Bu-Amphos by Shaughnessy (Figure 3A)[77] and the dicyclohexylarylphoshine ligand by Buchwald (Figure 3B)[78] have been used in combination with various palladium salts in Suzuki, Sonogashira, and Heck couplings of aryl bromides under mild conditions in aqueous solvents. Heck and Sonogashira couplings were carried out under mild conditions (50 and 80 °C, respectively) with unactivated aryl bromides to give coupled products in high yield. By using the dicyclohexylarylphoshine ligand, even the less reactive aryl chlorides give high yields of the corresponding Sonogashira coupling products.

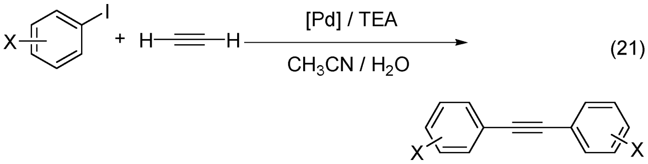
Diynes were similarly prepared by reaction of alkynyl bromide with terminal alkynes.[79]

Pd/C can also be used as an efficient catalyst instead of other homogeneous Pd(0) catalysts in a sequential two-step reaction for the coupling of 2-iodoaniline or 2-iodophenol with terminal alkynes to give the corresponding indoles or benzofurans in good yield (eq 20).[80] This methodology can tolerate a number of different functional groups, does not require the use of a phase-transfer catalyst or water-soluble phosphine ligands, and can be performed directly in water.



(20)

Li and co-workers reported a highly efficient coupling of acetylene gas with aryl halides in a mixture of acetonitrile and water (eq 21).[81] The conditions are generally milder and the yields are better than previously reported results in organic solvents. A variety of aromatic halides are coupled to give the corresponding bis-arylacetylenes. Both a water-soluble palladium catalyst (generated in situ from $Pd(OAc)_2$/TPPTS) and a water-insoluble catalyst (generated in situ from $Pd(OAc)_2/PPh_3$) can be used for the reaction. The reaction can be carried out in water alone. The reaction proceeds equally well with or without CuI as a cocatalyst. By using the palladium-catalyzed coupling between aryl halides with acetylene gas, Li et al. prepared a variety of poly(arene ethynylene)s from aryl diiodides.[82]

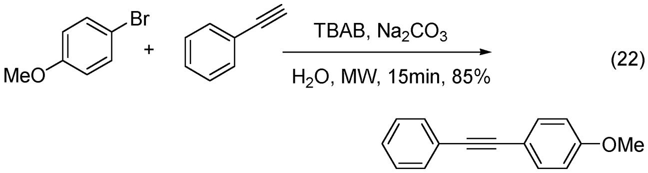


(21)

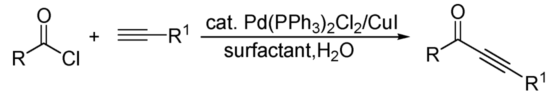
Alkenyl and aryl iodonium salts have also been coupled with terminal alkynes. Reaction of (*E*)-[α-(trifluoromethanesulfonyloxy)-1-alkenyl](phenyl) iodonium trifluoromethanesulfonate with terminal alkynes in the presence of catalytic amounts of dichloro(triphenylphosphine)palladium(II) and CuI in an aqueous medium proceeds stereospecifically to give the corresponding enynes in good yields.[83] $Ni(PPh_3)_2Cl_2$/CuI was also reported as a catalyst for such couplings in water.[84]

An interesting development is a microwave-assisted, transition-metal-free Sonogashira-type coupling reaction (eq 22). The reactions were performed in water without the use of copper(I) or a transition-metal−phosphane complex. A variety of different aryl and heteroaryl halides were reactive in water.[85] However, in light of the recent report by Leadbeater,[86] a trace amount of metal may be responsible for the Sonogashira reaction as well.

A highly effective direct coupling of acid chlorides with terminal alkynes catalyzed by $PdCl_2(PPh_3)_2$/CuI together with a catalytic amount of sodium lauryl sulfate as the surfactant and K_2CO_3 as the base provided ynones in high yields in water (eq 23). The desired product was obtained in 98% isolated yield. No reaction was observed when either Cu(I) alone or Pd(II) alone was used as the catalyst. Use of surfactant is also critical for the success of the reaction, possibly by temporarily stabilizing the acid chloride; without a surfactant/phase-transfer reagent the yield dropped from 98% to 9%.[87]



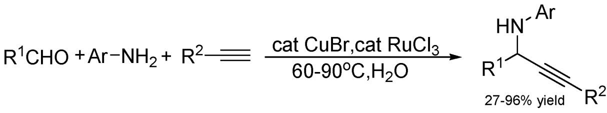
(22)



(23)

3.1.3. Reaction with Imines

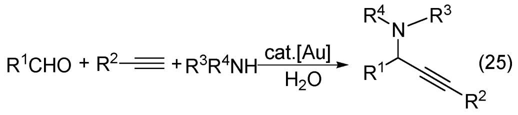
The direct 1,2-addition of terminal alkynes to the C═N double bond in imines and their derivatives via activation of the C−H bond in the terminal alkynes is a convenient route to synthesize propargylamines. Recently, Li and co-workers reported a highly efficient A^3 coupling (aldehyde−alkyne−amine) in water or neat.[88] It was found that phenylacetylene can react with an arylimine in the presence of a catalytic amount of Cu(I) in aqueous media to give the desired adducts in low conversions. When $RuCl_3$ was used as a cocatalyst, the reaction was more efficient. No desired product was found with $RuCl_3$ alone as the catalyst. A broad range of substituted aromatic imines and aliphatic imines (eq 24) were converted into propargylamines by this method. The additions were found to be also highly effective under solvent-free conditions.



(24)

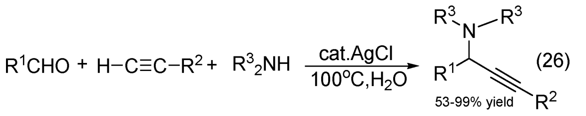
Li and co-workers also reported a copper-mediated coupling of alkynes with *N*-acylimines and *N*-acyliminium ions in water to generate propargyl amide derivatives.[89] *N*-Acylimines or *N*-acyliminium ions can be generated in situ from amines containing a good leaving group at the α position. For example, *R*-phenylsulfonyl *N*-acylamine and *R*-methoxy *N*-(alkoxycarbonyl) pyrrolidine and the products can be modified easily for various synthetic purposes. However, an excess amount of CuBr is required in this case.

Subsequently, Li and co-workers also found that the reaction is highly efficient and widely applicable with gold as the catalyst (eq 25).[90] No cocatalyst or activator is needed for the gold-catalyzed reaction. Less than 1 mol % of catalyst is enough to generate an excellent yield of the corresponding propargylamine products. Dialkylamines are good for the reaction, whereas anilines gave the corresponding products in lower yields. *N*-Alkylanilines did not form the desired products. Aromatic aldehydes reacted more efficiently, and nearly quantitative yields were obtained in most cases. Aliphatic aldehydes can also be used; however, some trimerizations of aldehydes were observed that decreased the yields of the propargylamine products. The properties of solvents significantly affect the reaction. Water is the best solvent, and the reaction process is very clean with almost quantitative yield; use of organic solvents such as THF, toluene, and DMF resulted in lower conversions and more byproducts.



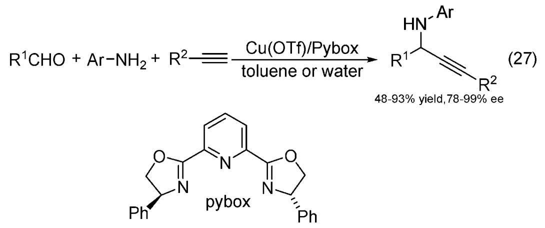
(25)

Following the success of copper and gold, it was found that AgCl, AgBr, and AgI showed good catalytic activity for the three-component coupling in water (eq 26).[91] No other additive was needed for this reaction either. In this reaction, aromatic aldehydes decreased the reactivity of the reaction, whereas aliphatic aldehydes displayed higher reactivity and cleaner reactions compared to the reaction catalyzed by copper and gold.



(26)

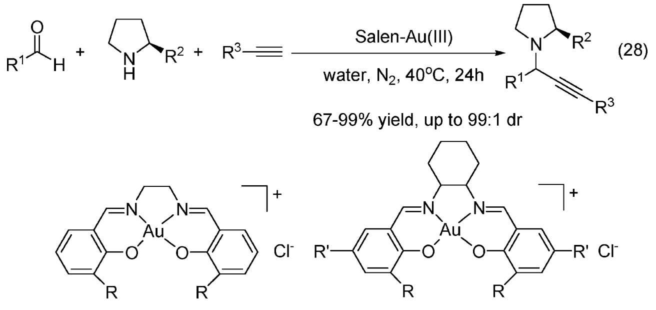
Recently, Li and co-workers reported a highly efficient AA^3 coupling (asymmetric aldehyde−alkyne−amine) in water (eq 27).[92] Use of the tridentate bis(oxazolinyl) pyridines (pybox) with Cu(OTf) afforded the product with both high yield and enantioselectivity up to 99.6% ee in organic solvent and 84% ee in water. In most cases, imines were formed in situ and the addition was very simple: mixing an aldehyde, an aniline, and an alkyne with the catalyst in one pot.



(27)

Tu and co-workers recently reported that a three-component coupling of aldehyde, alkyne, and amine via C−H activation catalyzed by CuI in water can be greatly accelerated using microwave irradiations. Using (*S*)-proline methyl ester as a chiral source, a direct and highly diastereoselective method for construction of chiral propargylamines was achieved.[93]

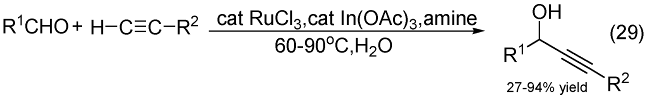
Recently, Che and co-workers also reported a gold-catalyzed three-component coupling of aldehyde, alkyne, and amine in water using gold(III)−salen complexes as precursors.[94] With chiral prolinol derivatives as the amine component, up to 99:1 diastereoselectivities were attained (eq 28). This coupling reaction has been applied to the synthesis of propargylamine-modified artemisinin derivatives with the delicate endoperoxide moieties remaining intact.



(28)

3.1.4. Reaction of Alkynes with Carbonyl Compounds

Li and co-workers developed a direct addition of terminal alkynes to aldehydes in water using a ruthenium−indium bicatalyst system (eq 29).[95]

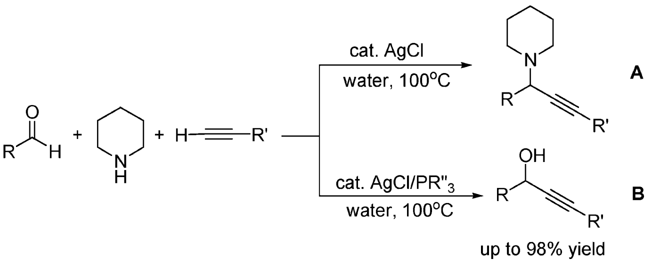


(29)

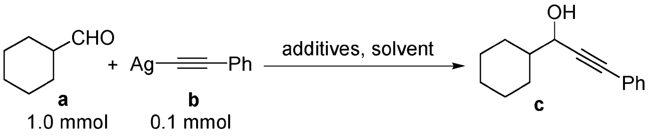
A Zn(OTf)$_2$-promoted addition of terminal alkynes to aldehydes was carried out in wet toluene (containing 80−1000 ppm water).[96] However, in this case, stoichiometric Zn(OTf)$_2$ has to be used. The intermediate in the reaction was studied by ReactIR, and formation of a π complex of alkynes with Zn(II) and subsequent generation of Zn−acetylides were believed to be the key steps in the reaction.[97]

Although the salts of metals in group IB, such as Cu(I), Ag(I), and Au(I), can activate the C−H bond of terminal alkynes to form metal acetylides very easily, it is widely accepted that these metal acetylides are only reactive to imines but fail to participate in the nucleophilic C═O addition.[98] Recently, Yao and Li reported a silver−phosphine complex-catalyzed alkynylation of aldehydes in water (Scheme 2).[99] Under the standard condition for A^3 addition (path A), if a phosphine ligand was added, the only detected product was from the alkynylation of aldehyde (path B) instead of the imine-addition product. In this reaction, the phosphine ligand served as a remarkable chemoswitch to control the direction of the reaction from A^3 addition to the alkynylation of aldehyde.

Scheme 2



Scheme 3

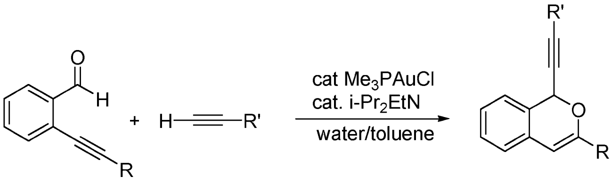


entry	conditions	result[a]
1	water, 95°C, overnight	no reaction
2	toluene, 95°C, overnight	no reaction
3	+ 0.11 mmol PCy$_3$ water, 35°C, overnight	68% of **c**
4	+ 0.11 mmol PCy$_3$ toluene, 35°C, 10h 80°C, overnight	no reaction trace
5	+ 0.11 mmol PCy$_3$, 1.5 mmol phenylacetylene, 2 mL H$_2$O,95°C, overnight	86% of **c**
6	+ 0.11 mmol PCy$_3$, 1.5 mmol phenylacetylene, 0.2 mmol i-Pr$_2$NEt, 2 mL H$_2$O,95°C, overnight	432% of **c**

[a] Yield was calculated based on substrate **b**

Electron-donating P ligands proved to favor the reaction, and combination of Cy_3PAgCl with 0.2 equiv of *i*-Pr_2NEt gave the best results. The reaction showed the best results in water alone as solvent. In toluene or neat conditions, no reaction was observed at all. Introduction of an organic solvent resulted in an obvious decrease in yield. The mechanism studied suggested that the silver acetylide was dually activated by both phosphine ligand and water (Scheme 3).

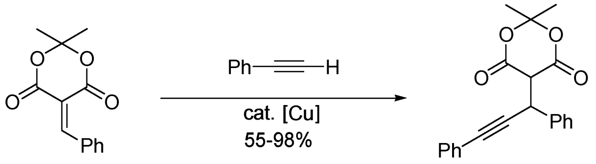
Very recently, Yao and Li also reported a water-triggered and gold(I)-catalyzed cascade addition/cyclization of terminal alkynes with *ortho*-alkynylaryl aldehyde leading to 1-alkynyl-1*H*-isochromenes (eq 30).[100] Similar to the situation in silver(I)-catalyzed direct addition of terminal alkynes to aldehydes in water, the reaction was dually promoted by an electron-donating phosphine ligand and water. Surprisingly, no catalytic activity for the alkynylation of phenylacetylene with benzaldehydes was observed using the same catalyst under standard conditions. This result suggests that the *o*-alkynyl in substrate might function as a chelating-activating group and that the reaction is chelation-controlled.



(30)

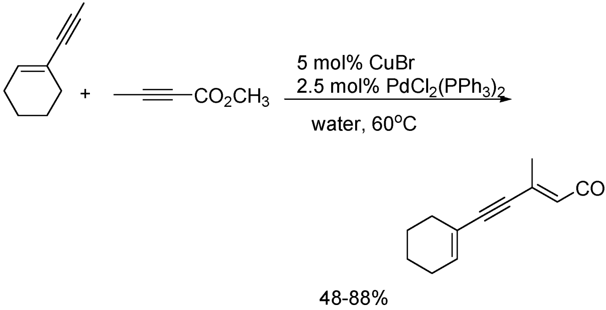
3.1.5. Conjugate Addition

For the conjugate addition of terminal alkynes to unsaturated carbonyl compounds, Carreira reported that alkynyl copper reagents, generated from terminal alkynes and catalytic $Cu(OAc)_2$ in the presence of sodium ascorbate, undergo additions to alkylidene Meldrum's acid at room temperature in aqueous media to give the corresponding adducts (eq 31).[101] The restriction to this methodology is that it is limited to highly activated alkylidene Meldrum's acid.



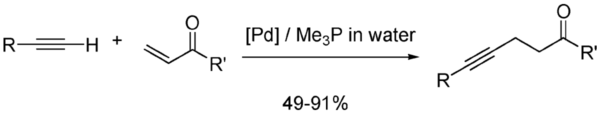
(31)

On the other hand, Chen and Li reported a facile and selective copper−palladium-catalyzed addition of terminal alkynes to activated alkynes in water without the competition of the homocoupling of the terminal alkynes (eq 32).[102]



(32)

Recently, Li and co-workers also reported a simple and highly efficient Pd-catalyzed addition of a terminal alkyne to a C=C double bond such as a conjugated enone, either in water or in acetone in air (eq 33).[103]



(33)

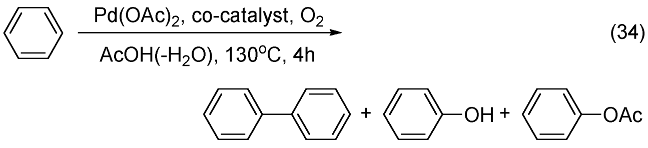
3.2. Activation of sp^2 C–H Bonds

Compared to the sp C−H bond, sp^2 C−H bonds are hard to activate. Many transition metals such as palladium, ruthenium, and rhodium, etc., were utilized to activate the C−H bonds on arenes.[104] In many cases, the mechanism requires the electrophilic attack by a cationic metal species in an acidic solvent system such as HOAc, TFA, etc. There are only a few examples involved in water, which usually was utilized as an additive instead of a solvent.

3.2.1. Oxidative Homocoupling of Benzene Ring

In 1995, Sawyer and co-workers reported an iron(II)-induced oxidative coupling reaction of benzene.[105] Fe(II)-(O)$(PPh_3)_4$ was used as a coupling catalyst with H_2O_2/HCl as an oxidant system in water or MeCN. However, only lower conversions (∼20%) were observed.

The combination of $Pd(OAc)_2$/molybdophosphoric acid ($H_3PMo_{12}O_{40}$)/O_2/AcOH−H_2O (2:1) has been found to oxidize benzene to give biphenyl by oxidative dimerization with 100% selectivity and 19% yield under the conditions of 130 °C, 10 atm, and 4 h.[106] Use of $PdHPMo_{12}O_{40}$ itself as catalyst was found to be effective and gave 95% selectivity of biphenyl with a lower yield (eq 34). Poly(oxy-1,4-phenylene) was obtained by electro-oxidative polymerization of *p*-bromophenol in aqueous NaOH solution. The yield increased when aqueous NaOH was replaced with aqueous KOH or the temperature increased. In contrast, *p*-chlorophenol dimerized to give 2,7-dichlorodibenzo-[1,4]-dioxin.[107]



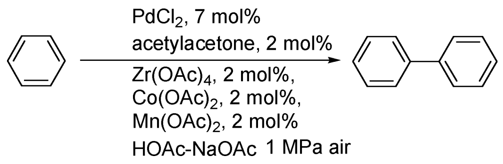
(34)

A similar system was also reported by Sasson's group. $PdCl_2$ was utilized as a coupling catalyst, and a combination of $Zr(OAc)_4$, $Co(OAc)_2$, and $Mn(OAc)_2$ promoters was employed as molecular oxygen fixators, together with acetylacetone. Water was found to be an important additive for improving the selectivities of the reaction with good to excellent conversion (Table 1).[108]

3.2.2. Cyclocarbonylation

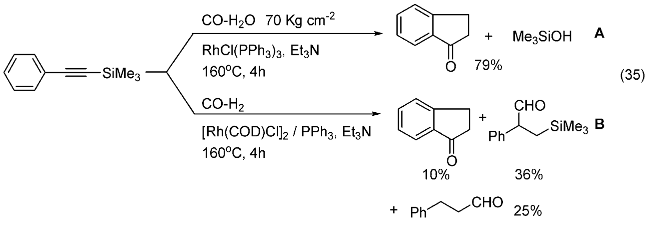
In many examples of the transition-metal catalyzed C−H bond activation of the aromatic ring, directing groups or assisting groups are usually needed.[109] Takeuchi and co-workers reported the cyclocarbonylation reaction of l-aryl-2-(trimethylsilyl)acetylenes. The acetylene group can also be used as a directing group. l-Aryl-2-(trimethylsilyl)-acetylenes undergo Rh-catalyzed desilylative cyclocarbonylation to give 2,3-dihydro-l*H*-inden-l-ones and trimethylsilanol (eq 35, path A).[110] A wide variety of functional groups such as methoxy, chloro, acetyl, ethoxycarbonyl, cyano, and trifluoromethyl are tolerated on the aromatic ring under the

Table 1. Oxidative Coupling of PhH with Water as Additive



entry	water (mol %)	conversion (%)	selectivity (%)
1	0	96	78
2	250	94	89
3	450	86	91

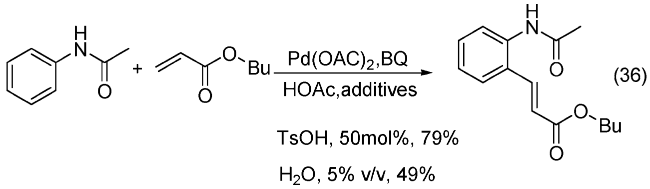
reaction conditions. The products were obtained in good to excellent yield whether the substituent on the aromatic ring was electron donating or electron withdrawing. The cyclizations of substrates bearing a meta substituent on the aromatic ring regiospecifically gave 5-substituted-2,3-dihydro-l*H*-inden-l-ones except when the meta substituent was a methoxy group. The reaction is initiated by π coordination of the acetylene to the rhodium, which induces oxidative addition of the ortho aromatic C−H bond.



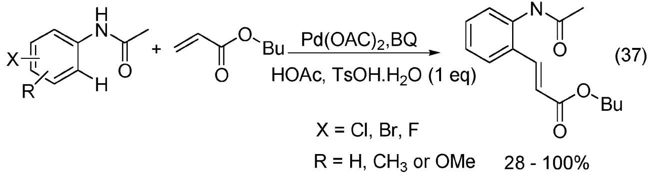
It is worth noting that the reaction was carried out under so-called “water gas shift reaction conditions”. The reaction gave no product in the absence of H_2O, and the starting material was recovered. Replacement of H_2O by D_2O gave the deuteriated product. The fact that deuterium atoms were incorporated into both of the methylene carbons of indenone shows that H_2O acts as the hydrogen source. Use of molecular hydrogen in place of H_2O resulted in a poor yield along with formation of hydroformylation products (eq 35, path B). The water gas shift reaction conditions were necessary for good yields of the reaction. On the other hand, bases can effectively promote the water gas shift reaction.[111] Et_3N is an effective additive for this cyclocarbonylation; in the absence of Et_3N, the reaction gave indenone in 2% yield. Furthermore, in the screening of the catalysts, hydrated rhodium(III) chloride gave the best selectivity and good yield.

3.2.3. Oxidative Coupling of Aromatic Ring with Olefins

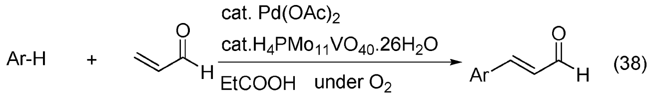
A $Pd(OAc)_2$-catalyzed reaction of functionalizing aniline derivatives with *n*-butyl acrylate at room temperature was reported by De Vries and Van Leeuwen (eq 36). Benzoquinone (BQ) was used as oxidant, and HOAc/toluene was employed as solvents. The presence of a substoichiometric amount (0.5−1.0 equiv) of *p*-toluenesulfonic acid (TsOH) had a large beneficial effect, resulting in a 72% isolated yield. On the other hand, water (5% v/v) as additive resulted in a 49% yield. However, this reaction was limited in the amide of aniline.[112]



A very similar reaction of halogenated acetanilides with acrylates was reported by Prasad and co-workers.[113] In this reaction, 1 equiv of water was introduced into the reaction using *p*-toluenesulfonic acid monohydrate as the acidic additive, and moderate to excellent yields were achieved (eq 37).



Yamada and Ishii et al. reported a direct oxidative coupling reaction of benzene with an α,β-unsaturated aldehyde through the C−H bond activation using the combined catalytic system of $Pd(OAc)_2$ with molybdovanadophosphoric acid (HPMoV) under atmospheric molecular oxygen.[114] Different from the examples above, no directing or assisting groups were needed in this reaction. Reaction of benzene with acrolein under molecular oxygen (1 atm) by using catalytic amounts of $Pd(OAc)_2$ and $H_4PMo_{11}VO_{40}{\cdot}26H_2O$ in the presence of dibenzoylmethane as a ligand in propionic acid at 90 °C for 1.5 h afforded cinnamaldehyde in 59% yield and β-phenylcinnamaldehyde in 5% yield (eq 38).

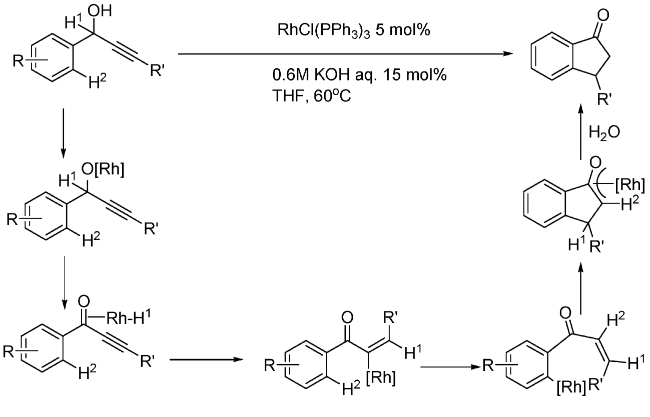


3.2.4. Isomerization of α-Arylpropargyl Alcohols to Indanones

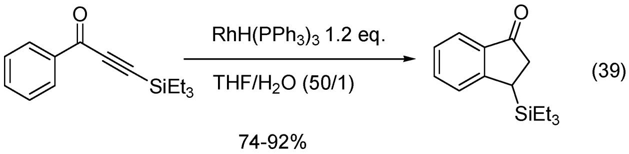
Recently, Hayashi’s group reported a rhodium-catalyzed isomerization of α-arylpropargyl alcohols to indanones in which diluted KOH aqueous solution was used as base (Scheme 4).[115]

The mechanism study showed that the reaction was initialized by coordination of alcohol with Rh(I) species and then followed by β-elimination to form the carbonyl and Rh−H species. The vinylrhodium intermediate formed from the hydrorhodation of the triple bond activated the C−H bond on the ortho position to form the indanone ring. The Rh−C bond was quenched by protonization through the rhodium−enolate intermediate with the assistance of water. The study

Scheme 4

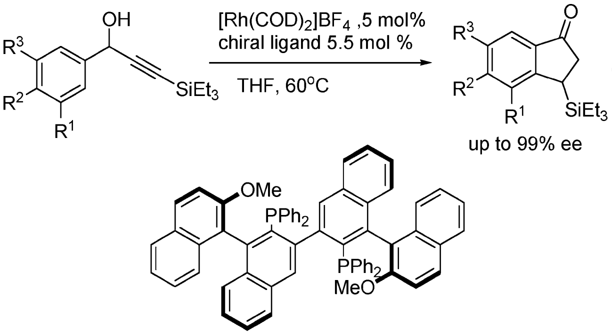


showed that water is necessary for the last step to provide protons to quench the Rh–C bond (eq 39).



(39)

Very recently, the enantioselective version of this reaction was developed under the same reaction conditions. Up to 99%ee was achieved using a novel BINAP-type chiral ligand (eq 40).[116]



(40)

3.3. Activation of sp^3 C–H Bonds

Generally, the sp^3 C–H bond has been considered less reactive in conventional organic chemistry than the sp^2 or sp C–H bonds. However, there are still some examples that have been reported in the past two decades about the C–C bond formation reaction via sp^3 C–H bond activation in aqueous conditions. These examples include the carboxylation of methane, carbene insertion into an alkane C–H bond, and aldol-type reaction of allylic alcohols. On the other hand, significant progress has been made in the catalytic reaction of C–H bonds adjacent to heteroatoms such as nitrogen and oxygen. As the representative example for these reactions, the cross-dehydrogenative coupling will be discussed in section 4.

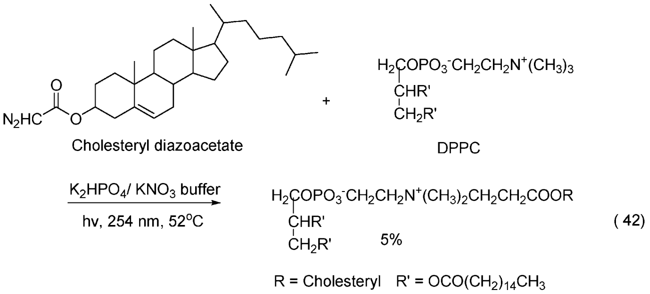
3.3.1. Carboxylation of Methane

As an important industry gas, C–H bond activation of methane has attracted much attention. Recently, it has been shown that it is possible to couple methane with CO to generate acetic acid in aqueous conditions by means of several catalysts (eq 41).[117]

$$CH_4 \xrightarrow[\text{water, pH = 7.3}]{\text{CO, air, NaVO}_3\text{, 80°C}} MeCO_2H + MeOH + HCHO \qquad (41)$$

3.3.2. Carbene Insertion into an Alkane C–H Bond

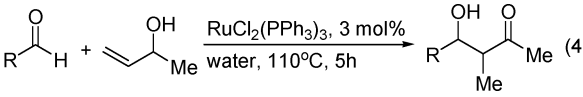
Carbon–carbon bond formation via carbene insertion into an alkane C–H bond[118] is also possible in aqueous media under photolytic conditions. Cholesteryl diazoacetate reacted with DPPC to give a C–H bond insertion product on the N-methyl group in low yield (eq 42).[119]



(42)

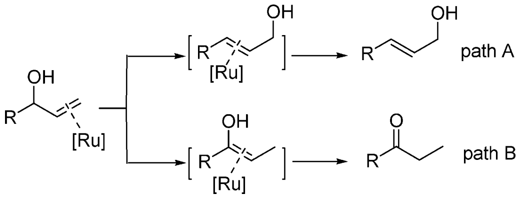
3.3.3. Aldol-type Reaction of Allylic Alcohols

A $RuCl_2(PPh_3)_3$-catalyzed rearrangement of functional groups of homoallylic alcohols in water was reported by Li and co-workers (Scheme 5, path A).[120] On the basis of the side reaction observed in the reaction (Scheme 5, path B), an aldol-type reaction of allylic alcohols with aldehyde was developed (eq 43).[121] In this reaction it was believed that the enol intermediate was formed via activation of the allylic C–H bond and subsequent rearrangement of the double bond. The presence of $In(OTf)_3$ promoted the aldol reaction with α-vinylbenzyl alcohol and aldehyde.[122]

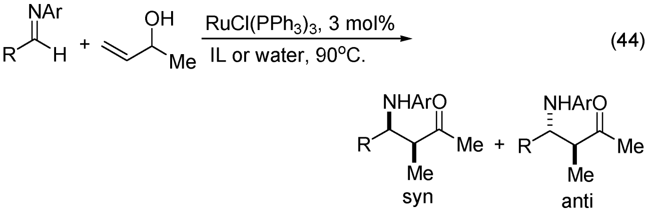


(43)

Scheme 5



In subsequent studies a Ru(II)-catalyzed Mannish-type reaction was reported in ionic liquid, based on the enol formed in situ (eq 44).[123] The solvent/catalyst system could be reused at least five times with no loss of reactivity. In this reaction, water also works as an efficient solvent and some moderate yields were achieved.



(44)

4. Multi-C–H Activations

C–C bond formations based on multi-C–H activations generate even high synthetic efficiency and allow the target molecules to be rapidly reached.[124] Recently, a cross-dehydrogenative coupling (CDC) methodology (Scheme 6) was developed to construct C–C bonds by directly using two C–H bonds.[125] Such a methodology will avoid preparation of functional groups and thus make synthetic schemes shorter and more efficient.[126]

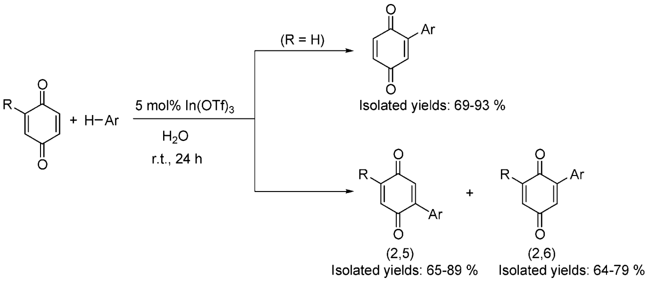
4.1. CDC Reactions

Substituted 1,4-benzoquinone derivatives exist widely in nature and exhibit various important biological activities.[127] Aryl-substituted 1,4-benzoquinone derivatives were successfully catalyzed by $In(OTf)_3$ via the coupling reactions of aromatic compounds and 1,4-benzoquinone in water (Scheme 7and Table 2).[128] When various organic solvents such as CH_3CN, CH_2Cl_2, and THF were used, low yields (trace to 25%)

Scheme 6. Various Cross-Coupling Methods for Formation of C−C Bonds

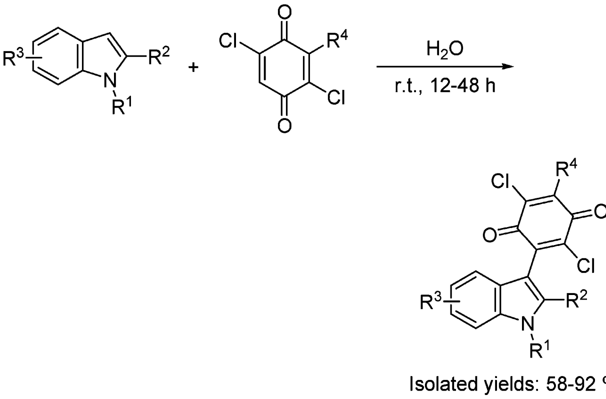
$$\mathrm{C{-}H} \;+\; \mathrm{H{-}C} \xrightarrow{\mathit{cat.}\ \mathrm{M}} \mathrm{C{-}C}$$

Scheme 7. In(OTf)$_3$-Catalyzed Arylation of 1,4-Quinones in Water



were obtained. When water was used as solvent, the desired products were obtained in up to 93% yield. Water not only serves as the reaction media but also promotes the reactions. Both mono- and bis-aryl-substituted 1,4-quinones were thus synthesized by 5 mol % In(OTf)$_3$ in water. High regioselectivities were observed for bis-aryl-substituted 1,4-quinones which depended on the reaction conditions and substrates. The reaction, however, proceeded by Friedel−Crafts-type conjugate addition followed by oxidation rather than C−H activation.

When indoles were used as aromatic components, 3-indolylquinones were obtained efficiently by the CDC reactions of indoles with 1,4-benzoquinones in water without any catalysts (eq 45).[129] A notable water acceleration was observed in these reactions which suggests a highly efficient direct coupling of indoles with 1,4-benzoquinones. Unsymmetric bis(indolyl)-1,4-quinones were also synthesized via two steps of CDC reactions in water exclusively without the use of any catalyst, additive, or organic solvent. Because the reactants were in a heterogeneous system, the "on water"[130] conditions contributed to reaction rate acceleration.

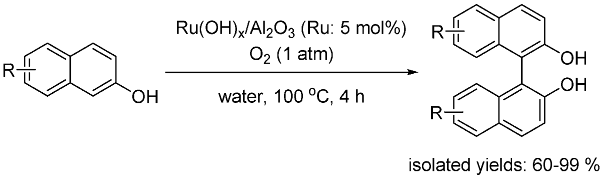


(45)

4.2. Homocoupling Reactions

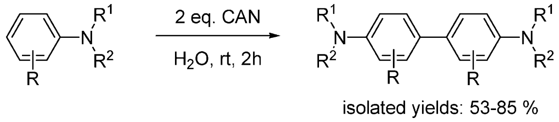
Compared to CDC reactions, homocoupling reactions are well established in chemical syntheses. Oxidative dimerization of aromatic compounds is an important method for constructing symmetric biaryl compounds. Generally, electron-rich aromatic compounds such as phenols, anilines, and naphthalenes are common substrates. Various kinds of metal salts, including Cu, Fe, Mn, Ru, and Ti, could be used as catalysts with other oxidants[131] or as stoichiometric oxidation reagents.[132] However, dimerization of aromatic compounds in aqueous media is still a challenging goal in organic synthesis.

Biaryl coupling of 2-naphthols and substituted phenols was efficiently promoted by a supported Ru catalyst using O$_2$ as an oxidant in water (eq 46).[133] The supported catalyst can be reused seven times without losing catalytic activity. The big advantages of this method are that an environmentally friendly oxidant (O$_2$) and solvent (H$_2$O) can be used. The studies on the mechanism behind the reaction showed that the Ru-catalyzed biaryl coupling reaction proceeds through the radical coupling mechanism. When FeCl$_3$ was used as a stoichiometric oxidation reagent and catalyst, homocoupling of 2-naphthols and substituted phenols successfully occurred in water.[134]



(46)

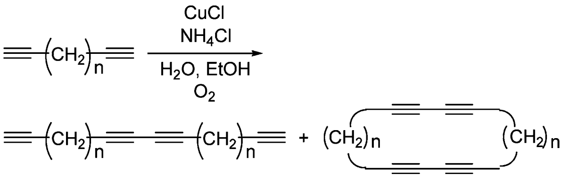
Benzidine derivatives were obtained via oxidative coupling of *N*,*N*-dialkylarylamines using CuBr as a catalyst and H$_2$O$_2$ as an oxidant in water.[135] When CAN was used as oxidant, homocoupling of *N*,*N*-dialkylarylamines was also effectively promoted using water as solvent (eq 47).[136] A rationale for the mechanism of this coupling reaction is proposed via dimerization of diradical cations. Unlike homocoupling of 2-naphthols and substituted phenols which gave ortho products to the OH group, *para*-substituted products were selectively formed for *N*,*N*-dialkylarylamines substrates.



(47)

Acetylenic coupling (Glaser-type reactions)[137] is another excellent example.[138] A copper catalyst, an organic base, an oxidant, and a polar solvent are typical reaction conditions in acetylenic coupling reactions. Unfortunately, most of results were obtained in organic solvents. The low efficiency of catalysts in an aqueous medium is the main reason for this problem.

The oxidative dimerization of terminal diacetylenes gave both linear and cyclic coupling products in the presence of a copper catalyst and a phase-transfer reagent in aqueous ethanol solution (eq 48).[139] The ratios of linear and cyclic coupling products are related with the numbers of bridged methylene. When deca-1,9-diyne and hexa-1,5-diyne were used, the linear products were the major products. However, when nona-1,8-diyne and hepta-1,6-diyne were used, the cyclic products were the major products.

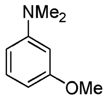
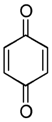
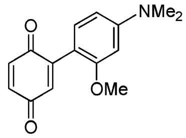
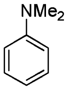
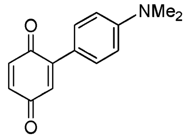
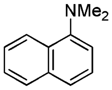
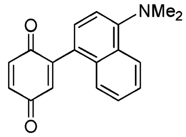
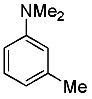
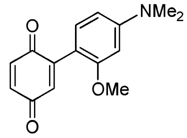
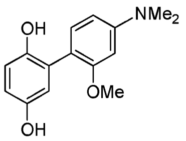
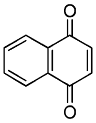
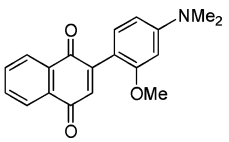
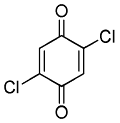
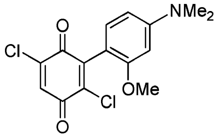
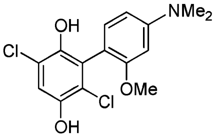
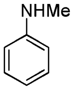
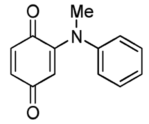
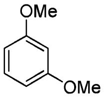
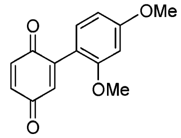
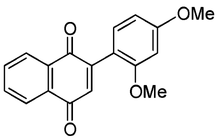
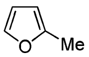
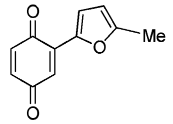


(48)

5. Conclusion

Development of organic transformations based on reaction of C−H bonds in water is a highly challenging subject because it is necessary to overcome some of the most

Table 2. Reactions of Ar−H with Quinones Catalyzed by Ln(OTf)$_3$[a] in Water

Entry	Ar-H[b]	Quinone[b]	Time (h)	Product	Yield[c] (%)
1			2		93
2			24		84
3			24		69
4			24	 **3d-1** + 	33+56
5			12		86
6			2	 **3f-1** + 	40+55
7			24		65+28
8			2		63
9			24	 + (2,6)-**4h**[d]	60+17
10			24		78
11			24		64

---

[a] Catalyst loading: 5 mol %. [b] Ar−H/quinone = 1:2. [c] Isolated yield. [d] Bis-substituted quinone, 4 h; see Table 3, entry 8.

fundamental concepts and theories such as classical reactivity and bond strength. Successful progress on the subject would require the conventionally and theoretically less reactive C−H bonds to react selectively in the presence of various functional groups. It further requires that the intermediates tolerate the solvent, water, to give the final desired products. Nevertheless, as shown by this review, reactions of C−H bonds in water can indeed occur, albeit still in a very limited way at present. From an economic or ecological point of view, it can be expected that C−H activations and reactions, especially multi-C−H bond reactions, have a bright future for chemical syntheses in water.

6. Acknowledgment

We thank the Canada Research Chair Foundation (to C.J.L.), NSERC, CFI, FQRNT, Merck Frosst, and CIC (Merck Frosst/Bohringer Ingelheim/AstraZeneca) for their support related to this subject. C.I.H. thanks the Spanish Ministry of Education and Science for a postdoctoral scholarship.

7. References

(1) Anastas, P. T.; Warner, J. C. *Green Chemistry Theory and Practice*; Oxford University Press: New York, 1998.

(2) (a) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev*. **2002**, *102*, 1731. (b) Dyker, G. *Angew. Chem., Int. Ed*. **1999**, *38*, 1698. (c) Naota, T.; Takaya, H.; Murahashi, S.-I. *Chem. Rev*. **1998**, *98*, 2599. (d) Chatani, N.; Asaumi, T.; Yorimitsu, S.; Ikeda, T.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc*. **2001**, *123*, 10935. (e) Gooâen, L. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 3775. (f) Arndtsen, B. A; Bergman, R. G.; Mobley, T. A.; Peterson, T. H. *Acc. Chem. Res*. **1995**, *28*, 154. (g) Chen, H.; Schlecht, S.; Semple, T. C.; Hartwig, J. F. *Science* **2000**, *287*, 1995. (h) Goldman, A. S. *Nature* **1993**, *366*, 514. (i) Crabtree, R. H. *J. Organomet. Chem.* **2004**, *689*, 4083. (j) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633. (k). Li, C.-J., Li, Z. *Pure Appl. Chem*. **2006**, *78*, 935.

(3) (a) Li, C.-J. *Chem. Rev.* **1993**, *93*, 2023. (b) Lindstrom, U. M. *Chem. Rev.* **2002**, *102*, 2751. (c) Li, C.-J. *Chem. Rev.* **2005**, *105*, 3095. (d) Li, C.-J.; Chan, T. H. *Organic Reactions in Aqueous Media*; Wiley: New York, 1997. (e) *Organic Synthesis in Water*; Grieco, P. A., Ed.; Thomson Science: Glasgow, 1998.

(4) (a) Gol'dshleger, N. F.; Es'kova, V. V.; Shilov, A. E.; Shteinman, A. A. *Zh. Fiz. Khim.* **1972**, *46*, 1353 (Engl. trans. **1972**, *12*, 895). (b) Es'kova, V. V.; Shilov, A. E.; Shteinman, A. A. *Kinet. Katal.* **1972**, *13*, 534.

(5) (a) Kushch, L. A.; Lavrushko, V. V.; Misharin, Y. S.; Moravskii, A. P.; Shilov, A. E. *Nouv. J. Chim.* **1983**, *7*, 729. (b) Shilov, A. E.; Shul'pin, G. B. *Chem. Rev.* **1997**, *97*, 2879. (c) Shilov, A. E.; Shul'pin, G. B. *Activation and Catalytic Reactions of Saturated Hydrocarbons in the Presence of Metal Complexes*; Kluwer Academic Publishers: Dordrecht, 2000.

(6) For example: (a) Horvath, I. T.; Cook, R. A.; Millar, J. M.; Kiss, G. *Organometallics* **1993**, *12*, 8. (b) Labinger, J. A.; Herring, A. M.; Lyon, D. K.; Luinstra, G. A.; Bercaw, J. E.; Horvath, I. T.; Eller, K. *Organometallics* **1993**, *12*, 895. (c) Luinstra, G. A.; Labinger, J. A.; Bercaw, J. E. *J. Am. Chem. Soc.* **1993**, *115*, 3004. (d) Luinstra, G. A.; Wang, L.; Stahl, S. S.; Labinger, J. A.; Bercaw, J. E. *Organometallics* **1994**, *13*, 755. (e) Luinstra, G. A.; Wang, L.; Stahl, S. S.; Labinger, J. A.; Bercaw, J. E. *J. Organomet. Chem.* **1995**, *504*, 75. (f) Hutson, A. C.; Lin, M.; Basickes, N.; Sen, A. *J. Organomet. Chem.* **1995**, *504*, 69. (g) Siegbahn, P. E. M.; Crabtree, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 4442. (h) Stahl, S. S.; Labinger, J. A.; Bercaw, J. E. *Angew. Chem., Int. Ed.* **1998**, *37*, 2180. (i) Mylvaganam, K.; Bacskay, G. B.; Hush, N. S. *J. Am. Chem. Soc.* **2000**, *122*, 2041. (j) Labinger, J. A.; Bercaw, J. E. *Nature* **2002**, *417*, 507. (k) Heyduk, A. F.; Driver, T. G.; Labinger, J. A.; Bercaw, J. E. *J. Am. Chem. Soc.* **2004**, *126*, 15034. (l) Driver, T. G.; Day, M. W.; Labinger, J. A.; Bercaw, J. E. *Organometallics* **2005**, *24*, 3644. (m) Owen, J. S.; Labinger, J. A.; Bercaw, J. E. *J. Am. Chem. Soc.* **2006**, *128*, 2005 and references therein.

(7) (a) Kao, L.-C.; Sen, A. *J. Chem. Soc., Chem. Commun.* **1991**, 1242. (b) Sen, A.; Benvenuto, M. A.; Lin, M.; Hutson, A. C.; Basickes, N. *J. Am. Chem. Soc.* **1994**, *116*, 998. (c) Basickes, N; Sen, A. *Polyhedron* **1995**, *14*, 197.

(8) (a) Sen, A.; Lin, M.; Kao, L.-C.; Hutson, A. C. *J. Am. Chem. Soc.* **1992**, *114*, 6385. (c) Sen, A.; Lin, M. *J. Chem. Soc., Chem. Commun.* **1992**, 508.

(9) Labinger, J. A.; Herring, A. M.; Bercaw, J. E. *J. Am. Chem. Soc.* **1990**, *112*, 5628.

(10) Freund, M. S.; Labinger, J. A.; Lewis, N. S.; Bercaw, J. E. *J. Mol. Catal.* **1994**, *87*, L11.

(11) Lin, M.; Shen, C.; Garcia-Zayas, E. A.; Sen, A. *J. Am. Chem. Soc.* **2001**, *123*, 1000.

(12) Dangel, B. D.; Jonson, J. A.; Sames, D. *J. Am. Chem. Soc.* **2001**, *123*, 8149.

(13) See, for example: (a) Periana, R. A.; Taube, D. J.; Gamble, S.; Taube, H.; Satoh, T.; Fujii, H. *Science* **1998**, *280*, 560. (b) Kua, J.; Xu, X.; Periana, R. A.; Goddard, W. A., III *Organometallics* **2002**, *21*, 511. (c) Periana, R. A.; Mironov, O.; Taube, D.; Bhalla, G.; Jones, C. *Science* **2003**, *301*, 814. (d) Xu, X.; Kua, J.; Periana, R. A.; Goddard, W. A., III *Organometallics* **2003**, *22*, 2057.

(14) Lin, M.; Hogan, T.; Sen, A. *J. Am. Chem. Soc.* **1997**, *119*, 6048.

(15) Shen, C.; Garcia-Zayas, E. A.; Sen, A. *J. Am. Chem. Soc.* **2000**, *122*, 4029.

(16) Bianchi, D.; Bortolo, R.; D'Aloisio, R.; Ricci, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 706.

(17) Le Bras, J.; Muzart, J. *Tetrahedron Lett.* **2002**, *43*, 431.

(18) Le Bras, J.; Muzart, J. *Tetrahedron: Asymmetry* **2003**, *14*, 1911.

(19) Lin, M.; Hogan, T. E.; Sen, A. *J. Am. Chem. Soc.* **1996**, *118*, 4574.

(20) Chepaikin, E. G.; Bezruchenko, A. P.; Leshcheva, A. A.; Boyko, G. N.; Kuzmenkov, I. V.; Grigoryan, E. H.; Shilov, A. E. *J. Mol. Catal. A* **2001**, *169*, 89.

(21) Tenaglia, A.; Terranova, E.; Waegell, B. *Tetrahedron Lett.* **1989**, *30*, 5271.

(22) Bakke, J. M.; Lundquist, M. *Acta Chem. Scand. Ser. B* **1986**, *40*, 340.

(23) (a) Tenaglia, A.; Terranova, E.; Waegell, B. *J. Chem. Soc., Chem. Commun.* **1990**, 1344. (b) Tenaglia, A.; Terranova, E.; Waegell, B. *J. Org. Chem.* **1992**, *57*, 5523. (c) Coudret, J.-L.; Waegell, B. *Inorg. Chim. Acta* **1994**, *222*, 115. (d) Bakke, J. M.; Frøhaug, A. E. *Acta Chem. Scand.* **2004**, *48*, 160. (e) Bakke, J. M.; Frøhaug, A. E. *J. Phys. Org. Chem.* **1996**, *9*, 507.

(24) Neumman, R.; Abu-Gnim, C. *J. Chem. Soc., Chem. Commun.* **1989**, 1324.

(25) (a) Bressan, M.; Morvillo, A.; Romanello, G. *J. Mol. Catal.* **1992**, *77*, 283. (b) Launay, F.; Roucoux, A.; Patin, H. *Tetrahedron Lett.* **1998**, *39*, 1353.

(26) Goldstein, A. S.; Drago, R. S. *J. Chem. Soc., Chem. Commun.* **1991**, 21.

(27) (a) Taqui Khan, M. M.; Shukla, R. S. *J. Mol. Catal.* **1988**, *45*, 25. (b) Taqui Khan, M. M.; Bajaj, H. C.; Shukla, R. S.; Mirza, S. A. *J. Mol. Catal.* **1988**, *45*, 51. (c) Taqui Khan, M. M.; Shukla, R. S. *J. Mol. Catal.* **1988**, *45*, 25. (d) Taqui Khan, M. M.; Shukla, R. S.; Prakash Rao, A. *Inorg. Chem.* **1989**, *28*, 452. (e) Taqui Khan, M. M.; Shukla, R. S. *J. Mol. Catal.* **1992**, *71*, 157. (f) Taqui Khan, M. M.; Shukla, R. S. *J. Mol. Catal.* **1992**, *77*, 221.

(28) Murria, R. W.; Iyanar, K.; Chen, J.; Wearing, J. T. *Tetrahedron Lett.* **1995**, *36*, 6415.

(29) (a) Yamazaki, S.; Espenson, J. H.; Huston, P. *Inorg. Chem.* **1993**, *32*, 4683. (b) Abu-Omar, M. M.; Hansen, P. J.; Espenson, J. H. *J. Am. Chem. Soc.* **1996**, *118*, 4966.

(30) Yamanaka, I.; Furukawa, T.; Otsuka, K. *Chem. Commun.* **2000**, 2209.

(31) See, for instance: (a) Ridder, L.; Mulholland, A. J.; Vervoort, J.; Rietjens, I. M. C. M. *J. Am. Chem. Soc.* **1998**, *120*, 7641. (b) Shapiro, S.; Caspi, E. *Tetrahedron* **1998**, *54*, 5005. (c) Aranda, G.; Bertranne-Delahaye, M.; Lallemand, J.-Y.; Azerad, R.; Maurs, M.; Cortes, M.; Lopez, J. *J. Mol. Catal. B* **1998**, *5*, 203.

(32) Bühler, B.; Schmid, A. In *Handbook of C-H Transformations;* Dyker, G., Ed.; Wiley-VCH: Weinheim, 2005; p 516.

(33) For instance, see: (a) Bossert, I. D.; Whited, G.; Gibson, D. T.; Young, L. Y. *J. Bacteriol.* **1989**, *276*, 21381. (b) Rabus, R.; Kube, M.; Beck, A.; Widdel, F.; Reinhardt, R. *Arch. Microbiol.* **2002**, *178*, 506.

(34) For instance, see: (a) van den Heuvel, R. H. H.; Laane, C.; van Berkel, W. J. H. *Adv. Synth. Catal.* **2001**, *343*, 515. (b) van den Heuvel, R. H. H.; Fraaije, M. W.; Mattevi, A.; Laane, C.; van Berkel, W. J. H. *J. Mol. Catal. B* **2001**, *11*, 185.

(35) For instance. see: (a) van Deurzen, M. P. J.; Seelbach, K.; Sheldon, R. A. *Tetrahedron* **1997**, *53*, 13183. (b) van Rantwijk, F.; Sheldon, R. A. *Curr. Opin. Biotechnol.* **2000**, *11*, 554.

(36) For recent reviews. see: (a) Holland, H. L. *Organic Synthesis with Oxidative Enzymes*; Wiley-VCH: New York, 1992. (b) Holland, H. L. In *Biotransformations 1*; Kelly, D. R., Ed.; Wiley-VCH: Weinheim, 1998; Vol.8a, p 475. (c) May, S. W. *Curr. Opin. Biotechnol.* **1999**, *10*, 370. (d) Patel, R. N. *Stereoselective Biocatalysis*; Marcel Dekker: New York, 2000. (e) Schmid, A.; Dordick, J. S.; Hauer, B.; Kiener, A.; Wubbolts, M.; Witholt, B. *Nature* **2001**, *409*, 258. (f) Flitsch, S. L.; Schmid, A.; Hollmann, F.; Bühler, B.; Grogan, G.; van Pée, K.-H. In *Enzyme Catalysis in Organic Synthesis*, 2nd ed.; Drauz, K., Waldmann, H., Eds.; Wiley-VCH: Weinheim, 2002; Vol. III, p 1065. (g) Mihovilovic, M. D.; Müller, B.; Stanetty, P. *Eur. J. Org. Chem.* **2002**, *1*, 3711. (h) van Beilen, J. B.; Duetz, W. A.; Schmid, A.; Witholt, B. *Trends Biotechnol.* **2003**, *21*, 170. (i) Faber, K. *Biotransformations in Organic Synthesis*, 5th ed.; Springer: Berlin, 2004. (j) Li, Z.; Chang, D. L. *Curr. Org. Chem.* **2004**, *8*, 1647. (k) Gillam, E. M. *Clin. Exp. Pharmacol, P* **2005**, *32*, 147.

(37) For some reviews, see: (a) Ortiz de Montellano, P. R. *Cytochrome P450 Structure, Mechanism, and Biochemistry*, 2nd ed.; Plenum Press: New York, 1995. (b) Holm, R. H.; Kennepohl, P.; Solomon, E. I. *Chem. Rev.* **1996**, *96*, 2239 (c) Solomon, E. I.; Sundaram, U. M.; Machonkin, T. E. *Chem. Rev.* **1996**, *96*, 2563. (d) Klinman, J.

P. *Chem. Rev.* **1996**, *96*, 2541. (e) Wallar, B. J.; Lipscomb, J. D. *Chem. Rev.* **1996**, *96*, 2625. (f) Schneider, S.; Wubbolts, M. G.; Oesterhelt, G.; Sanglard, D.; Witholt, B. *Biotechnol. Bioeng.* **1999**, *64*, 333. (g) Solomon, E. I.; Brunold, T. C.; Davis, M. I.; Kemsley, J. N.; Lee, S.-K.; Lehnert, N.; Neese, F.; Skulan, A. J.; Yang, Y.-S.; Zhou, J. *Chem. Rev.* **2000**, *100*, 235. (h) Urlacher, V.; Schmid, R. D. *Curr. Opin. Biotechnol.* **2002**, *13*, 557. (i) Bugg, T. D. H. *Tetrahedron* **2003**, *59*, 7075. (j) Baik, M. H.; Newcomb, M.; Friesner, R. A.; Lippard, S. J. *Chem. Rev.* **2003**, *103*, 2385. (k) Hausinger, R. P. *Crit. Rev. Biochem. Mol. Biol.* **2004**, *39*, 21. (l) Coon, M. J. *Annu. Rev. Pharmacol.* **2005**, *45*, 1.

(38) For some recent reviews, see: (a) Simándi, L. I. *Catalytic Activation of Dioxygen by Metal Complexes*; Kluwer: Dordrecht, 1992. (b) Reedijk, J. *Bioinorganic Catalysis*; Marcel Dekker: New York, 1993. (c) Montanari, F.; Casella, L. *Metalloporphyrins Catalyzed Oxidations*; Kluwer: Dordrecht, 1994. (d) Sheldon, R. *Metaloporphyrins in Catalytic Oxidations*; Marcel Dekker: New York, 1994. (e) Funabiki, T. *Oxygenases and Model Systems*; Kluwer: Dordrecht, 1997. (f) Shilov, A. E. *Metal Complexes in Biomimetic Chemical Reactions*; CRC Press: Boca Raton, 1997. (g) Meunier, B. *Biomimetic Oxidations Catalyzed by Transition Metal Complexes*; Imperial College Press: London, 2000. (h) Costas, M.; Chen, K.; Que, L. *Coord. Chem. Rev.* **2000**, *200−202*, 517. (i) Westerheide, L.; Pascaly, M.; Krebs, B. *Curr. Opin. Chem. Biol.* **2000**, *4*, 235. (j) Likhtenshtein, G. I. *New Trends in Enzyme Catalysis and Biomimetic Chemical Reactions*; Kluwer: Dordrecht, 2002. (k) Costas, M.; Mehn, M. P.; Jensen, M. P.; Que, L. *Chem. Rev.* **2004**, *104*, 939. (l) Kim, E.; Chufan, E. E.; Kamarai, K.; Karlin, K. D. *Chem. Rev.* **2004**, *104*, 1077. (m) Bassan, A.; Blomberg, M. R. A.; Siegbahn, P. E. M.; Que, L. *Chem. Eur. J.* **2005**, *11*, 692.

(39) De Poorter, B.; Ricci, M.; Bortolini, O.; Meunier, B. *J. Mol. Catal.* **1985**, *31*, 221.

(40) Collman, J. P.; Tanaka, H.; Hembre, R. T.; Brauman, J. I. *J. Am. Chem. Soc.* **1990**, *112*, 3689.

(41) De, Poorter, B.; Ricci, M.; Meunier, B. *Tetrahedron Lett.* **1985**, *26*, 4459.

(42) Balahura, R. J.; Sorokin, A.; Bernadou, J.; Meunier, B. *Inorg. Chem.* *36*, 3488.

(43) Mello, R.; Fiorentino, M.; Sciacovelli, O.; Curci, R. *J. Org. Chem.* **1988**, *53*, 3891.

(44) Groves, J. T.; Neumann, R. *J. Am. Chem. Soc.* **1989**, *111*, 2900.

(45) Banfi, S.; Maiocchi, A.; Moggi, A.; Montanari, F.; Quici, S. *J. Chem. Soc., Chem. Commun.* **1990**, 1794.

(46) Querci, C.; Ricci, M. *Tetrahedron Lett.* **1990**, *31*, 1779.

(47) Zheng, T.-C.; Richardson, D. E. *Tetrahedron Lett.* **1995**, *36*, 837.

(48) (a) Breslow, R.; Huang, Y.; Zhang, X.; Yang, J. *Proc. Natl. Acad. Sci. U.S.A.* **1997**, *94*, 11156. (b) Breslow, R.; Zhang, X.; Huang, Y. *J. Am. Chem. Soc.* **1997**, *119*, 4535. (c) Breslow, R.; Gabriele, B.; Yang, J. *Tetrahedron Lett.* **1998**, *39*, 2887. (d) Yang, J.; Breslow, R. *Angew. Chem., Int. Ed.* **2000**, *39*, 2692. (e) Yang, J.; Gabriele, B.; Belvedere, S.; Huang, Y.; Breslow, R. *J. Org. Chem.* **2002**, *67*, 5057. (f) Breslow, R.; Yang, J.; Yan, J. *Tetrahedron* **2002**, *58*, 653. (g) Breslow, R.; Yan, J.; Belvedere, S. *Tetrahedron Lett.* **2002**, *43*, 363. (h) Fang, Z.; Breslow, R. *Biorg. Med. Chem. Lett.* **2005**, *15*, 5463.

(49) Rabion, A.; Buchanan, R. M.; Seris, J.-L.; Fish, R. H. *J. Mol. Catal. A* **1997**, *116*, 43.

(50) (a) Neimann, K.; Neumann, R.; Rabion, A.; Buchanan, R. M.; Fish, R. H. *Inorg. Chem.* **1999**, *38*, 3575. (b) Fish, R. H.; Rabion, A.; Neimann, K.; Neumann, R.; Vincent, J.-M.; Contel, M.; Izuel, C.; Villuendas, P. R.; Alonso, P. J. *Top. Catal.* **2005**, *32*, 185.

(51) Hussain, A.; Shukla, R. S.; Thorat, R. B.; Padhiyar, H. J.; Bhatt, K. N. *J. Mol. Catal. A* **2003**, *193*, 1.

(52) For some examples, see: (a) Shilov, A. E.; Shul'pin, G. B. In *Activation and Catalytic Reactions of Saturated Hydrocarbons in the Presence of Metal Complexes*; Kluwer Academic Publishers: Dordrecht, 2000; p 21. (b) Fokin, A. A.; Schreiner, P. R. *Adv. Synth. Catal.* **2003**, *245*, 1035 and references therein. (c) Schreiner, P. R.; Fokin, A. A. *Chem. Record* **2004**, *3*, 247 and references therein.

(53) For example, see: Mleczko, L.; Buchholz, S.; Münnich, C. In *Handbook of C-H Transformations*; Dyker, G., Ed.; Wiley-VCH: Weinheim, 2005; p 11 and references therein.

(54) Harustiak, M.; Hronec, M.; Ilavsk, J. *React. Kinet. Catal. Lett.* **1988**, *37*, 215.

(55) Harustiak, M.; Hronec, M.; Ilavsk, J. *J. Mol. Catal.* **1988**, *48*, 335.

(56) For some reviews, see: (a) Adam, W. *Peroxide Chemistry: Mechanistic and Preparative Aspect of Oxygen Transfer*; Wiley-VCH: Weinheim, 2000. (b) Adam, W.; Saha-Moller, C. R.; Ganeshpure, P. A. *Chem. Rev.* **2001**, *101*, 3499. (c) Shi, Y. *Acc. Chem. Res.* **2004**, *37*, 488. (c) Curci, R.; D'Accolti, L.; Fusco, C. *Acc. Chem. Res.* **2006**, *39*, 1.

(57) Yang, D.; Wong, M.-K.; Wang, X.-C.; Tang, Y.-C. *J. Am. Chem. Soc.* **1998**, *120*, 6611.

(58) (a) Adam, W.; Saha-Möller, C. R.; Zhao, C.-G. *Tetrahedron: Asymmetry* **1998**, *9*, 4117. (b) Adam, W.; Saha-Möller, C. R.; Zhao, C.-G. *J. Org. Chem.* **1999**, *64*, 7492.

(59) Pramod, K.; Eaton, P. E.; Gilardi, R.; Flippen-Anderson, J. L. *J. Org. Chem.* **1990**, *55*, 6105.

(60) (a) Schreiner, P. R.; Lauenstein, O.; Kolomitsyn, I. V.; Nadi, S.; Fokin, A. A. *Angew. Chem., Int. Ed.* **1998**, *37*, 1895. (b) Schreiner, P. R.; Lauenstein, O.; Butova, E. D.; Fokin, A. A. *Angew. Chem., Int. Ed.* **1999**, *38*, 2786. (c) Lauenstein, O.; Fokin, A. A.; Schreiner, P. R. *Org. Lett.* **2000**, *2*, 2201. (d) Fokin, A. A.; Lauenstein, O.; Gunchenko, P. A.; Schreiner, P. R. *J. Am. Chem. Soc.* **2001**, *123*, 1842. (e) Schreiner, P. R.; Lauenstein, O.; Butova, E. D.; Gunchenko, P. A.; Kolomitsin, I. V.; Wittkopp, A.; Feder, G.; Fokin, A. A. *Chem. Eur. J.* **2001**, *7*, 4997. (f) Schreiner, P. R.; Fokin, A. A.; Lauenstein, O.; Okamoto, Y.; Wakita, T.; Rinderspacher, C.; Robinson, G. H.; Vohs, J. K.; Campana, C. F. *J. Am. Chem. Soc.* **2002**, *124*, 13348. (g) Fokin, A. A.; Schreiner, P. R.; Berger, R.; Robinson, G. H.; Wei, P.; Campana, C. F. *J. Am. Chem. Soc.* **2006**, *128*, 5332.

(61) A similar reaction of adamantane but in a classical free-radical halogenation with Br_2/H_2O yielded ~50:50 of 1-adamantane and 2-adamantane, see: Minisci. F.; Fontana, F.; Zhao, L.; Banfi, S.; Quici, S. *Tetrahedron Lett.* **1994**, *35*, 8033.

(62) Shaw, H.; Perlmutter, H. D.; Gu, C. *J. Org. Chem.* **1997**, *62*, 236.

(63) Kikuchi, D.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **1998**, *63*, 6023.

(64) Horvath, I. T.; Cook, R. A.; Millar, J. M.; Kiss, G. *Organometallics* **1993**, *12*, 8.

(65) Strauss, F. *Annalen* **1905**, *342*, 201.

(66) Baidossi, W.; Goren, N.; Blum, J. *J. Mol. Catal.* **1993**, *85*, 153.

(67) Trost, B. M.; Chan, C.; Ruhter, G. *J. Am. Chem. Soc.* **1987**, *109*, 3486.

(68) Masuda, Y.; Murata, M.; Sato, K.; Watanabe, S. *Chem. Commun.* **1998**, *7*, 807.

(69) Chen, X.; Xue, P.; Sung, H. H. Y.; Williams, I. D.; Peruzzini, M.; Bianchini, C.; Jia, G. *Organometallics* **2005**, *24*, 4330.

(70) Sonogashira, K. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley: Hoboken, NJ, 2002; p 493.

(71) Calsalnuovo, A. L.; Calabreze, J. C. *J. Am. Chem. Soc.* **1990**, *112*, 4324.

(72) Liang, B.; Dai, M.; Chen, J.; Yang, Z. *J. Org. Chem.* **2005**, *70*, 391.

(73) (a) Genet, J. P.; Blart, E.; Savignac, M. *Synlett* **1992**, 715. (b) Genin, E.; Amengual, R.; Michelet, V.; Savignac, M.; Jutand, A.; Neuville, L.; Genet, J.-P. *Adv. Synth. Catal.* **2004**, *346*, 1733.

(74) (a) Davydov, D. V.; Beletskaya, I. P. *Russ. Chem. Bull.* **1995**, *44*, 965. (b) Bumagin, N. A.; Bykov, V. V.; Beletskaya, I. P. *Russ. J. Org. Chem.* **1995**, *31*, 348.

(75) (a) Bhattacharya, S.; Sengupta, S. *Tetrahedron Lett.* **2004**, *45*, 8733. (b) Wolf, C.; Lerebours, R. *Org. Biomol. Chem.* **2004**, *2*, 2161. (c) Bhattacharya, S.; Sengupta, S. *Tetrahedron Lett.* **2004**, *45*, 8733.

(76) Davydov, D. V.; Beletskaya, I. P. *Russ. Chem. Bull.* **1995**, *44*, 965.

(77) DeVasher, R. B.; Moore, L. R.; Shaughnessy, K. H. *J. Org. Chem.* **2004**, *69*, 7919.

(78) Anderson, K. W.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 6173.

(79) Vlassa, M.; Tarta, I. C.; Margineanu, F.; Oprean, I. *Tetrahedron* **1996**, *52*, 1337.

(80) (a) Pal, M.; Subramanian, V.; Yeleswarapu, K. R. *Tetrahedron Lett.* **2003**, *44*, 8221. (b) Uozumi, Y.; Kobayashi, Y. *Heterocycles* **2003**, *59*, 71.

(81) Li, C.-J.; Chen, D. L.; Costello, C. W. *Org. Res. Process Dev.* **1997**, *1*, 325.

(82) (a) Li, C.-J.; Slaven, W. T.; John, V. T.; Banerjee, S. *J. Chem. Soc., Chem. Commun.* **1997**, 1569. (b) Li, C.-J.; Slaven, W. T., IV; Chen, Y. P.; John, V. T.; Rachakonda, S. H. *Chem. Commun.* **1998**, 1351.

(83) (a) Pirguliyev, N. Sh.; Brel, V. K.; Zefirov, N. S.; Stang, P. J. *Tetrahedron* **1999**, *55*, 12377. (b) Sheremetev, A. B.; Mantseva, E. V. *Tetrahedron Lett.* **2001**, *42*, 5759.

(84) Beletskaya, I. P.; Latyshev, G. V.; Tsvetkov, A. V.; Lukashev, N. V. *Tetrahedron Lett.* **2003**, *44*, 5011.

(85) Appukkuttan, P.; Dehaen, W.; Van der Eycken, E. *Eur. J. Org. Chem.* **2003**, 4713.

(86) Arvela, R. K.; Leadbeater, N. E.; Sangi, M. S.; Williams, V. A.; Granados, P.; Singer, R. D. *J. Org. Chem.* **2005**, *70*, 161.

(87) Chen, L.; Li, C.-J. *Org. Lett.* **2004**, *6*, 3151.

(88) Li, C.-J.; Wei, C. *Chem. Commun.* **2002**, 268.

(89) Zhang, J. H.; Wei, C.; Li, C.-J. *Tetrahedron Lett.* **2002**, *43*, 5731.

(90) (a) Wei, C.; Li, C.-J. *J. Am. Chem. Soc.* **2003**, *125*, 9584. (b) Huang, B.; Yao, X.; Li, C.-J. *Adv. Synth. Catal.* **2006**, *348*, 1528.

(91) Wei, C.; Li, Z. G.; Li, C.-J. *Org. Lett.* **2003**, *5*, 4473.

(92) (a) Wei, C.; Li, C.-J. *J. Am. Chem. Soc.* **2002**, *124*, 5638. (b) Wei, C.; Mague, J. T.; Li, C.-J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5749.

(93) Shi, L.; Tu, Y.-Q.; Wang, M.; Zhang, F.-M.; Fan, C.-A. *Org. Lett.* **2004**, *6*, 1001.

(94) Lo, V. K.-Y.; Liu, Y.; Wong, M.-K.; Che, C.-M. *Org. Lett*. **2006**, *8*, 1529.

(95) Wei, C. M.; Li, C.-J. *Green Chem.* **2002**, *4*, 39.

(96) Boyall, D.; Frantz, D. Z.; Carreira, E. M. *Org. Lett.* **2002**, *4*, 2605.

(97) Fässler, R.; Tomooka, C. S.; Frantz, D. E.; Carreira, E. M. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5843.

(98) See ref 97. Takita, R.; Fukuta, Y.; Tsuji, R.; Ohshima, T.; Shibasaki, M. *Org. Lett.* **2005**, *7*, 1363.

(99) Yao, X.; Li, C.-J. *Org. Lett.* **2005**, *7*, 4395.

(100) Yao, X.; Li, C.-J. *Org. Lett.* **2006**, *8*, 1953.

(101) Knoepfel, T. F.; Carreira, E. M. *J. Am. Chem. Soc*. **2003**, *125*, 6054.

(102) Chen, L.; Li, C.-J. *Tetrahedron Lett.* **2004**, *45*, 2771.

(103) Chen, L.; Li, C.-J. *Chem. Commun*. **2004**, 2362.

(104) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res*. **2001**, *34*, 633.

(105) Sawyer, D. T.; Hage, J. P.; Sobkowiak, A. *J. Am. Chem. Soc.* **1995**, *117*, 106

(106) (a) Okamoto, M.; Watanabe, M.; Yamaji, T. *J. Organomet. Chem*. **2002**, *664*, 59. (b) Burton, H. A.; Kozhevnikov, I. V. *J. Mol. Catal. A: Chem*. **2002**, *185*, 285. (c) Jintoku, T.; Taniguchi, H.; Fujiwara, Y. *Chem. Lett*. **1987**, 1865

(107) Taj, S.; Ahmed, M. F.; Sankarapapavinasam, S. *J. Chem. Res. Synop.* **1993**, 232.

(108) Mukhopadhyay, S.; Rothenberg, G.; Lando, G.; Agbaria, K.; Kazanci, M.; Sasson, Y. *Adv. Synth. Catal.* **2001**, *343*, 455.

(109) Dyker, G. *Angew. Chem., Int. Ed*. **1999**, *38*, 1698.

(110) Takeuchi, R.; Yasue, H. *J. Org. Chem.* **1993**, *58*, 5386.

(111) (a) Kang, H.-C.; Maddin, C. H.; Cole, T.; Slegeir, W.; Cann, K.; Pettit, R. *J. Am. Chem. Soc.* **1977**, *99*, 8323. (b) Laine, R. M. *J. Am. Chem. Soc.* **1978**, *100*, 6451.

(112) Boele, M. D. K.; Van Strijdonok, G. P. F.; De Vries, A. H. M.; Kamer, P. C. J.; De Vries, J. G.; Van Leeuwen, P. W. N. M. *J. Am Chem. Soc*. **2002**, *124*, 1586.

(113) Lee, G. T.; Jiang, X.; Prasad, K.; Repic, O.; Blacklock, T. G. *Adv. Synth. Catal.* **2005**, *347*, 1921.

(114) Yamada, T.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **2005**, *70*, 5471.

(115) Shintani, R.; Okamoto, K.; Hayashi, T. *J. Am. Chem. Soc*. **2005**, *127*, 2872.

(116) Shintani, R.; Yashio, K.; Nakamura, T.; Okamoto, K.; Shimada, T.; Hayashi, T. *J. Am. Chem. Soc*. **2006**, *128*, 2772.

(117) (a) Lin, M.; Sen, A. *Nature* **1994**, *368*, 613. (b) Nizova, G. V.; Shul'pin, G. B.; Nizova, G. V.; Suss-Fink, G.; Stanislas, S. *Chem. Commun*. **1998**, 1885. (c) Asadullah, M.; Taniguchi, Y.; Kitamura, T.; Fujiwara, Y. *Appl. Organomet. Chem*. **1998**, *12*, 277.

(118) Recent review: Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev*. **2003**, *103*, 2861.

(119) Keilbaugh, S. A.; Thornton, E. R. *Biochemistry* **1983**, *22*, 5063.

(120) Li, C.-J.; Wang, D.; Chen, D. L. *J. Am. Chem. Soc.* **1995**, *117*, 12867.

(121) Wang, M. W.; Li, C.-J. *Tetrahedron Lett.* **2002**, *43*, 3589.

(122) Wang, M.; Yang, X.; Li, C.-J. *Eur. J. Org. Chem*. **2003**, 998.

(123) Yang, X.; Wang, M.; Li, C.-J. *Org. Lett.* **2003**, *5*, 657.

(124) For example: Luo, Y.; Li, Z.; Li, C.-J. *Org. Lett*. **2005**, *7*, 2675.

(125) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2006**, *128*, 56 and references therein.

(126) For representative references, see: (A) sp^3 C−H and sp C−H: (a) Murahashi, S.-I.; Komiya, N.; Terai, H.; Nakae, T. *J. Am. Chem. Soc.* **2003**, *125*, 15312. (b) Murata, S.; Teramoto, K.; Miura, M.; Nomura, M. *J. Chem. Res. Miniprint* **1993**, 2827. (B) sp^2 C−H and sp^2 C−H: (a) Hatamoto, Y.; Sakaguchi, S.; Ishii, Y. *Org. Lett.* **2004**, *6*, 4623. (b) Yokota, T.; Tani, M.; Sakaguchi, S.; Ishii, Y. *J. Am. Chem. Soc.* **2003**, *125*, 1476. (c) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633. (d) Tsuji, J.; Nagashima, H. *Tetrahedron* **1984**, *40*, 2699. (C) sp^2 C−H and sp^3 C−H: DeBoef, B.; Pastine, S. J.; Sames, D. *J. Am. Chem. Soc.* **2004**, *126*, 6556. (D) sp C−H and sp C−H: Nicolaou, K. C.; Zipkin, R. E.; Petasis, N. A. *J. Am. Chem. Soc.* **1982**, *104*, 5558.

(127) Thomson, R. H. *Naturally Occuring Quinones IV*; Blackie Academic & Professional, London, 1997.

(128) Zhang, H.-B.; Liu, L.; Chen, Y.-J.; Wang, D.; Li, C.-J. *Adv. Synth. Catal.* **2006**, *348*, 229.

(129) Zhang, H.-B.; Liu, L.; Chen, Y.-J.; Wang, D.; Li, C.-J. *Eur. J. Org. Chem.* **2006**, 869.

(130) (a) Narayan, S.; Muldoon, J.; Finn, M. G.; Fokin, V. V.; Kolb, H. C.; Sharpless, K. B. *Angew. Chem., Int. Ed*. **2005**, *44*, 3275. (b) Rideout, D. C.; Breslow, R. *J. Am. Chem. Soc*. **1980**, *102*, 7816.

(131) (a) Sharma, V. B.; Jain, S. L.; Sain, B. *Tetrahedron Lett.* **2003**, *44*, 2655. (b) Yadav, J. S.; Reddy, B. V. S.; Gayathri, K. U.; Prasad, A. R. *New J. Chem.* **2003**, *27*, 1684. (c) Iwai, K.; Yamauchi, T.; Hashimoto, K.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *Chem. Lett.* **2003**, *32*, 58.

(132) (a) Doussot, J.; Guy, A.; Ferroud, C. *Tetrahedron Lett.* **2000**, *41*, 2545 and references therein. (b) Toda, F.; Tanaka, K.; Iwata, S. *J. Org. Chem.* **1989**, *54*, 3007.

(133) Matsushita, M.; Kamata, K.; Yamaguchi, K.; Mizuno, N. *J. Am. Chem. Soc.* **2005**, *127*, 6632.

(134) Wallis, P. J.; Booth, K. J.; Patti, A. F.; Scott, J. L. *Green Chem.* **2006**, *8*, 333.

(135) Jiang, Y.; Xi, C.; Yang, X. *Synlett* **2005**, 1381.

(136) Xi, C.; Jiang, Y.; Yang, X. *Tetrahedron Lett.* **2005**, *46*, 3909.

(137) (a) Glaser, C. *Ann. Chem. Pharm.* **1870**, *154*, 137. (b) Glaser, C. *Ber. Dtsch. Chem. Ges.* **1869**, *2*, 422.

(138) Siemsen, P.; Livingston, R. C.; Diederich, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 2632 and references therein.

(139) Sondheimer, F.; Amiel, Y; Wolovsky, R. *J. Am. Chem. Soc.* **1957**, *79*, 6263.

CR050980B