1

The Applications of Water as Reagents in Organic Synthesis

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1.1 Introduction

Water due to its low cost, easy availability, nontoxic and nonflammable properties has been considered one of the most ideal and promising solvents in organic synthesis from the green and sustainable point of view. Furthermore, with regard to enormous enzyme-catalyzed biosynthesis in nature, water serves as a favorable medium for the versatile synthesis of a variety of complicated molecules and compounds. Over the past decades, considerable efforts had been devoted into the organic reactions by using water as solvent from economy and environment perspectives [1]. Even more, the proposed concept of "in-water" and "on-water" further stimulated the booming development of the utilization of water as solvent for organic synthesis [1e, 2]. Therefore, in recent years, more and more general organic reactions were successfully exploited to perform in water instead of organic solvents to achieve sustainable and environmental benefits.

From a different perspective, the water itself could also be applied as a useful reagent to participate in the reaction through incorporating a hydrogen or oxygen atom or hydroxyl group into the target product. Generally, water is indispensable for various hydrolysis reactions. As a hydrogen source, water is used to quench numerous susceptible reaction systems by providing active hydrogen. Meanwhile, as a versatile nucleophile, the hydroxyl group could be readily introduced into the specific reaction sites by the employment of water as hydroxyl precursor. The hydroxyl group could also be readily oxidized to carbonyl group during the reaction. It is worth mentioning that, in some cases, the presence of water could obviously improve the efficiency of the reaction, albeit the exact reason is elusive for some special reactions.

This chapter is divided into the following four parts for further discussion: (i) incorporation of hydrogen atom from water; (ii) incorporation of oxygen atom from water; (iii) incorporation of hydroxyl group from water; and (iv) traceless promotion of the reactions by water.

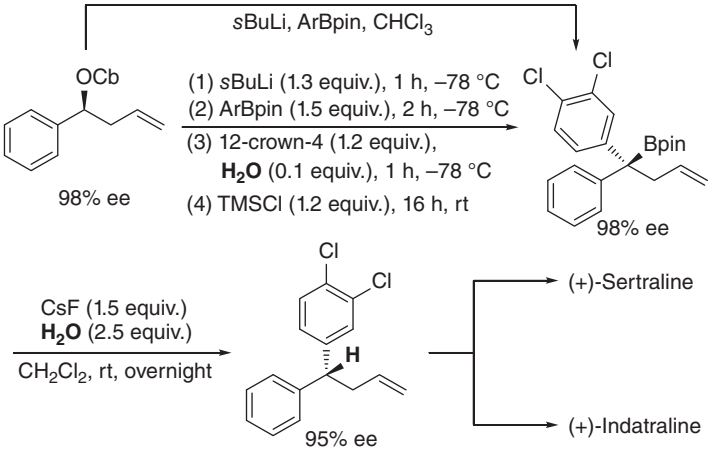
Solvents as Reagents in Organic Synthesis: Reactions and Applications,
First Edition. Edited by Xiao-Feng Wu.

1.2 Incorporation of Hydrogen Atom from the Water

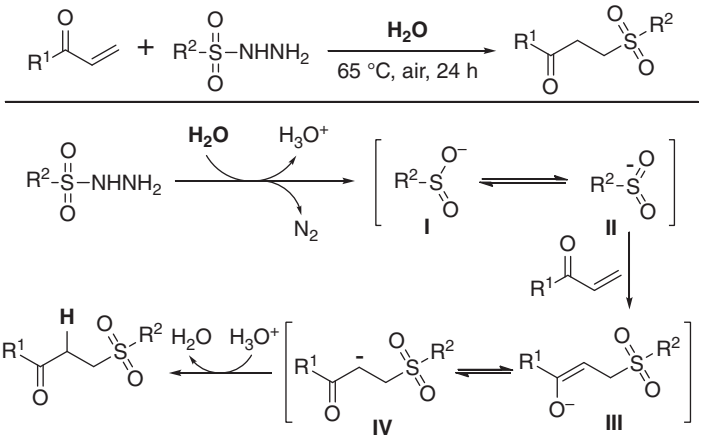
Aggarwal and coworkers demonstrated a versatile strategy through lithiation/borylation/protodeboronation of a homoallyl carbamate for the highly enantioselective synthesis of (+)-sertraline and (+)-indatraline, which served as potent inhibitors (Scheme 1.1) [3]. It was observed that the presence of the alkene could hamper the lithiation/borylation process, so the modifications of the reaction conditions were necessary by the use of 12-crown-4, TMSCl, H_2O or a solvent switch to achieve 1,2-metalate rearrangement in order to ensure high yields and enantioselectivity. As for the protodeboronation step of tertiary boronic ester, the amount of water played a crucial role in the reaction. In 2010, the same group had disclosed a simple approach for the protodeboronation of tertiary boronic esters employing CsF-H_2O or TBAF·3H_2O with complete stereoselectivity to access to diverse enantioenriched tertiary alkanes [4].

A catalyst-free sulfonylation of activated alkenes with sulfonyl hydrazides in water for highly efficient construction of monosubstituted ethyl sulfones was demonstrated by Wang and coworkers (Scheme 1.2) [5]. Remarkably, the reaction proceeded through without any catalyst, additive, ligand, or organic solvent, with the release of N_2 as single by-product. The results of control experiments indicated that an anion pathway was involved in the reaction and the α-hydrogen atom of β-sulfone esters originated from water.

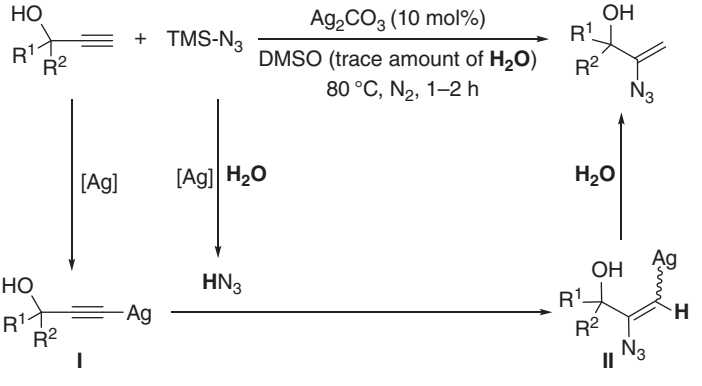
The sulfinyl anion **I** was first formed assisted by water with the release of one molecule of N_2, which could transform into sulfur-centered anion **II** through resonance process in the presence of water. The sulfur-centered anion readily added to the activated alkene to give the oxygen-centered anion **III**, followed by another resonance interaction leading to the carbon-centered anion **IV**. Finally, the proton transfer of intermediate **IV** from hydronium ions to deliver the desired β-sulfone ester product.



Scheme 1.1 Enantioselective synthesis of (+)-sertraline and (+)-indatraline.



Scheme 1.2 Catalyst-free sulfonylation of activated alkenes in water.



Scheme 1.3 Silver(I)-catalyzed hydroazidation of ethynyl carbinols.

A silver(I)-catalyzed chemo- and regioselective hydroazidation of ethynyl carbinols for the construction of 2-azidoallyl alcohols was developed by Bi and coworkers (Scheme 1.3) [6]. In this transformation, trimethylsilyl azide (TMS-N_3) was chosen as the optimal azide source and the pendent hydroxyl group directed the chemo- and regioselectivity of hydroazidation by stabilizing the vinyl azide products. Catalyzed by 10 mol% Ag_2CO_3, a wide range of secondary and tertiary ethynyl carbinols bearing different substituents could be transformed into the corresponding products in good to excellent yields.

The observation data of control experiments implied that the residual water in the DMSO played the critical role in the reaction. The initial step of the plausible pathway involved the generation of silver acetylide intermediate **I**. Meanwhile, the hydrazoic acid (HN_3) was *in situ* formed by silver-catalyzed hydrolysis of TMS-N_3, which added to the intermediate **I** to lead to vinyl silver intermediate **II**. Under the promotion of a trace amount of H_2O in the DMSO solvent, the protonation of intermediate **II** released the final product. As a class of functionalized

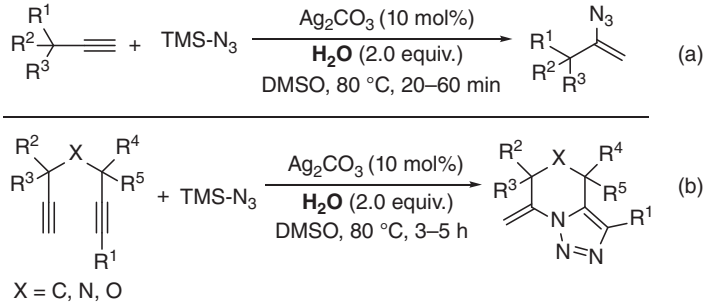
synthetic intermediates, 2-azidoallyl alcohols could be readily transformed into NH aziridines under the mild reaction conditions.

1.2.1 1,2,3-Triazoles

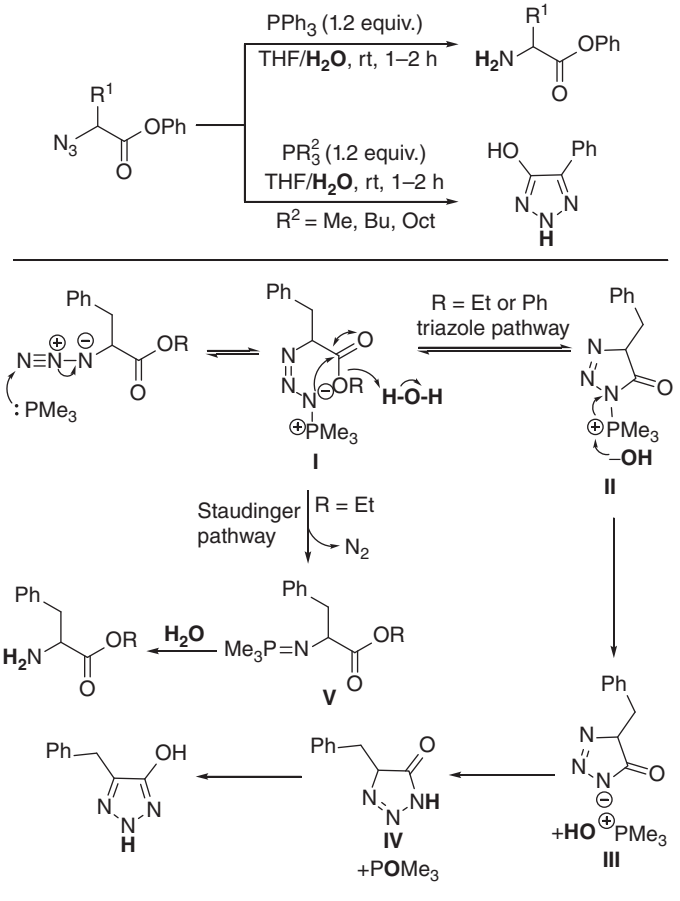
Inspired by the previous work of silver(I)-catalyzed hydroazidation of ethynyl carbinols, Bi and coworkers extended their study to the general hydroazidation of unactivated alkynes (Scheme 1.4a) [7]. The key point of the progress lay in the necessity of a trace amount of water in DMSO with regard to hydroazidation of ethynyl carbinols. Therefore, it was speculated that a stoichiometric amount of H_2O could enhance the reactivity of the reaction and the relevant experiments confirmed the hypothesis. The condition screening of the amount of H_2O demonstrated 2.0 equiv. of H_2O was appropriate for high efficiency. Furthermore, it was essential to control the reaction time to circumvent the further conversion of vinyl azides to nitriles. The protocol featured readily accessible starting materials, mild reaction conditions, broad substrate scope, and good scalability.

The significance of the aforementioned synthetic method was embodied in the application for the assembly of several valuable heterocyclic frameworks. In 2015, the strategy of hydroazidation of unactivated alkynes was combined with alkyne-azide 1,3-dipolar cycloaddition reaction to access to a variety of piperidine-fused 1,2,3-triazoles by Bi and coworkers (Scheme 1.4b) [8]. Under silver-catalyzed conditions, the treatment of diyne with TMS-N_3 in the presence of H_2O gave rise to pharmaceutically relevant 1,5-fused 1,2,3-triazoles in excellent yields. The reaction was assumed to undergo the tandem hydroazidation/alkyne-azide 1,3-dipolar cycloaddition sequence, which presented a concise method for the synthesis of structurally complicated fused heterocyclic compounds in one pot.

Taylor and coworkers developed a variant of Staudinger reaction on α-azido esters with trialkyl phosphines for the formation of 2*H*-1,2,3-triazol-4-ols (Scheme 1.5) [9]. In this reaction, phosphazides were generated from the reaction of trialkyl phosphines with α-azido esters in THF/H_2O, which underwent intramolecular cyclization to afford the desired products. Upon using PPh_3, the major product was the reduced amine from the classic Staudinger pathway [10]. As shown in Scheme 1.5, phosphazide **I** could cyclize to deliver intermediate



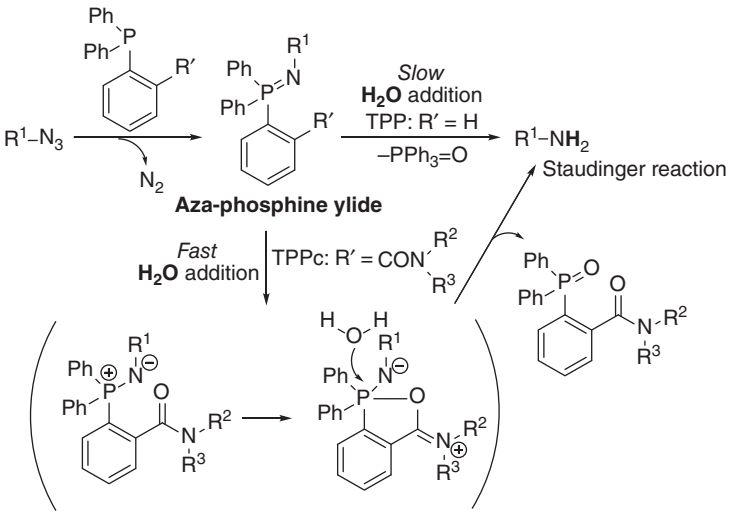
Scheme 1.4 Silver-catalyzed hydroazidation of alkynes and the application to access to 1,5-fused 1,2,3-triazoles.



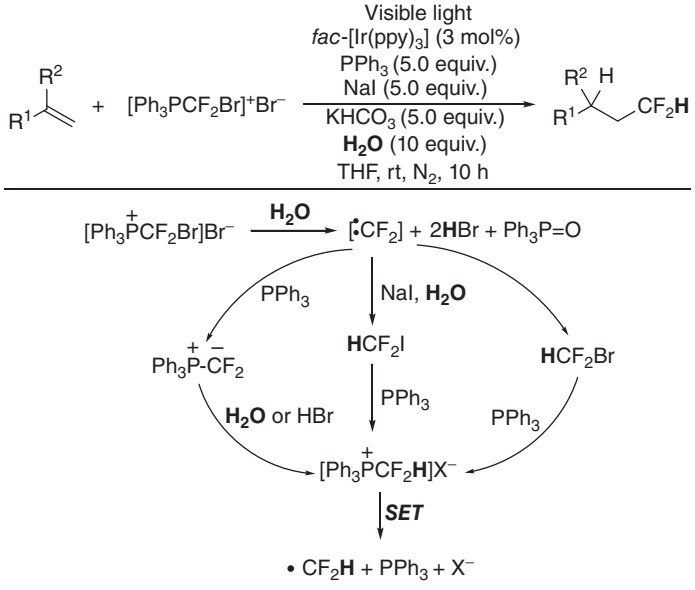
Scheme 1.5 Formation of 2*H*-1,2,3-triazol-4-ols from α-azido esters.

II, which occurred hydrolysis to give intermediate **III**. The final product was formed by the protonation of intermediate **III** and the following isomerization. Notably, phosphazide **I** could lose nitrogen and release iminophosphorane **V**, followed by the hydrolysis of intermediate **V** to produce α-amino ester.

In 2014, an efficient modification toward Staudinger reaction for the facile reduction of azides had been realized by Ito, Abe, and coworkers (Scheme 1.6) [11]. As for traditional Staudinger reaction, the formed iminophosphorane intermediate could undergo additional hydrolysis process for long reaction times to convert into the primary amines. In the current transformation, the triphenylphosphinecarboxamide (TPPc) derivatives were designed depending on the fact that the specific substituent was introduced at the *ortho* position of the phenyl ring of triphenylphosphine (TPP), which could promote the hydrolysis process through neighboring group participation effect. Under the improved conditions, the reaction could be completed in 10 min to 2 h to produce the primary amines in high yields without the need for additional hydrolysis process.



Scheme 1.6 Triphenylphosphinecarboxamide: An effective reagent for the reduction of azides.



Scheme 1.7 Visible-light-induced hydrodifluoromethylation of alkenes.

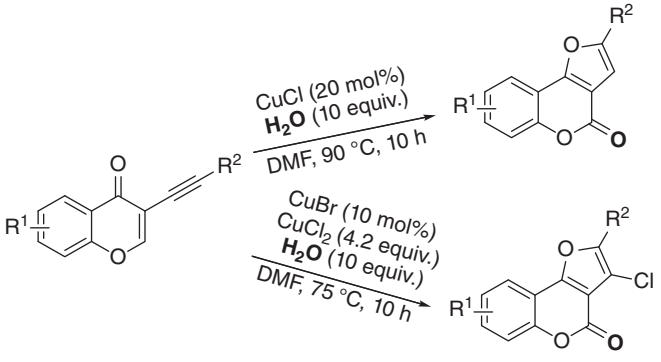
A visible-light-induced hydrodifluoromethylation of alkenes by the use of bromodifluoromethylphosphonium bromide as the precursor of difluorocarbene for the direct synthesis of the difluoromethylated alkanes was achieved by Qing and coworkers (Scheme 1.7) [12]. For the first time, the CF_2H radical was generated from fluorinated phosphonium salts, which could be readily synthesized from the reaction of PPh_3 and CF_2Br_2 in quantitative yield. The results of mechanistic

investigations implied that the formation process of CF_2H radical (Scheme 1.7). The reaction of bromodifluoromethylphosphonium bromide with H_2O generated difluorocarbene, from which the HCF_2I or HCF_2Br was formed and reacted with PPh_3 to give difluoromethylphosphonium salts. Another pathway involved the capture of difluorocarbene by PPh_3 and subsequent treatment of H_2O or HBr to deliver difluoromethylphosphonium salts, which could undergo a single-electron transfer (SET) process mediated by *fac*-$[Ir^{III}(ppy)_3]^*$ to lead to the CF_2H radical.

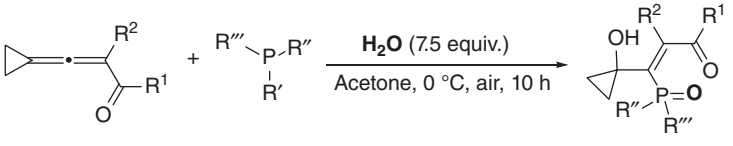
1.3 Incorporation of Oxygen Atom from the Water

Two facile one-pot copper-catalyzed reactions for the generation of furo[3,2-*c*] coumarins and chlorofuro[3,2-*c*]coumarins using 2-(1-alkynyl)-2-alken-1-one derivatives as starting materials was disclosed by Hu and Cheng (Scheme 1.8) [13]. One reaction involved CuCl-catalyzed cascade addition/cyclization/oxidation sequence of 2-(1-alkynyl)-2-alken-1-one in the presence of water. Another protocol utilized CuBr as catalyst and excess $CuCl_2$ as chlorinated reagent. The proposed mechanism indicated that in the two processes, Lewis acid Cu(I) salt activated the carbonyl group to facilitate the Michael addition of H_2O to the C=C bond, which was the key step of the reaction.

An unexpected example about the hydroxyphosphinylation reaction of 3-cyclopropylideneprop-2-en-1-ones for the introduction of hydroxyl group and phosphorus group via C—P bond cleavage was developed by Wu and coworkers (Scheme 1.9) [14]. The transformation utilized a highly activated analogue of



Scheme 1.8 Two cascade reactions to synthesize substituted furocoumarins.



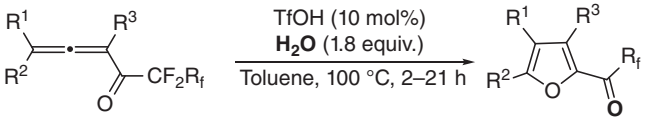
Scheme 1.9 Hydroxyphosphinylation reaction of 3-cyclopropylideneprop-2-en-1-ones.

allene and tertiary phosphine as starting material to construct highly functionalized 1-dialkylphinyl-3-oxo-(1*Z*)-alkenyl cyclopropanols in a regio- and stereoselective manner under the metal-free conditions. Mechanistic study indicated that the high strain in the C=C bond of allene substrate played a significant role in the hydroxyphosphinylation reaction. Intriguingly, based on the proposed mechanism, the oxygen atom of hydroxyl group in the product originated from O_2 and the oxygen atom of P=O bond came from additional H_2O.

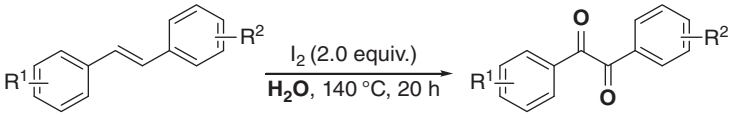
A metal-free TfOH-catalyzed domino cycloisomerization/hydrolytic defluorination reaction of *n*-perfluoroalkyl allenones for the assembly of furanyl perfluoroalkyl ketones was developed by Ma and coworkers (Scheme 1.10) [15]. The additional water was necessary for the reaction since the oxygen atom of the carbonyl group in the product came from H_2O based on ^{18}O-labelling experiments. The reaction proceeded through nucleophilic attack from the carbonyl oxygen, 1,2-phenyl shift, aromatization, nucleophilic attack of water, and elimination of HF sequence. The whole domino reaction process was solely catalyzed by H^+ from TfOH to deliver a wide range of furan-2-yl perfluoroalkyl ketones in good yields.

In 2013, Sun and coworkers described an I_2–H_2O mediated highly chemoselective synthesis of benzyl derivatives through oxidation of stilbenes without the use of any acid and metal (Scheme 1.11) [16]. A wide variety of substituted stilbenes were viable substrates for the protocol and the corresponding benzyl products could be constructed in high yields. Isotopic labeling experiments verified that the oxygen atom of the benzils derived from water and molecular oxygen participated in the reaction. The reaction pathway presumably involved the generation of an iodonium ion, the attack of water to the iodonium ion and sequential oxidation with iodine in water under air.

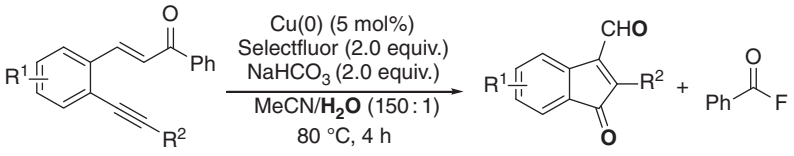
A Cu(0)/Selectfluor mediated oxidative cyclization of 1,5-enynes in the presence of water with C—C bond cleavage for the synthesis of 3-formyl-1-indenone derivatives was described by Liu and coworkers (Scheme 1.12) [17]. The reaction involved water-participated oxygen-insertion β-carbon elimination and the cleavage of C—C bond sequence. The ^{18}O-labeling experiment unambiguously suggested that both of the carbonyl oxygen atoms in the product came from water. On the basis of preliminary mechanistic studies, the *o*-alkynyl epoxide served



Scheme 1.10 TfOH-catalyzed domino cycloisomerization/hydrolytic defluorination of 2,3-allenyl perfluoroalkyl ketones.



Scheme 1.11 Synthesis of benzyl derivatives via oxidation of stilbenes in an I_2–H_2O system.

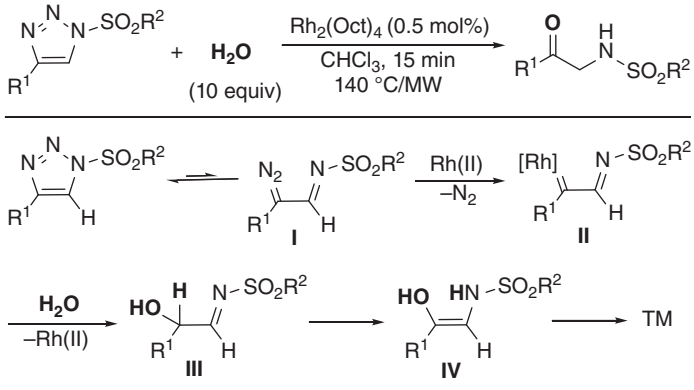


Scheme 1.12 Copper-catalyzed oxidative cyclization of 1,5-enynes to access to 3-formyl-1-indenones.

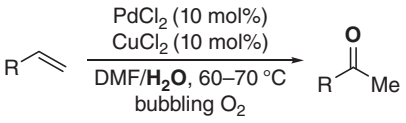
as an intermediate for the reaction and oxycupration of the triple bond and the following ring opening of the epoxide moiety constituted the key steps of the reaction. The C—C bond was cleaved assisted by Selectfluor to deliver benzoyl fluoride.

A Rh(II)-catalyzed denitrogenative hydration reaction of *N*-sulfonyl-1,2,3-triazoles with water for the synthesis of a series of biologically active α-amino ketones was demonstrated by Murakami and coworkers (Scheme 1.13) [18]. *N*-Sulfonyl-1,2,3-triazoles could be readily available from copper-catalyzed 1,3-dipolar cycloaddition reaction (CuAAC) of *N*-sulfonyl azides and terminal alkynes. In the transformation, the key intermediate α-imino rhodium-(II) carbenoid **II** was *in situ* generated assisted by rhodium catalyst, which underwent insertion into the O—H bond of water to produce α-imino alcohol **III**. Finally, the imine–enamine tautomerization and the following keto–enol tautomerization sequence led to the desired α-amino ketone products. The protocol achieved regioselective 1,2-aminohydroxylation of terminal alkynes, which served as a complement to the example reported by Chang and Fokin employing a copper(I) catalyst to realize 1,1-aminohydroxylation of terminal alkynes [19].

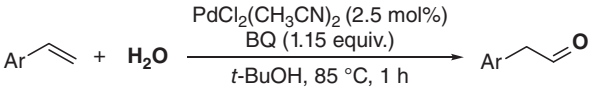
The Wacker oxidation reaction was a typical and powerful tool for the oxidation of olefins to synthesize ketones in the presence of palladium(II) catalyst, water, and co-oxidant [20]. Usually, the reaction occurred in Markovnikov selectivity from the majority of terminal olefins. In 1959, researchers at Wacker Chemie utilized catalytic $PdCl_2$ and a stoichiometric amount of $CuCl_2$ with bubbling O_2 to realize the hydration of olefins (Scheme 1.14). Afterward, the Wacker process



Scheme 1.13 Rh(II)-catalyzed denitrogenative hydration reaction of *N*-sulfonyl-1,2,3-triazoles.



Scheme 1.14 The Wacker oxidation reaction for the synthesis of methyl ketones.



Scheme 1.15 Efficient and highly aldehyde selective Wacker oxidation.

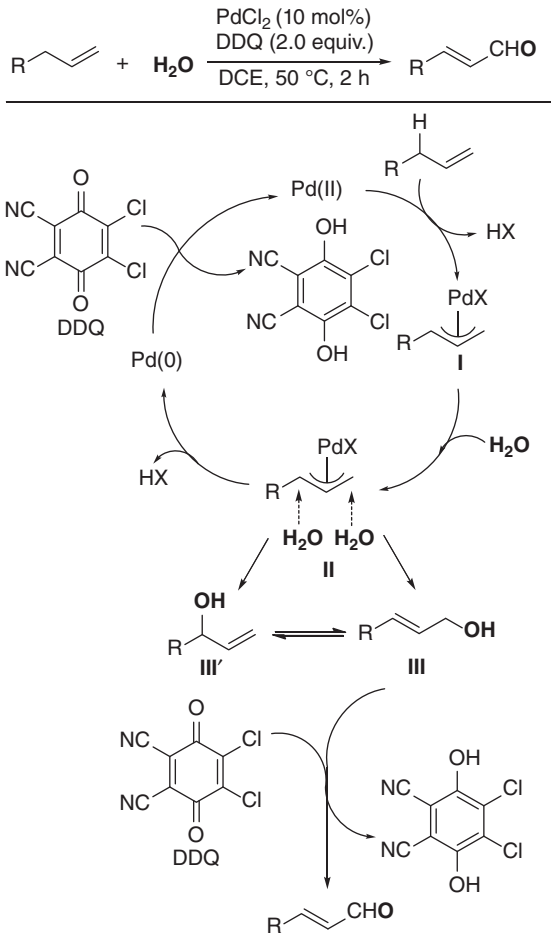
was extensively investigated by synthetic chemists to overcome several key limitations. In recent years, the aldehyde-selective Wacker oxidation had been well developed in the field of anti-Markovnikov functionalization of unbiased alkenes, which could produce a range of synthetically versatile aldehydes.

A Pd(II)-catalyzed aldehyde-selective Wacker oxidation of aryl-substituted olefins in the presence of 1,4-benzoquinone was described by Grubbs and coworkers (Scheme 1.15) [21], which was greatly different from the classical Wacker oxidation of providing methyl ketones. As demonstrated by the previous works, *t*-BuOH was used in Wacker oxidation to improve the aldehyde selectivity and BQ was widely applied as a hydrogen acceptor and two-electron oxidant in Pd(II)-catalyzed reactions. Noteworthy was that high yield of aldehyde products was obtained with respect to more electron-deficient aromatic substrates. The reaction mechanism was similar to the previous work of the same author, in which the Pd-catalyzed oxidation and acid-catalyzed hydrolysis process were involved in the reaction.

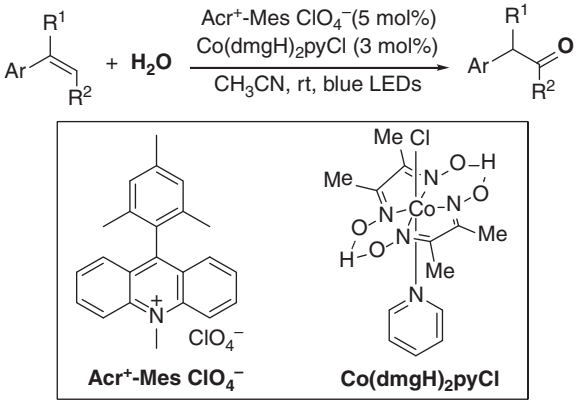
The direct oxygenation of an allylic C—H bond catalyzed by palladium using H_2O as oxygen source for the production of (*E*)-alkenyl aldehydes was developed by Jiang and coworkers (Scheme 1.16) [22]. During the process, allylic C—H bond cleavage occurred and an allyl-palladium species was formed as the key intermediate. The choice of DDQ as oxidant could greatly promote the reaction efficiency. The substrate scope was broad and diverse (*E*)-alkenyl aldehyde products were afforded in high yields with good stereoselectivity. The kinetic isotopic experiments implied that the activation of the allyl C(sp^3)—H bond was involved in the rate-determining step.

A plausible reaction mechanism is shown in Scheme 1.16. π-Allylpalladium species **I** was generated from the reaction of alkene and Pd(II) through the allylic C—H bond activation. Subsequently, the nucleophilic attack of H_2O into intermediate **I** afforded the oxidative allylic oxygenation products **III** and **III′**, which existed as an equilibrating mixture. Finally, the desired aldehyde product was formed by DDQ promoted oxidation of **III** and **III′**.

The direct anti-Markovnikov dehydrogenative oxygenation of β-alkyl styrenes under external-oxidant-free conditions by the use of the synergistic effect of photocatalysis and proton-reduction catalysis was presented by Lei and coworkers (Scheme 1.17) [23]. In this transformation, water was applied as single terminal oxidant for the construction of a series of carbonyl compounds. The



Scheme 1.16 Pd(II)-catalyzed direct oxygenation of allylic C—H bond with H_2O.



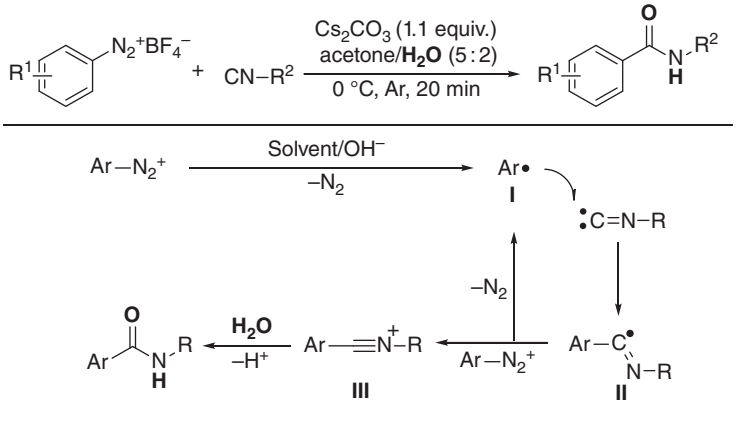
Scheme 1.17 Anti-Markovnikov oxidation of β-alkyl styrenes with H_2O as the terminal oxidant.

reaction proceeded through an alkene radical cation intermediate, which was *in situ* formed by the photoinduced system, followed by the nucleophilic attack of water to give distonic radical cation. Subsequently, the deprotonation of the distonic radical cation produced the anti-Markovnikov intermediate, which underwent single-electron oxidation, elimination, and keto–enol tautomerism sequence to lead to the final carbonyl products. The synergistic effect of this dual catalytic system was vital for the single anti-Markovnikov selectivity. The results of control experiments indicated that the oxygen atom of carbonyl group was derived from water.

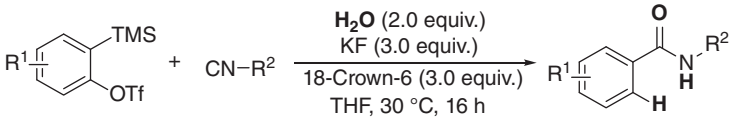
A transition-metal-free carboxyamidation reaction by the use of aryl diazonium tetrafluoroborates and isocyanides as coupling partners for the synthesis of arylcarboxyamides under mild conditions was achieved by Zhu and Xia (Scheme 1.18) [24]. It is worth mentioning that arylcarboxyamides could not be directly assembled by the aminocarbonylation of aryl diazonium salts with amines in the presence of CO. The reaction was realized in the absence of transition-metal catalysts in aqueous media at low temperature and exhibited broad substrate scope with moderate to high efficiency.

A radical mechanism involving hydroxide- or polar-solvent-induced dediazoniation is proposed in Scheme 1.18. Aryl radical **I** was first formed via homolytic dediazoniation process, which included SET from hydroxide or acetone to aryl diazonium salt. The reaction of aryl radical **I** with isocyanide delivered a key imidoyl radical intermediate **II**, followed by oxidation by aryl diazonium cation to lead to a nitrilium intermediate **III**. Finally, the hydration and tautomerization of intermediate **III** in the presence of H_2O could afford the desired arylcarboxyamide product.

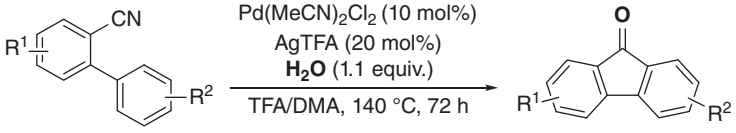
One year later, the transition-metal-free multicomponent reaction involving arynes and isocyanides with H_2O for the preparation of benzamide derivatives was reported by Biju and coworkers (Scheme 1.19) [25]. The 1,3-zwitterionic intermediate generated from isocyanide and aryne could be intercepted by different electrophiles for the synthesis of diverse benzannulated heterocycles. The treatment of isocyanide and 2-(trimethylsilyl)aryl triflate mediated by KF



Scheme 1.18 Synthesis of arylcarboxyamides from aryl diazonium salts and isocyanides.



Scheme 1.19 Synthesis of benzamides by a multicomponent reaction involving arynes, isocyanides, and H_2O.

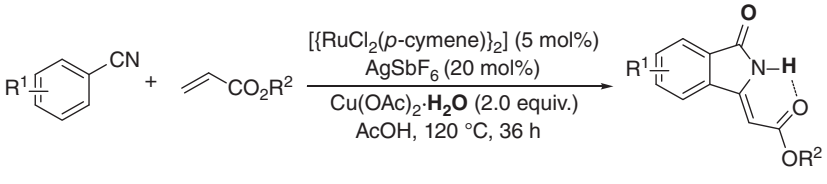


Scheme 1.20 Pd(II)-catalyzed nitrile-directed C—H activation for the synthesis of fluorenones.

in the presence of 18-crown-6 in THF, followed by the addition of water led to benzamide products in good yields. The reaction proceeded through the protonation of *in situ* generation of 1,3-zwitterionic aryl anion intermediate and the subsequent hydrolysis of the resultant iminium species with H_2O. By contrast, the formation of amides through the reaction of isocyanides and water with an aryne from aryldiazonium 2-carboxylate had been previously described by Rigby and Laurent [26], which exhibited narrow substrate scope and moderate isolated yields.

A palladium-catalyzed nitrile-directed remote C—H activation with the insertion of nitrile for the construction of a range of polysubstituted fluorenones was developed by Hsieh and coworkers (Scheme 1.20) [27]. The reaction parameters were evaluated to promote the cyclization of the nitrile substrate instead of hydrolysis to amide. AgTFA was found to reduce the rate of hydrolysis and the combination of TFA and DMA was chosen as the optimal cosolvent to suppress the formation of amide. The reaction was supposed to undergo nitrile-directed remote C—H bond activation catalyzed by $Pd(TFA)_2$ to form imine-palladium intermediate, followed by the hydrolysis in the presence of H_2O and TFA to furnish the desired product. The dual C—H bond activation protocol could be realized by the use of aryl nitrile and aryl iodine with the slightly modified reaction conditions.

A ruthenium-catalyzed oxidative annulation of aromatic nitriles with activated alkenes to provide various *Z*-stereoselective 3-methyleneisoindolin-1-ones was disclosed by Jeganmohan and Reddy (Scheme 1.21) [28]. In this reaction,



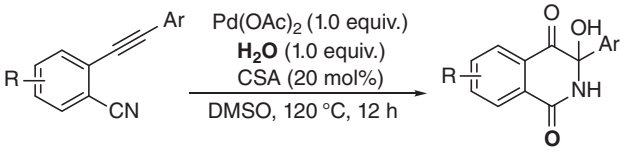
Scheme 1.21 Ruthenium-catalyzed cyclization of aromatic nitriles with alkenes.

$Cu(OAc)_2$ was applied as a Lewis acid to activate the nitrile group of benzonitrile, followed by hydration in the presence of H_2O to deliver benzamide. In fact, the amide group was the actual directing group of the reaction. Subsequently, the transformation proceeded through *ortho*-metalation with ruthenium catalyst, coordinative insertion of alkene into the Ru—C bond, and β-hydride elimination sequence to furnish the alkenylated product. Finally, ruthenium species assisted aza-Michael addition to produce the 3-methyleneisoindolin-1-one product. Of note, the *Z*-stereoselectivity of product was controlled by the intramolecular hydrogen-bonding.

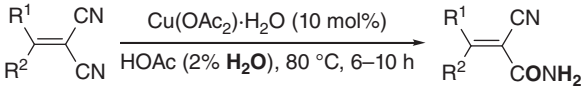
A $Pd(OAc)_2/H_2O$-mediated simultaneous alkyne oxidation and nitrile hydration of *ortho*-alkynylarenenitriles for the construction of various 3,3-disubstituted 2,3-dihydroazanaphthoquinones were accomplished by Srinivasan and Sakthivel (Scheme 1.22) [29]. Although the reaction required stoichiometric amount of expensive $Pd(OAc)_2$ to ensure high efficiency, the alternative condition of choosing 4 equiv. of iodine at 150 °C also enabled the completion of reaction with some compromise in the 70% yield. It is noteworthy that the alkyne moiety was oxidized by DMSO with the assistance of $Pd(OAc)_2$ and the nitrile group underwent hydrolysis to form amide with water. In addition, the alkyne oxidation preceded nitrile hydration process.

The hydration of nitriles to amides gained tremendous attention in the past decades due to the great importance of functionalized amides, which could be applied as versatile building blocks and pharmacologically interesting molecules. Traditionally, the hydration of nitriles was realized by the use of strong acid or base catalysis [30], suffering from numerous drawbacks, such as harsh reaction conditions and excessive hydrolysis. Therefore, the considerable efforts had been made to develop efficient catalytic hydration of nitriles [31]. Nevertheless, the hydration of dinitriles had only a few reports since the challenge was that the possibility of mono- and dehydration was equal.

A facile method for the $Cu(OAc)_2 \cdot H_2O$ catalyzed homogeneous and highly stereoselective monohydration of substituted methylenemalononitriles to furnish (*E*)-2-cyanoacrylamides was described by Dong and coworkers (Scheme 1.23) [32]. The highest yield of 82% was observed when the reaction was performed in the acetic acid containing 2% water, while the dried acetic



Scheme 1.22 Synthesis of 3,3-disubstituted 2,3-dihydroazanaphthoquinones.



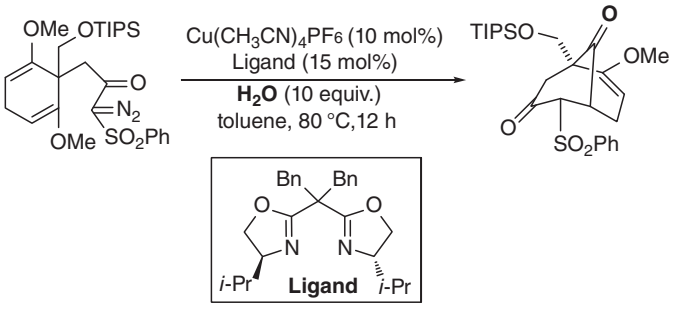
Scheme 1.23 Cu(II)-catalyzed monohydration of methylenemalononitriles.

acid gave a low conversion of the reaction. The results of deuterated experiment demonstrated that the hydrogen atom of amide did not originate from acetic acid, different from the conventional acid catalyzed hydration of nitriles. Under the optimized conditions, the monohydration of dicyanobenzenes and 2-substituted malononitriles were also smoothly achieved in comparable yields.

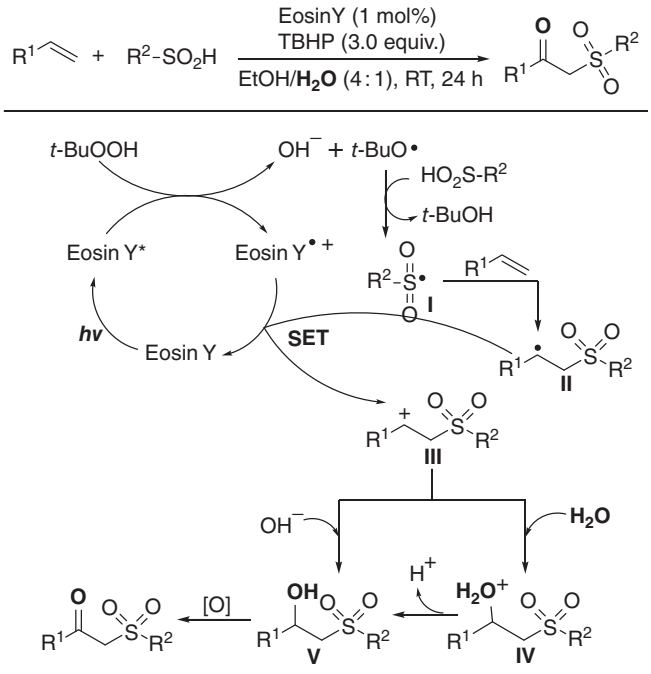
The catalytic asymmetric intramolecular cyclopropanation (CAIMCP) of α-diazo β-keto sulfone for the formation of the skeleton of polycyclic polyprenylated acylphloroglucinols (PPAPs) was reported by Nakada and coworkers (Scheme 1.24) [33]. In fact, the CAIMCP of an α-diazo ketone for total synthesis of four different PPAPs had been previously disclosed by the same group, albeit low enantioselectivity was obtained. In the current reaction, the desired product was produced in good yields with high enantioselectivity by the use of chiral bisoxazoline ligand. The CAIMCP reaction of α-diazo β-keto sulfone proceeded through divergent pathways in terms of different additives. In the presence of molecular sieves 4 Å, a rearrangement product was formed. In contrast, a by-product from ring-opening of the desired cyclopropane was observed with the addition of 10 equiv. of H_2O. Notably, the transformation of this byproduct afforded relevant synthetic intermediates, which could be applied to synthesize nemorosone, garsubellin A, clusianone, and hyperforin.

The direct oxysulfonlyation of alkenes with sulfinic acids initiated by visible light under mild conditions for the synthesis of useful β-ketosulfone derivatives was achieved by Yang, Wang, and coworkers (Scheme 1.25) [34]. In this transformation, visible light was regarded as a powerful reaction promoter and organic dye eosin Y was chosen as efficient photoredox catalyst. As for solvents, EtOH/H_2O ($v_1/v_2 = 4:1$) was superior to other solvents and the oxygen of carbonyl group in β-ketosulfone was partially derived from H_2O. The substrate scope of the reaction was broad, and a variety of functional groups, including electron-donating groups or electron-withdrawing groups, were smoothly tolerated in the reaction, affording the corresponding β-ketosulfone products in moderate to good yields.

The preliminary mechanistic investigation indicated that the reaction could undergo a radical process and continuous visible light irradiation was necessary for the high efficiency of the transformation. A proposed mechanism was depicted in Scheme 1.25. Initiated by visible light, a SET process occurred



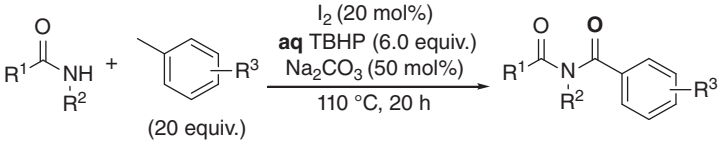
Scheme 1.24 Enantioselective approach to polycyclic polyprenylated acylphloroglucinols via CAIMCP.



Scheme 1.25 Visible-light-initiated direct oxysulfonylation of alkenes.

between excited eosin Y* and TBHP to deliver *tert*-butoxyl radical and hydroxyl anion. The sulfonyl radical **I** was formed by the interaction of *tert*-butoxyl radical and sulfinic acid, followed by the addition of radical **I** to alkene affording the carbon centered radical **II**. Subsequently, the carbocation intermediate **III** could be generated from radical **II** by SET process. At this stage, the nucleophilic attack of hydroxyl anion or H_2O on the intermediate **III** gave intermediates **IV** and **V**, which underwent oxidative process to produce the desired β-ketosulfone product. Notably, the source of the carbonyl oxygen atom of the β-ketosulfone was TBHP and H_2O in the protocol.

A metal-free I_2/aqueous TBHP-mediated coupling reaction of NH-amides and methylarenes for the synthesis of imides was presented by Singh and coworkers (Scheme 1.26) [35]. The ^{18}O labeling experiment suggested the additional oxygen in the imides originated from water in aqueous TBHP. The initial step of the reaction presumably was that the methylarene was first transformed into benzyl alcohol and then oxidized to benzaldehyde through radical pathway with the

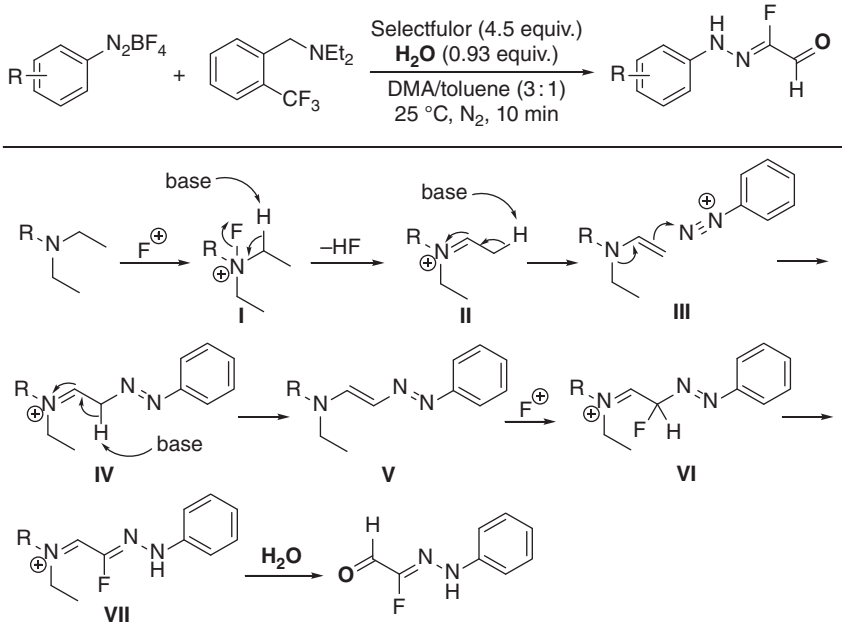


Scheme 1.26 I_2/aqueous TBHP-catalyzed coupling of amides with methylarenes.

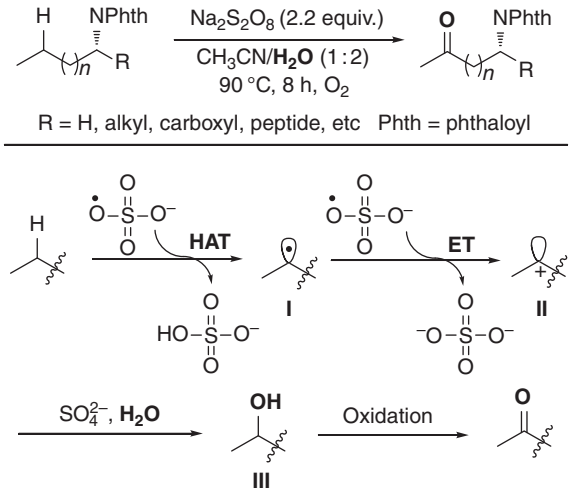
assistance of I_2/aqueous TBHP catalytic system. Subsequently, the coupling of benzaldehyde with amide furnished the final imide product via a SET process. Not surprisingly, benzaldehydes and benzyl alcohols could also serve as ideal coupling partners for the reaction to provide identical products.

The fluorinated arylhydrazones was regarded as important synthons to construct a myriad of fluorinated nitrogen-containing heterocycles. The first example of a cascade metal-free reaction for the preparation of monofluorinated arylhydrazones in the presence of Selectfluor from aryl diazonium salts and trialkylamine was achieved by Tang and coworkers (Scheme 1.27) [36]. It was envisioned that trialkylamine could be oxidized by Selectfluor to give reactive enamine *in situ*, which was applied as key intermediate in the transformation. Therefore, various trialkylamines were evaluated and *N*,*N*-diethyl-2-trifluoromethyl-benzenemethanamine could enable the best results. It was worth mentioning that the *gem*-difluorinated azo compounds were afforded in the absence of H_2O.

Mechanistic observations demonstrated that the hydrogen atom of the product was from trialkylamine and the oxygen atom came from H_2O. The trialkylamine was oxidized to fluorinated quaternary ammonium salt **I**, which was converted into iminium ion **II** and further into enamine **III**. The interaction between aryldiazonium ion and enamine **III** formed the azo complex **VI**, which could generate **V** in the presence of base. The intermediate **V** reacted with F^+ reagent and subsequent isomerized to monofluorinated intermediate **VII**. The latter could react with H_2O to give rise to the desired monofluorinated arylhydrazone product.



Scheme 1.27 Synthesis of monofluorinated arylhydrazones.

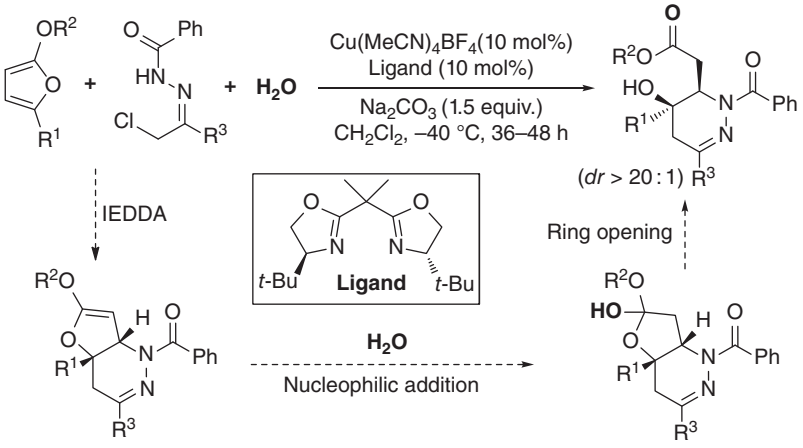


Scheme 1.28 Oxidation of aliphatic C—H bonds in amino-containing molecules.

A simple and transition-metal-free system for the site-selective oxidation for the remote secondary and tertiary C—H bonds in diverse phthaloyl-protected primary amines and amino acid derivatives was achieved by Shi and coworkers (Scheme 1.28) [37]. The employment of readily available sodium persulfate and environmentally benign O_2 rendered this protocol more practical and appealing. Under the standard conditions, methylenes could be oxidized to carbonyls and tertiary C—H bonds were oxidized to hydroxyl groups. A wide range of *N*-Phth-protected amines and amino acid molecules were successfully oxidized to the corresponding oxo products in moderate to high yields. Moreover, the elegant methodology could be applied to modify the synthetic peptides and assemble complex molecules.

The mechanistic studies indicated that the oxygen atom in the product came from water, instead of from dioxygen or persulfates and the reaction might involve a radical process. First, the sulfate radical anions were formed by thermally induced pyrolysis of persulfate. The intermolecular H-abstraction of substrate by sulfate radical gave a carbon radical **I**, which was further oxidized by another sulfate radical to deliver carbocation **II**. Subsequently, the carbocation **II** reacted with nucleophilic H_2O to produce the alcohol intermediate **III**, followed by the oxidation process to lead to the final product. Some calculation investigations demonstrated the possibility of SET between PhthN group and sulfate radical.

Wang and coworkers reported a Cu(I)-catalyzed multicomponent cascade asymmetric inverse-electron-demand Aza-Diels–Alder (IEDDA)/nucleophilic addition/ring-opening reaction using 2-methoxyfurans as dienophiles for the efficient synthesis of tetrahydropyridazine derivatives bearing enantioenriched functionalized γ-hydroxyl ester moiety (Scheme 1.29) [38]. By the employment of α-chloro *N*-benzoyl hydrazine as azoalkene precursor in the presence of base, the combination of Lewis acid $Cu(MeCN)_4BF_4$ catalyst and chiral (S,S)-*t*Bu-BOX



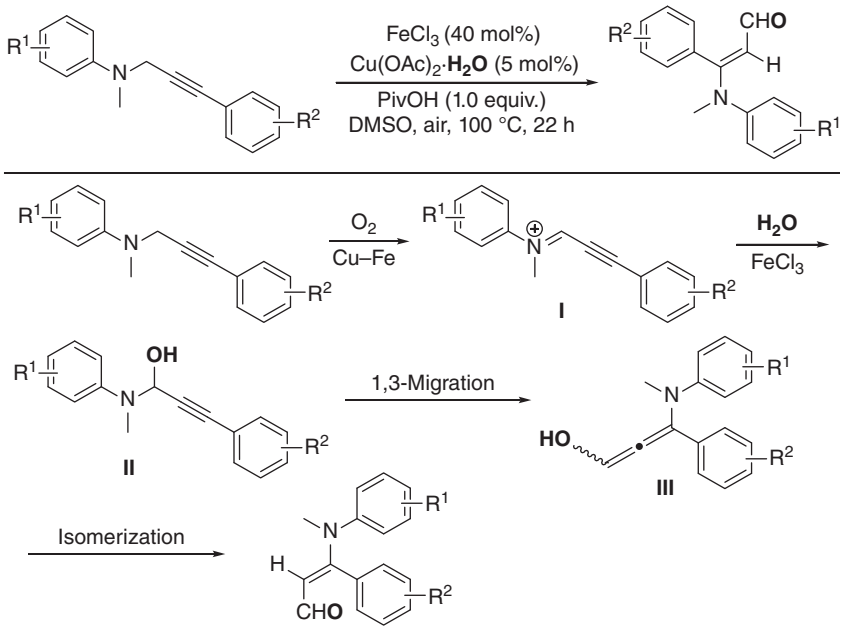
Scheme 1.29 Cu(I)-catalyzed Aza-Diels–Alder/nucleophilic addition/ring-opening reaction.

ligand could enable the reaction with high efficiency and enantioselectivity. Under the current conditions, a wide range of tetrahydropyridazines containing stable γ-hydroxyl ester moiety were produced in good to excellent yields with exclusive regioselectivity.

Inspired by the previous azoalkene involved IEDDA reaction, the anticipated bicyclic heterocycle product would be formed. But in this reaction, the *in situ* generated cycloadduct was further attacked by the nucleophilic H_2O and subsequent ring opening of tetrahydrofuran led to biologically significant tetrahydropyridazine derivatives bearing γ-hydroxyl esters, which could be utilized as versatile building blocks. It is noteworthy that the protocol constituted the first example of applying furans as dienophiles in a catalytic asymmetric IEDDA reaction.

Huang and coworkers presented a Cu/Fe-cocatalyzed Meyer–Schuster-like rearrangement of propargylic amines for the simple construction of β-aminoacryaldehydes under aerobic conditions (Scheme 1.30) [39]. The classical Meyer–Schuster (M.S.) rearrangement of propargylic alcohols was widely used in organic synthesis to access to versatile enone derivatives. In this protocol, propargylic amines were applied as readily available materials via Meyer–Schuster-like rearrangement reaction to build β-aminoacryaldehydes, which were difficult to obtain by other methods. Under the optimized conditions, numerous substituted β-aminoacryaldehyde scaffolds could be afforded with excellent *E* selectivity, presumably owing to the steric hindrance.

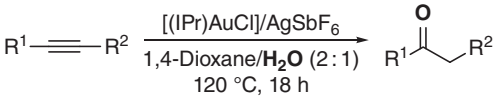
The proposed reaction pathway is shown in Scheme 1.30. The immonium intermediate **I** was initially formed by O_2-mediated oxidation of propargylic amine. Subsequently, Lewis acid $FeCl_3$-promoted nucleophilic attack of H_2O into intermediate **I** delivered intermediate **II**. Then, Cu-catalyzed Meyer–Schuster-like rearrangement occurred to generate allenol complex **III** via 1,3-migration, followed by the ready isomerization to enable the formation of the final α,β-unsaturated carbonyl product.



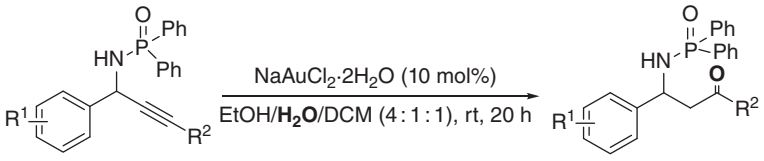
Scheme 1.30 Cu/Fe-cocatalyzed Meyer–Schuster-like rearrangement of propargylic amines.

The alkyne hydration reaction, observed by Kucherov in 1881 [40], has gained tremendous development of various metal-based catalytic systems for the formation of carbonyl derivatives [41]. Considering the easy availability of alkynyl substrates and the wide application fields of the carbonyl motifs, the hydration of alkynes is of great significance among chemical community. In addition, the alkyne hydration reaction has also been combined with other reaction patterns, such as carbocyclization of alkynes, to construct a variety of functionalized carbocyclic or heterocyclic products [42]. In the context, several representative examples of alkyne hydration reaction were introduced to highlight its importance in the field of organic synthesis.

An efficient [(NHC)Au^{I}]-based catalytic reaction for the hydration of diverse alkynes under acid-free conditions with very low catalyst loadings was described by Nolan and coworkers (Scheme 1.31) [43]. In this reaction, the choice of suitable ligand was significant for high efficiency. *N*-Heterocyclic carbenes (NHCs) were successfully identified as powerful ligands to promote the development of homogeneous gold catalysis and efficient catalytic systems at low catalyst loadings. Advantage of this protocol is that the low catalyst loading could result in good yields and high TON value with respect to a majority of alkynes.



Scheme 1.31 [(NHC)Au^{I}]-catalyzed acid-free alkyne hydration.

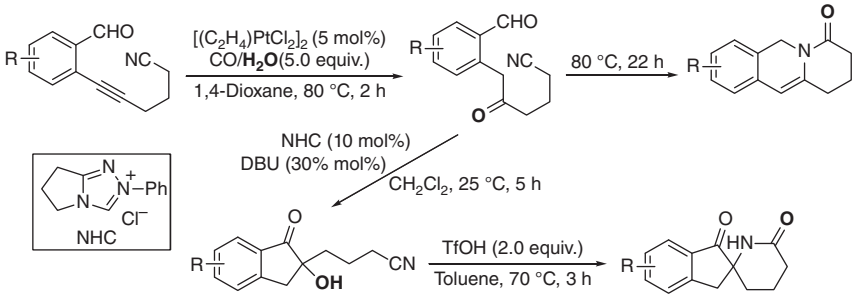


Scheme 1.32 Regiospecific hydration of *N*-(diphenylphosphinoyl)propargyl amines.

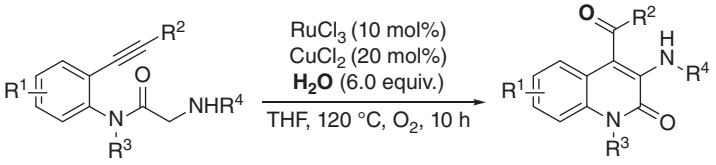
Pu and Ying developed a Au(III)-catalyzed hydration of *N*-(diphenylphosphinoyl)propargyl amines for the construction of a variety of β-amino ketones (Scheme 1.32) [44]. The *N*-(diphenylphosphinoyl) group was utilized to direct the regioselective hydration of the alkyne in the reaction, which led to the hydration position to specifically locate at the 3-position of the propargyl amine. A mixed solvent of EtOH/H_2O/DCM was chosen as optimal solvent. The gold complex $NaAuCl_4$ was previously applied as effective catalyst for the hydration of alkynes[45] and also used for the suitable catalyst for the current transformation. The control experiment of involving $H_2{}^{18}O$ indicated that the ^{18}O atom was incorporated into the ketone group but not in the phosphinoyl group. With regard to the enantiomerically enriched substrate, the high enantiomeric purity was maintained in the product after hydration.

Two platinum-catalyzed hydrative carbocyclizations of oxo-alkyne-nitrile functionalities were disclosed by Liu and coworkers for the production of nitrogen-containing heterocycles (Scheme 1.33) [46]. Upon the Pt(II)-catalyzed hydrative process, the dicarbonyl nitrile intermediates were easily formed, which could proceed through a prolonged heating to deliver 2,3-dihydro-1*H*-pyrido[1.2-*b*]-isoquinolin-4(6*H*)-ones in good yields. Alternative pathway lay in the treatment of the isolated dicarbonyl nitriles with NHC and DBU to give spiro alcohols, followed by TfOH-promoted hydrolysis of nitrile and intramolecular cyclization sequence to release spiro[indene-2,2′-piperidine]-1,6′(3*H*)-dione frameworks.

In 2011, Li and coworkers described a ruthenium-catalyzed oxidative deprotonation and carbocyclization of alkyne with a sp^3 carbon at the α-position of an amide for the synthesis of 3,4-disubstituted quinolin-2(1*H*)-one derivatives (Scheme 1.34) [47]. The combination system of catalytic $RuCl_3$ and $CuCl_2$ under



Scheme 1.33 Pt(II)-catalyzed hydrative carbocyclizations of oxo-alkyne-nitrile functionalities.



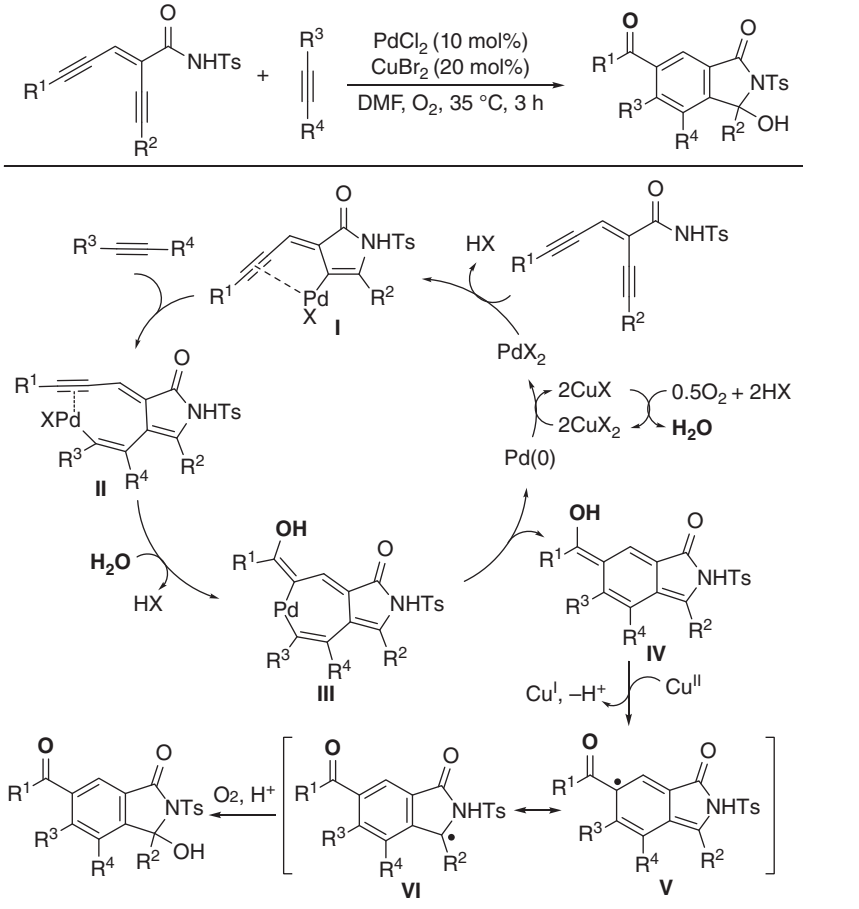
Scheme 1.34 Ruthenium-catalyzed intramolecular carbocyclization of alkynes.

the atmosphere of O_2 afforded the best results, devoid of the usage of other peroxide oxidants. The observation of control experiments suggested that the oxygen atom of the product was from the additional water through the hydration reaction. After the hydration of alkynes, Ru-catalyzed C(sp^3)—H functionalization was involved in the rate-limiting step and subsequent α-NHAc elimination as well as oxidative dehydrogenation process to furnish the final product.

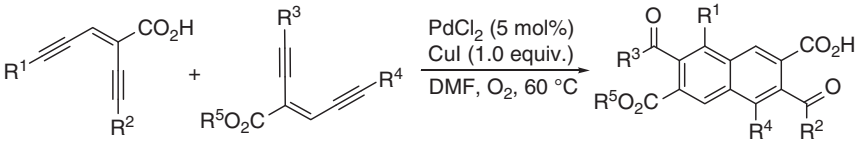
A Pd/Cu-catalyzed tandem coupling–ketooxygenation reaction of enediyne-carboxylic compounds and inner alkynes under mild reaction conditions for the assembly of diverse isoindolinones and *o*-acylbenzoic acids was disclosed by Ma and coworkers (Scheme 1.35) [48]. The protocol involved a formal [4+2] benzannulation-diketonization of enediynes and alkynes through coupling and decoupling strategy. The isotopic labeling experiments employing $^{18}O_2$ and $H_2{}^{18}O$ in the reaction demonstrated that the oxygen atom of the hydroxyl group originated from O_2 and the oxygen atom of the carbonyl group was from H_2O. Intriguingly, the water could be *in situ* generated from catalyst regeneration process with O_2 as the terminal oxidant. The radical trapping experiment by the use of radical scavenger 2,2,6,6-tetramethyl-1-piperidine-1-oxyl (TEMPO) implied that a benzyl radical was involved in the reaction, and, thereby, the subsequent O_2 activation step was reasonable.

The plausible reaction pathway is depicted in Scheme 1.35. The vinylpalladium species **I** was initially formed by an intramolecular antiaminopalladation of enediyne, followed by the syn insertion of alkyne onto species **I** to afford intermediate **II**. Subsequently, the nucleophilic attack of H_2O on the triple bond of intermediate **II** could deliver complex **III**, which underwent reductive elimination to release enol intermediate **IV**. At this stage, Cu(II) species mediated one-electron oxidation of enol **IV** enabled the generation of a benzyl radical **VI** from aromatization of tentative radical **V**. Finally, the radical **VI** could react with O_2 via O_2 activation involving an intermediate superoxo radical to lead to the desired product. Of note, the trapping of radical **VI** with TEMPO would give rise to TEMPO coupling adduct.

Later on, the same group described a palladium-catalyzed aerobic bimolecular carbocyclization reaction of enediynes for the preparation of structurally diverse 2,6-diacylnaphthalenes in mild conditions (Scheme 1.36) [49]. In this transformation, the oxygenative homo- and heterodimerization processes of enediyne-carboxylic acids and esters was involved to provide a series of multi-substituted naphthalenes with high efficiency through a directing-group-assisted coupling and decoupling strategy. Similar to the previous work of the author, mechanistic investigations suggested that the two oxygen atoms incorporated



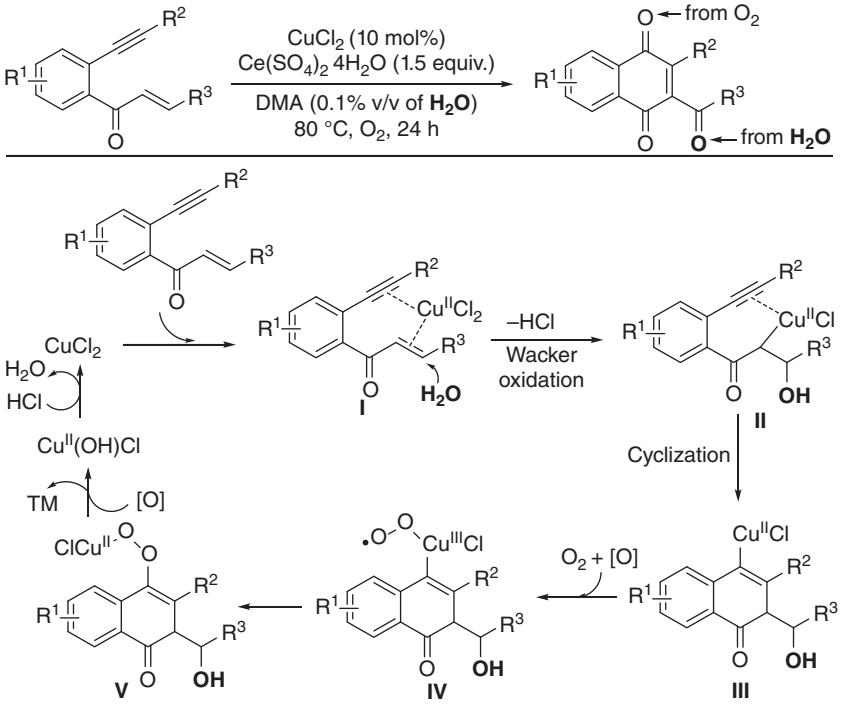
Scheme 1.35 Pd/Cu-catalyzed intermolecular cyclization of enediyne compounds and alkynes.



Scheme 1.36 Pd(II)-catalyzed bimolecular carbocyclizations of enediynes to 2,6-diacylnaphthalenes.

into the desired products came from atmospheric molecular oxygen and *in situ* generated H_2O, respectively.

Copper-catalyzed intramolecular oxidative 6-*exo*-trig cyclization of 1,6-enynes with H_2O and O_2 for the preparation of 1,4-naphthoquinones was reported by Li and coworkers (Scheme 1.37) [50]. It was notable that two additional oxygen atoms of the product were incorporated from H_2O and O_2, respectively.

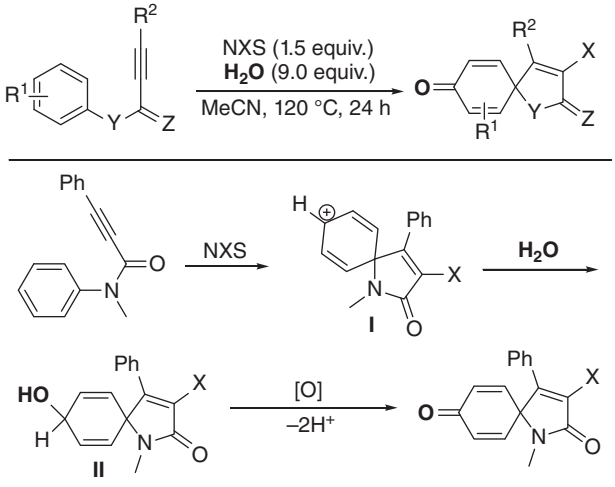


Scheme 1.37 Copper-catalyzed intramolecular oxidative 6-*exo*-*trig* cyclization of 1,6-enynes.

Extensive condition screening revealed that $Ce(SO_4)_2$ was the most efficient oxidant additive for the reaction. Substrates bearing various substituents were compatible with the reaction conditions to afford structurally diversified 1,4-naphthoquinones in acceptable to good yields. Mechanistic investigations indicated the reaction did not involve the alkyne hydrolysis and the reaction possibly proceeded through a radical process.

The proposed mechanism is depicted in Scheme 1.37. The intermediate **I** was formed through the coordination of $CuCl_2$ with 1,6-enyne, followed by the Wacker oxidation of the C—C double bond with H_2O to yield intermediate **II**. Subsequently, intramolecular cyclization of **II** afforded intermediate **III**, which underwent oxidation process with the assistance of O_2 and oxidative additive to lead to peroxycopper(III) complex **IV**. Reductive elimination of complex **IV** enabled the formation of intermediate **V**. Finally, the desired product would be produced by the O—O bond cleavage of the intermediate **V** and further oxidization.

A general method for the assembly of 3-halospiro[4,5]trienones by the electrophilic *ipso*-cyclization of *para*-unsubstituted arylalkynes in the presence of halide electrophiles and water was developed by Li and coworkers (Scheme 1.38) [51]. As early as 2003, Fanghänel and coworkers had reported an intramolecular electrophilic cyclization of bis(4-methoxybenzylthio)acetylene with ICl, Na_2CO_3, and H_2O to afford the spiro[4,5]trienone product [52]. ^{18}O-labeling experiments indicated that the oxygen atom source of the ketone

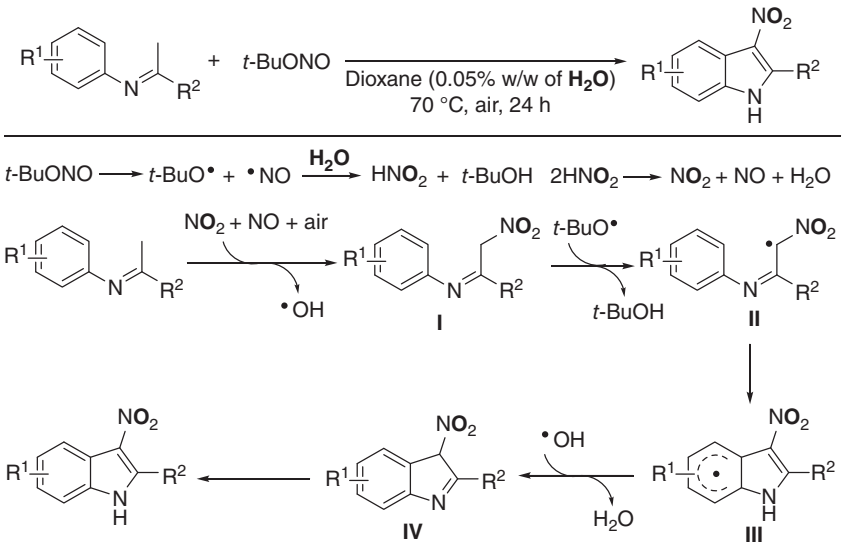


Scheme 1.38 Intramolecular *ipso*-halocyclization of 4-(*p*-unsubstituted-aryl)-1-alkynes leading to spiro[4,5]trienones.

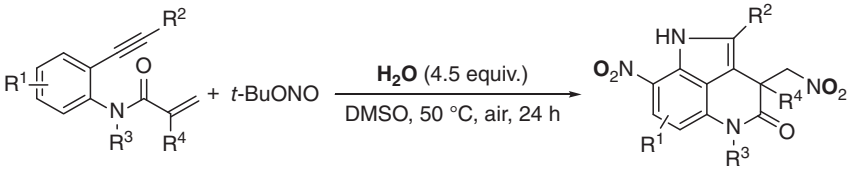
moiety in the product originated from H_2O with respect to the substrate bearing no *para*-methoxy group. The reaction possibly proceeded through the intramolecular *ipso*-halocyclization, the nucleophilic attack of H_2O to cation **I**, and the following oxidation of alcohol **II** to furnish the desired spiro[4,5]trienone product.

In 2014, Li and coworkers demonstrated a metal-free approach for the formation of a series of 3-nitroindoles by the nitrative cyclization of readily available *N*-aryl imines with *tert*-butyl nitrite (Scheme 1.39) [53]. *tert*-Butyl nitrite is a safe and commonly used nitrating reagent in organic synthesis and had been frequently reported as the nitrogen source to construct heterocycles. The reaction was assumed to proceed through a radical process and *tert*-butyl nitrite was used as versatile NO_2 source. Notably, a trace amount of water in the solvent and air played a fundamental role in the reaction. Under the optimized conditions, a range of functional groups were smoothly tolerated and the corresponding 3-nitroindole products were provided in comparable yields and good regioselectivity.

The tentative pathway of the transformation is shown in Scheme 1.39. *t*-BuONO was initially divided into a *t*-BuO·radical and an NO·radical induced by heating. The reaction of NO·radical with H_2O yielded HNO_2, which was readily decomposed into NO_2, NO, and H_2O, verified by the ^{18}O-labeled experiment. The substrate *N*-aryl imine could be transformed into intermediate **I** in the presence of NO_2, NO, and air, which was attacked by the *t*-BuO·radical to generate radical intermediate **II** through hydrogen-abstraction process. Subsequently, the intramolecular cyclization of intermediate **II** gave intermediate **III**, which proceeded through dehydrogenation and isomerization to produce the final product. The protocol was regarded to take place through an oxidative dehydrogenation, radical nitration, intramolecular cyclization, and isomerization sequence.



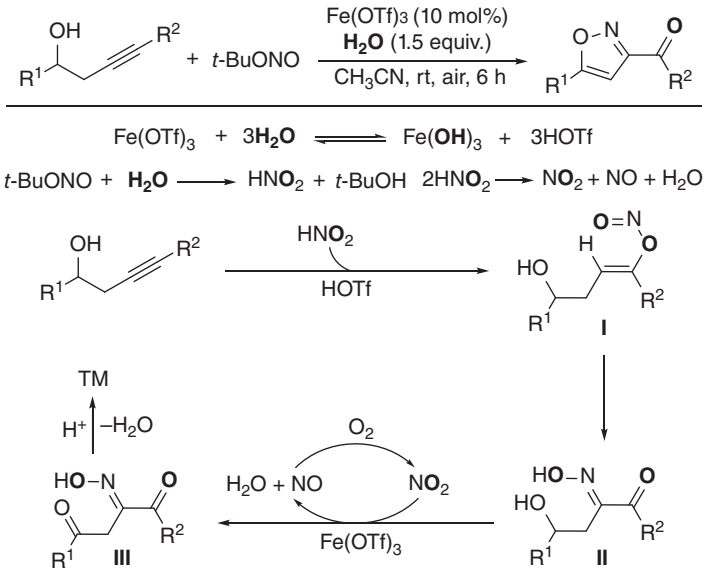
Scheme 1.39 Nitrative cyclization of *N*-aryl imines with *t*-BuONO to 3-nitroindoles.



Scheme 1.40 Cascade nitration/cyclization of 1,7-enynes with *t*-BuONO and H_2O.

Encouraged by the previous work of nitrative cyclization by using *t*-BuONO, Li and coworkers reported a powerful strategy for one-pot self-assembly of pyrrolo[4,3,2-de]quinolinones by cascade nitration/cyclization sequence of 1,7-enynes with *t*-BuONO and H_2O under metal-free conditions (Scheme 1.40) [54]. A wide variety of *N*-methyl-*N*-(2-(arylethynyl)phenyl)methacrylamides were subjected to *t*-BuONO and H_2O to construct biologically interesting pyrrolo[4,3,2-de]quinolinone scaffolds with good substituent compatibility and high efficiency. In addition, the reaction could be easily scaled up without the loss of reactivity. More importantly, the amount of H_2O had an essential influence on the reaction, as demonstrated by the participation in the formation of NO or NO_2 with *t*-BuONO. The results of ^{18}O-labeling experiment with $H_2{}^{18}O$ implied that the oxygen atoms of the nitro groups in the product did not solely originate from H_2O. The cascade reaction presumably proceeded through alkene nitration, intramolecular 6-*exo*-trig cyclization, C—H nitration, and redox cyclization sequence.

Li and coworkers disclosed an iron-catalyzed aerobic oxidative reaction of homopropargylic alcohol with *t*-BuONO and H_2O for the regioselective construction of disubstituted isoxazoles (Scheme 1.41) [55]. The transformation

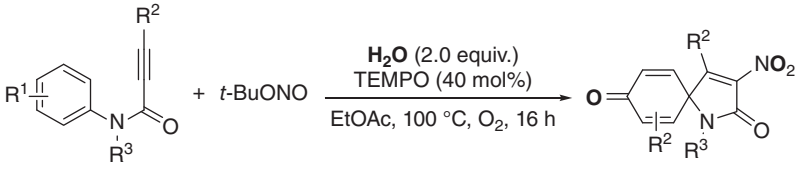


Scheme 1.41 Synthesis of disubstituted isoxazoles from homopropargylic alcohol.

was presumably achieved through the formation of C=N bond and C=O bond, C—H oxidation, and intramolecular cyclization sequence. Among various metal Lewis acid catalysts, $Fe(OTf)_3$ was the optimal choice to improve the overall yield of the reaction. The addition of water was also essential for the reaction. The preliminary investigation toward the mechanism suggested the oxygen atom of the product was from *t*-BuONO and H_2O.

The plausible mechanism was proposed as shown in Scheme 1.41. The addition of HNO_2 into the triple bond of homopropargylic alcohol initially generated a vinyl nitrite intermediate **I** catalyzed by HOTf, which was produced from $Fe(OTf)_3$. Subsequently, the isomerization of intermediate **I** could give the acyloxime intermediate **II**, which underwent aerobic oxidation process to furnish intermediate **III**. Finally, intramolecular dehydrated cyclization of intermediate **III** could enable the formation of the desired product by the assistance of acid.

Spirocyclic rings are important frameworks widely found in natural products and bioactive molecules. A TEMPO-mediated nitrative spirocyclization of alkynes for the preparation of nitrated spirocycles by the use of *tert*-butyl nitrite and water as the nitro source was achieved by Li and coworkers (Scheme 1.42) [56]. In this transformation, a catalytic amount of TEMPO and O_2 were applied



Scheme 1.42 Nitrative spirocyclization mediated by TEMPO.

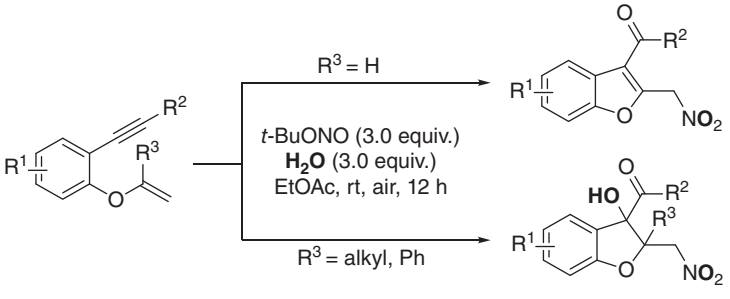
as oxidants to realize the oxidative alkyne difunctionalization through a radical pathway. The substrate scope of this protocol was rather broad, and a library of nitrated spirocycle products was obtained under the optimized conditions. The mechanistic insights illustrated that both a nitro oxygen atom and the new carbonyl oxygen atom came from H_2O, instead of O_2.

A similar nitrative cyclization example was described by Li and coworkers in 2015. They presented a metal-free method for the assembly of 3-carbonylated benzofuran scaffolds from 1-ethynyl-2-(vinyloxy)benzenes in the presence of *tert*-butyl nitrite (*t*-BuONO) and water (Scheme 1.43) [57]. In this reaction, a dioxygen activation process occurred to introduce an oxygen atom into the carbonyl group. The mechanism was similar to the previous nitrative reactions. The reaction proceeded through addition of NO_2 to the alkene, intramolecular cyclization, trapping of radical intermediate by O_2, the formation of cation intermediate by O—O bond cleavage/isomerization. At this stage, on the basis of the substitution type of R^3, the cation intermediate underwent two pathways to deliver different products. The nucleophilic addition of H_2O to cation intermediate could lead to hydroxyl-containing product.

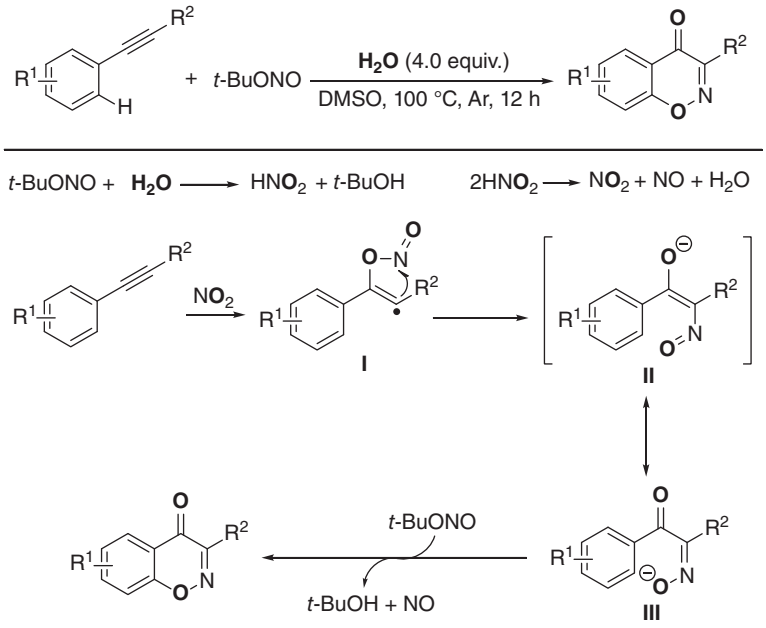
A metal-free radical-mediated [4+2] annulation protocol for the assembly of benzo[*e*]-[1,2]oxazin-4-ones from internal arylalkynes and with *tert*-butyl nitrite (*t*-BuONO) was presented by Li and coworkers (Scheme 1.44) [58]. The internal arylalkynes served as 4-carbon units and *t*-BuONO acted as reactant and oxidant. The addition of H_2O had an important influence on the reaction as demonstrated that two oxygen atoms in the product originated from water on the basis of ^{18}O-labeling experiment. As for terminal arylalkynes, the reaction proceeded through sequential dimerization of alkynes and annulation with *t*-BuONO to deliver isoxazoles product, instead of desired benzoxazines.

The possible reaction mechanism is shown in Scheme 1.44. Similar to the previous work, the interaction of *t*-BuONO with H_2O and sequential decomposition of HNO_2 afforded NO_2. Afterward, the radical intermediate **I** was formed through the addition of NO_2 across the C—C triple bond. The isomerization of intermediate **I** could afford intermediates **II** and **III**, which underwent intramolecular C—O bond formation via C(sp^2)—H oxidation assisted by *t*-BuONO to give rise to the final benzo[*e*][1,2]oxazin-4-one product.

Later on, Li and coworkers reported a palladium-catalyzed oxidative 6-*exo*-*trig* cyclization of 1,6-enynes under mild conditions by the use of *t*BuONO as an



Scheme 1.43 Nitrative cyclization of 1-ethynyl-2-(vinyloxy)benzenes with *t*-BuONO.

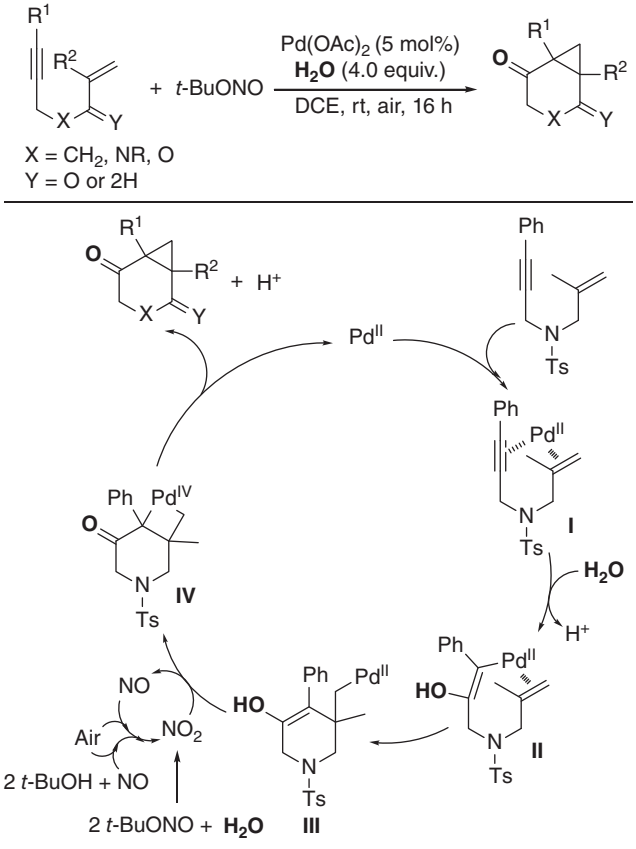


Scheme 1.44 Metal-free [4+2] annulation of arylalkynes with *tert*-butyl nitrite.

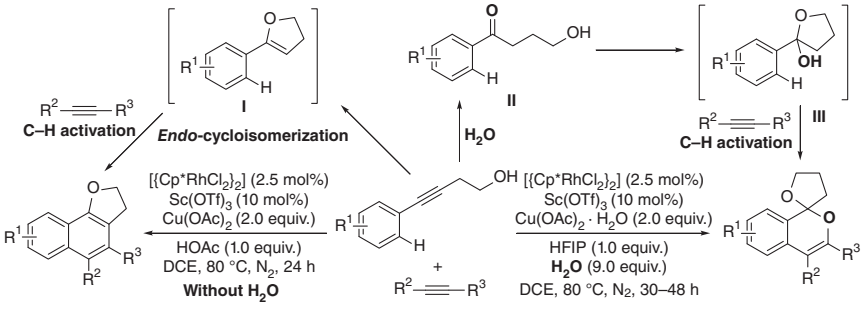
oxidant for the production of 3-bicyclo[4.1.0]heptan-5-ones (Scheme 1.45) [59]. Note that in this reaction, NO_2 generated from the interaction of *t*BuONO and H_2O acted as oxidant, instead of NO_2 source. The reaction condition optimization revealed that the amount of water had an obvious influence on the reaction and O_2 exerted a positive effect on the conversion. The cascade strategy constituted a general transition-metal-catalyzed oxidative cyclization of 1,6-enynes in a 6-*exo-trig* manner.

The proposed catalytic cycle is outlined in Scheme 1.45. First, the coordination of active Pd^{II} species with alkene bond and alkyne bond gave intermediate **I**, followed by the hydration of the C—C triple bond with H_2O led to intermediate **II**. Subsequently, intramolecular cyclization process could take place to deliver intermediate **III**, which underwent oxidative cyclization promoted by NO_2 and air to produce Pd^{IV} intermediate **IV**. Finally, the desired product was delivered by reductive elimination of the Pd^{IV} intermediate **IV**. In general, the 1,6-enyne cyclization reaction involved hydration, 6-*exo-trig* cyclization, and cyclopropanation sequence, providing a straightforward access to complicated bicyclo[4.1.0]-heptan-5-one skeletons.

Two tunable cascade reactions of alkynols and internal alkynes catalyzed by the combination of $Sc(OTf)_3$ and rhodium was reported by Liu and coworkers (Scheme 1.46) [60]. For this reaction, there were two different pathways. In the absence of H_2O, the reaction involved *endo*-cycloisomerization/C—H activation cascade to product 2,3-dihydronaphtho[1,2-*b*]furans. Alternatively, in the presence of H_2O, the hydration of alkynol could form intermediate **II**, which underwent intramolecular addition of the hydroxy group to the carbonyl group to give



Scheme 1.45 Palladium-catalyzed oxidative 6-*exo-trig* cyclization of 1,6-enynes.



Scheme 1.46 Tunable cascade reactions of alkynols with alkynes.

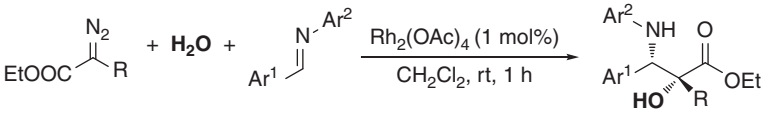
hemiketal **III**, followed by the [Cp*Rh^{III}]-catalyzed hydroxy-directed C—H activation with alkyne to access to 4,5-dihydro-3*H*-spiro[furan-2,1′-isochromene] derivatives. It should be notable that the hydration of the triple bond of alkynols had a crucial role in switching between the two reaction pathways on the basis of mechanistic studies.

1.4 Incorporation of Hydroxyl Group from Water

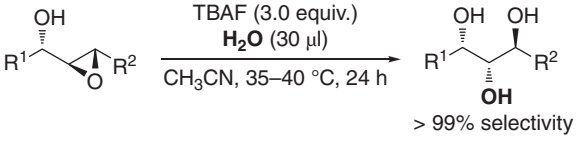
A Rh(II)-catalyzed three-component reactions of ethyl diazoacetate, H_2O, and aryl imines for the preparation of a variety of β-aryl isoserine derivatives with high diastereoselectivity was developed by Hu and coworkers (Scheme 1.47) [61]. In this transformation, the oxonium ylide could be *in situ* generated from water and ethyl diazoacetate and readily reacted with aryl imines in the presence of rhodium acetate to lead to β-aryl isoserine esters in good yields. Under the current conditions, most of substrates participated smoothly in the reaction to produce the desired product with high chemo- and diastereoselectivity. Apart from this reaction, there were other three-component reactions involving phenyldiazoacetate as substrate accompanied with water [62].

A TBAF/H_2O-promoted highly regio- and stereoselective hydrolysis of α,β-epoxyalcohols at the disfavored α-position for the rapid assembly of *arabino*- or *lyxo*-configured triols was reported by Schroeder and coworkers (Scheme 1.48) [63]. The starting materials α,β-epoxyalcohols could be readily obtained by Sharpless epoxidation/kinetic resolution with high stereoselectivity. The employment of TBAF in the presence of small amounts of CH_3CN and H_2O was necessary for the high stereoselectivity without any loss of diastereomeric purity. Noteworthy is that specific hydrogen bonding interactions could facilitate the disfavored α-attack in TBAF/CH_3CN/H_2O mixture of this transformation.

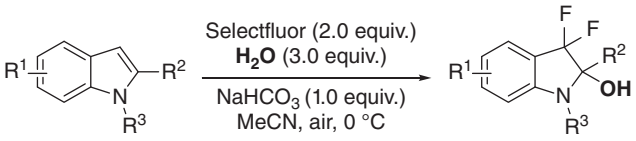
A facile difluorohydroxylation of substituted indoles to access 3,3-difluoroindolin-2-ols by the use of Selectfluor as the electrophilic fluorinating reagent under mild conditions was observed by Jiao and coworkers (Scheme 1.49) [64]. The indole rings were difluorinated at the C3 carbon site with high regioselectivity in this strategy. Another electrophilic fluorinating reagent, such as NFSI, was also well compatible with the reaction even at −20 °C to give rise to the desired difluorinated product in 81% yield. The water not only was the source of the hydroxyl group in the product but also assisted to dissolve $NaHCO_3$ and Selectfluor to react with indoles. The results of control experiment suggested that the monofluorinated indole was an intermediate in the transformation. The



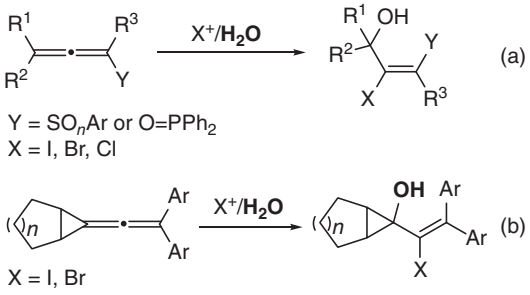
Scheme 1.47 Rh(II)-catalyzed three-component reactions leading to β-aryl isoserine derivatives.



Scheme 1.48 Highly α-selective hydrolysis of α,β-epoxyalcohols.



Scheme 1.49 Difluorohydroxylation of indoles using Selectfluor as a fluorinating reagent.

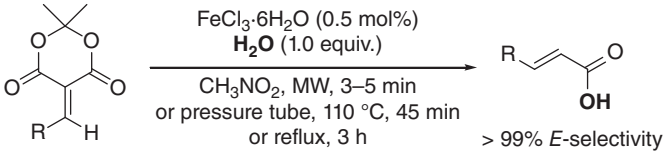


Scheme 1.50 Halohydroxylation reaction of allenes.

reaction involved the formation of an unstable 3,3-difluoroindoline cation and the following nucleophilic attack by H_2O to release the final product.

Previous examples of halohydroxylation reaction of allenes for the regio- and stereoselective synthesis of a series of 2-halogen-substituted allylic alcohols were reported by Ma and coworkers (Scheme 1.50a) [65]. The allene attaching a heteroatom such as sulfur or phosphorus was chosen as model substrate to react with different halogenated reagents and water. It is worth mentioning that the neighboring group participation effect of the heteroatom was involved in the whole transformation and the nucleophilic H_2O could attack the heteroatom to afford the final product through hydrolysis process. Therefore, the oxygen atom of H_2O was located at O=P (or S) bond instead of hydroxyl group. Another halohydroxylation reaction of vinylidenecyclopropanes for the assembly of vinylbicyclo[(*n*+2).1.0]alkanols was disclosed by Wu and coworkers (Scheme 1.50b) [66]. In this reaction, the oxygen atom of pendent hydroxyl group in the product was from H_2O due to the direct nucleophilic attack of water into the *in situ* formed three-membered cyclic halonium ion.

An inexpensive Lewis acid $FeCl_3 \cdot 6H_2O$-catalyzed reaction to achieve α,β-unsaturated carboxylic acids from alkylidene Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione) derivatives in the presence of H_2O was described by Bhat and Mohite (Scheme 1.51) [67]. The reaction could proceed under both



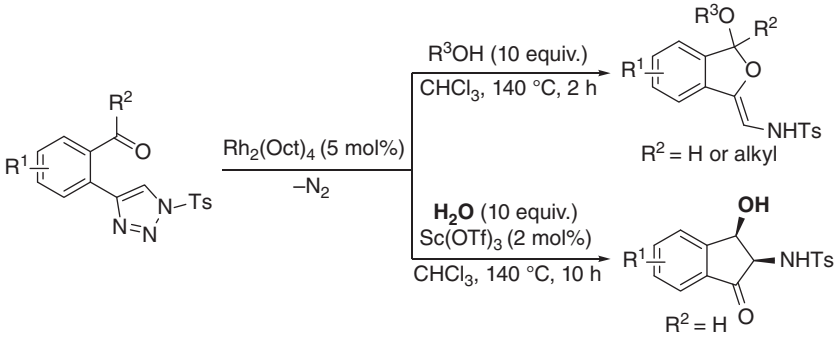
Scheme 1.51 Lewis-acid-catalyzed synthesis of (*E*)-α,β-unsaturated acids.

microwave irradiation (2.5 GHz) and conventional heating conditions with high *E*-stereoselectivity. It was observed that CH_3NO_2 and water were crucial for the high conversion of the reaction. The reaction could perform on gram scale with a low catalyst loading, providing a practical and convenient method for the preparation of α,β-unsaturated carboxylic acids.

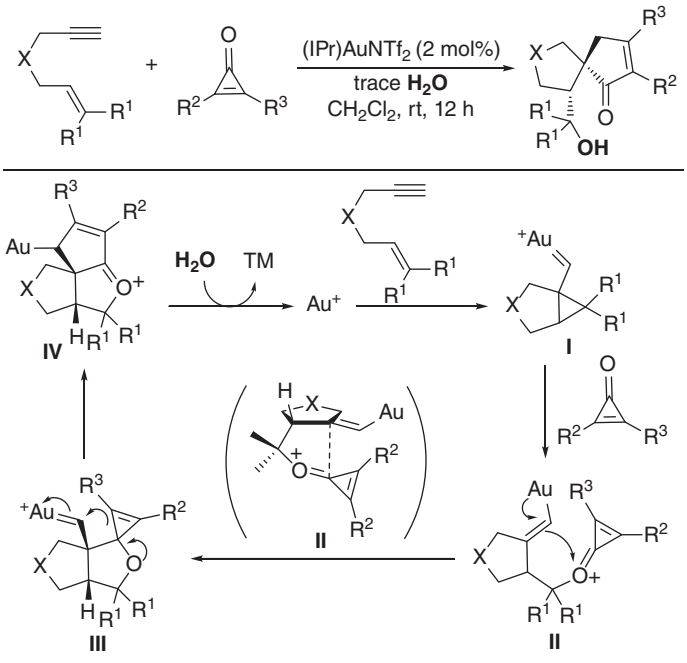
In 2014, two Rh(II)-catalyzed tandem reactions of *N*-sulfonyl 1,2,3-triazole derivatives for the construction of dihydroisobenzofuran and indanone compounds were developed by Yang, Gong, and coworkers (Scheme 1.52) [68]. It was envisaged that the formed highly reactive rhodium(II) azavinyl carbene intermediate could be trapped by the carbonyl group and undergo subsequent annulation reactions to give relevant heterocyclic products in the presence of nucleophilic partners. In the light of different kinds of substrates and nucleophiles (alcohol and water), structurally diverse dihydroisobenzofurans and 2-amino-3-hydroxyl indanones were produced in good yields with high regioselectivities.

A gold(I)-catalyzed ring-expanding spiroannulation reaction of cyclopropenones with enynes for the formation of [4.4]-spirocyclic cyclopentenones containing an alcohol functionality with high diastereoselectivity was accomplished by Matsuda and coworkers (Scheme 1.53) [69]. The additional hydroxy group derived from the trace of water was present in the solvent. The plausible mechanism is depicted in Scheme 1.53. The reaction of enyne and Au(I) catalyst produced (cyclopropylcarbene)gold(I) species **I**, which was attacked by the carbonyl group of cyclopropenone to deliver oxocarbenium ion intermediate **II** through ring opening process. The alkenylgold(I) moiety **II** attacked the carbonyl carbon to lead to carbenegold(I) **III** with the generation of oxabicyclo[3.3.0]octane system, followed by the migration of cyclopropene sp^2 carbon onto the α-carbon of Au(I) to result in tricyclic oxocarbenium ion **IV**, along with the ring expansion. Finally, the intermediate **IV** was hydrolyzed in the presence of residuary water in the solvent to furnish the desired product.

A formal anti-Markovnikov hydration of nonactivated terminal olefins by the use of a triple relay catalysis system was achieved by Grubbs and coworkers



Scheme 1.52 Rh(II)-catalyzed tandem reactions for the syntheses of dihydroisobenzofurans and indanones.

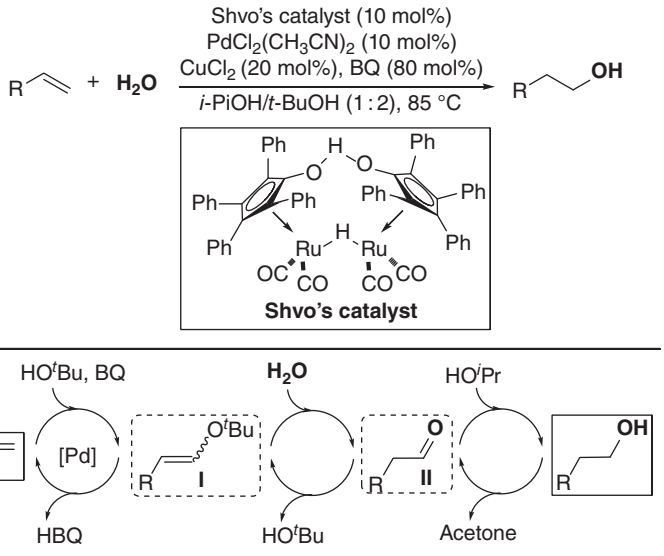


Scheme 1.53 Gold(I)-catalyzed ring-expanding spiroannulation of cyclopropenones with enynes.

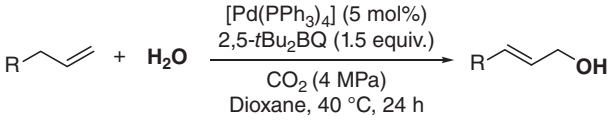
(Scheme 1.54) [70]. The reaction proceeded through a palladium-catalyzed oxidation, acid-catalyzed hydrolysis, and ruthenium-catalyzed reduction sequence. According to the Markovnikov's rule, the proton located at the less substituted carbon of alkenes, so the precise control of the anti-Markovnikov selectivity of the reaction constituted a big challenge. To overcome this obstacle, the solvent effect and chloride-ligand factor were taken into consideration to investigate the regioselectivity. The *i*-PrOH and Shvo's catalyst were chosen as a useful combination for the reduction cycle. $CuCl_2$ and BQ were applied as co-oxidant to exert a crucial influence on the reaction. It was to be expected that removal of water from the reaction failed to enable the formation of oxygenated product.

The proposed reaction pathway involving a triple relay catalysis is shown in Scheme 1.54. Initially, the *tert*-butyl ether **I** was generated from Pd-catalyzed oxidation of olefin, where the linear vinyl ether was preferentially formed due to the bulkiness of *t*-BuOH with the release of hydroquinone. The key step was responsible for the anti-Markovnikov selectivity of the reaction. Subsequently, upon acid-catalyzed hydrolysis with water, ether **I** could be transformed into aldehyde **II**, which underwent Ru-catalyzed transfer-hydrogenation to give the final primary alcohol product.

A homogeneous Pd-catalyzed rapid transformation of terminal alkenes into primary allylic alcohols was realized by Tokunaga and coworkers (Scheme 1.55) [71]. The CO_2 pressure was necessary for the high reactivity due to the *in situ*



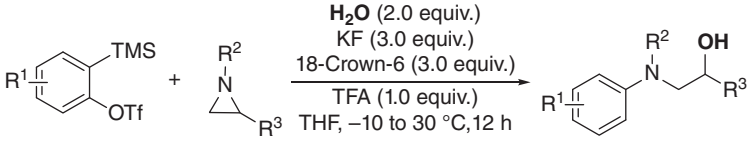
Scheme 1.54 Anti-Markovnikov hydration of alkenes via triple relay catalysis.



Scheme 1.55 Pd-catalyzed transformation of terminal alkenes into primary allylic alcohols.

formation of H_2CO_3 with H_2O. $[Pd(PPh_3)_4]$ was the best catalyst and the specific structure of BQ could affect the yield and selectivity of the reaction. In the catalytic cycle, BQ could stabilize the Pd^0 intermediate and enhance the reactivity of H_2CO_3. A possible mechanism involved the addition of oxygen nucleophile such as $^-HCO_3$ at the less-hindered terminal position of π-allyl Pd intermediate.

Later on, Biju and coworkers demonstrated a TFA-promoted three-component coupling reaction of aziridines, arynes, and water for the construction of an array of pharmaceutically relevant *N*-aryl β-amino alcohols (Scheme 1.56) [72]. Compared with the previous work of benzamide synthesis, the additional TFA was identified as the efficient additive to enhance the yield of product. The mechanistic investigations provided the evidence that the alcohol oxygen was derived from TFA or H_2O in light of different pathways. The reaction scope was broad and a variety of differently substituted arynes and aziridines could smoothly undergo the coupling reaction under the present reaction conditions, except for aziridines

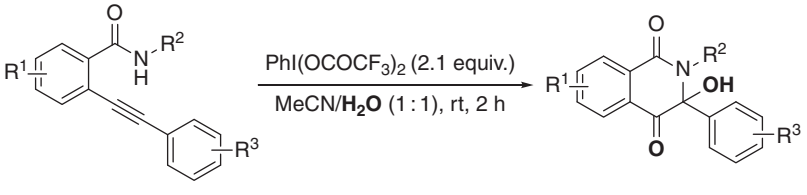


Scheme 1.56 Synthesis of *N*-aryl β-amino alcohols from aziridines, arynes, and water.

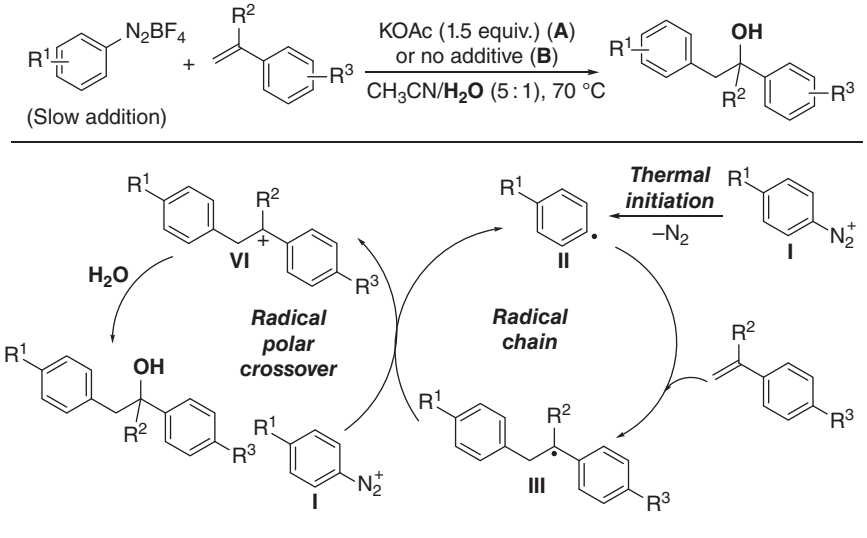
derived from sulfonamides. The nucleophilic attack of H_2O into aziridine leading to ring opening and the subsequent N-arylation with aryne could enable the formation of desired product.

A $PhI(OCOCF_3)_2$-mediated intramolecular cyclization of *o*-(1-alkynyl) benzamides for the metal-free synthesis of 3-hydroxy-2,3-dihydroisoquinoline-1,4-diones was disclosed by Du, Zhao, and coworkers (Scheme 1.57) [73]. The screening of reaction conditions suggested that the source of the oxygen and hydroxyl group in the product came from the residual water in the untreated acetonitrile, because the pure, dried acetonitrile resulted in only trace of the desired product. Therefore, a mixture of acetonitrile and water was applied as the optimal solvent. The possible reaction pathway involved PIFA-promoted intramolecular cyclization to deliver the cationic intermediate, which was trapped by water. The resulting compound could be oxidized by PIFA to access to iminium salt intermediate, followed by the nucleophilic attack of water to furnish the final product. Consequently, the involvement of water in the reaction was inevitable.

The thermally induced radical carbohydroxylation of styrenes with aryldiazonium salts under mild conditions for the construction of a variety of alcohols was developed by Heinrich and coworkers (Scheme 1.58) [74]. Upon the optimization



Scheme 1.57 $PhI(OCOCF_3)_2$-mediated cyclization of *o*-(1-alkynyl)benzamides.



Scheme 1.58 Carbohydroxylation of styrenes with aryldiazonium salts.

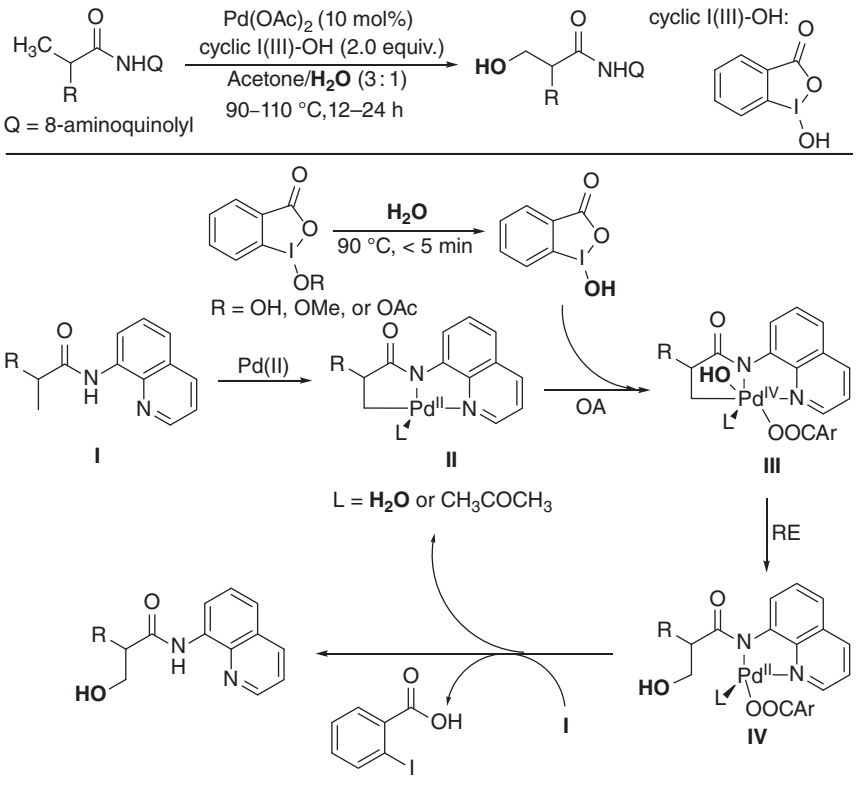
of reaction conditions, a suitable weak base such as potassium acetate could efficiently promote the reaction. Alternatively, the reaction was also initiated by simple heating in the absence of base to provide the desired product in high yields. The observation data demonstrated that a certain amount of free diazonium ions were essential for the reaction. Under the optimized conditions, the carbohydroxylation of styrenes performed smoothly and structurally diverse alcohols were furnished. In addition, carboetherification and lactonization possibly occurred with regard to different solvents and substrates.

It is noteworthy that the radical-polar crossover step was possibly involved in the reaction mechanism. Upon thermal initiation, the aryl radical **II** was generated from diazonium ion **I**, which could undergo addition to alkenes to give intermediate **III**. Under the oxidation of diazonium ion, the radical **I** was converted into cation **VI**, followed by the nucleophilic attack by H_2O to the desired alcohol products. In this Meerwein arylation reaction, the diazonium ion acted as an oxidant to propagate the radical chain and promote the radical-polar crossover step. Water was readily trapped by cation **VI** and was the source of hydroxyl group in the obtained alcohols. Therefore, the stability of cation **VI** was vital for the reaction, so the substituents with comparable stabilization effect could improve the yield of the final product.

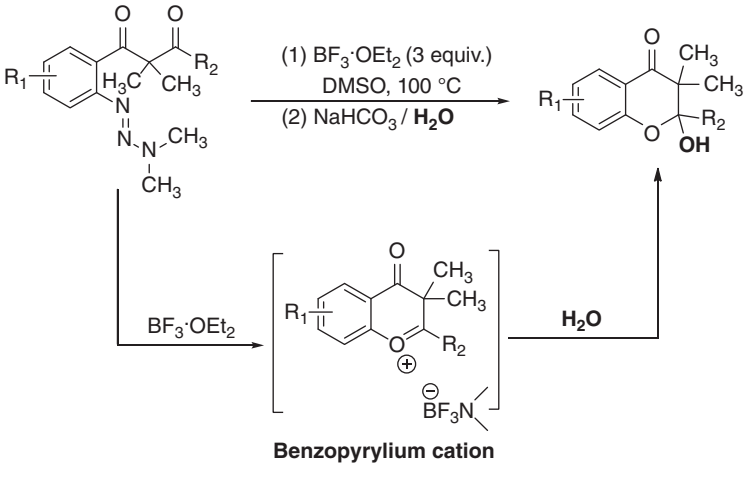
A palladium-catalyzed hydroxylation of unactivated aliphatic C(sp^3)—H bonds using water as the oxygen source was developed by Rao, Chen, and coworkers (Scheme 1.59) [75]. Compared to the Pd(II)/(0) catalytic cycle, Pd(II)/(IV) pathway was considered to be involved in the hydroxylation reaction due to their strong eletrophilicity and less sensibility to water. A variety of oxidants were tested in the reaction, and Dess–Martin Periodinane (DMP) could give a relatively lower yield, illustrating *in situ* generated hypervalent iodine (I^{3+}) reagent presumably functioned as the true oxidant. Hence, three readily available cyclic I^{3+} reagents were examined and acceptable yields of the hydroxylated products were obtained. The mechanistic study involving the use of H_2O^{18} evidently implied the oxygen atom in the hydroxyl group came from water.

On the basis of the data of experimental and computational studies, the plausible mechanism is outlined in Scheme 1.61. A bicyclic five-membered cyclopalladated intermediate **II** was formed by palladium-catalyzed AQ-directed C(sp^3)—H activation, followed by the oxidative addition through a ligand exchanged cyclic I^{3+} reagent to give the Pd(IV) complex **III**. The reductive elimination could afford the Pd(II) coordinated hydroxylated product, which reacted with another substrate **I** to deliver the desired product. It is worth mentioning that the obtained hydroxylated products could be readily transformed into diverse valuable derivatives.

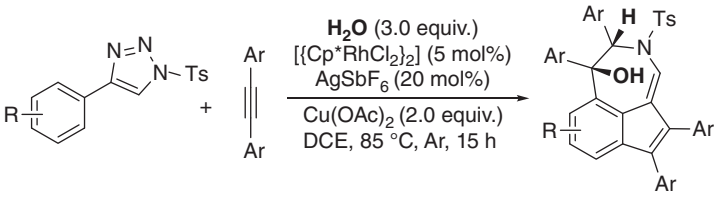
2-Hydroxyflavanones are a class of important but extremely rare natural product skeletons and only a few synthetic approaches were known for the synthesis of these bioactive compounds. The Lewis acid $BF_3{\cdot}OEt_2$-promoted annulation reaction of triazene diketones for the preparation of structurally special 2-hydroxyflavanones was disclosed by Ren and coworkers (Scheme 1.60) [76]. It was believed that the reaction involved a tandem *O*-arylation/hydroxylation reaction sequence to furnish a series of 2-hydroxyflavanone products in moderate to excellent yields.



Scheme 1.59 Palladium-catalyzed C(sp^3)–H hydroxylation with H_2O as the oxygen source.



Scheme 1.60 Synthesis of functionalized 2-hydroxyflavanone derivatives.



Scheme 1.61 Rh(III)-catalyzed [3+2]/[5+2] annulation of 4-aryl 1,2,3-triazoles with internal alkynes.

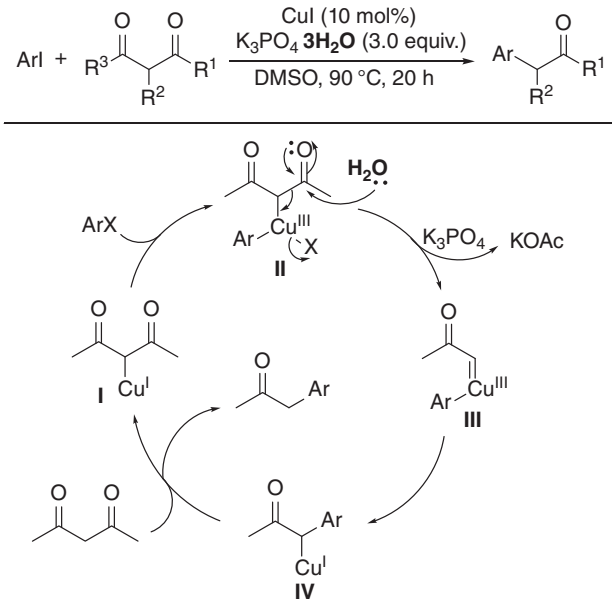
The reaction was supposed to start with the formation of aryl cation with the assistance of $BF_3 \cdot OEt_2$, followed by the nucleophilic attack of the carbonyl oxygen to the aryl cation to generate the key benzopyrylium cation complex, which was regarded as basic units of flavonoid pigments found in tissues of plants and flowers. Finally, the trapping of benzopyrylium cation by nucleophilic H_2O afforded the 2-hydroxyflavanone product. It was intriguing that the carbonyl group was first applied as nucleophile in this reaction, which was distinct from common nucleophiles, such as hydroxyl, amino, and ester groups.

Azepine derivatives are important seven-membered structural motifs with various biological and medicinal properties. Li and coworkers demonstrated a Rh(III)-catalyzed [3+2]/[5+2] annulation of 4-aryl 1-tosyl-1,2,3-triazoles with internal alkynes for the efficient synthesis of indeno[1,7-cd]azepine compounds (Scheme 1.61) [77]. It was well known that 1-sulfonyl-1,2,3-triazoles were favorable precursors of Rh^{II} azavinyl carbenes and were frequently applied to construct numerous nitrogen-containing heterocycles with suitable coupling partners. Extensive screening of the conditions revealed that a combination of $[\{Cp^*RhCl_2\}_2]$, $AgSbF_6$, and $Cu(OAc)_2$ was necessary for high efficiency of the reaction. In this transformation, the external water was the source of hydroxyl group and tertiary hydrogen. Other nucleophiles including alcohols could also participate in the annulation reaction, albeit with less reactivity.

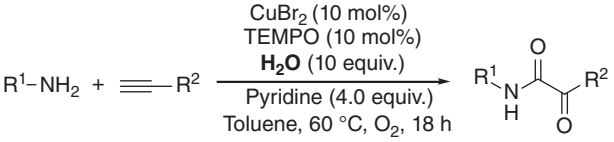
1.5 Traceless Promotion of the Reactions by Water

A copper-catalyzed arylation/C—C bond activation process using $K_3PO_4 \cdot 3H_2O$ as the base without any ligands for the efficient preparation of α-aryl ketones was achieved by Lei and coworkers (Scheme 1.62) [78]. The screening of reaction parameters suggested Cu(I) and Cu(II) salts showed similar catalytic effects. The substrate scope of the reaction was relatively broad as illustrated that an array of aryl halides and β-diketones were smoothly compatible with the reaction to deliver desired α-aryl diketone products in moderate to good yields. It was speculated that the presence of H_2O could assist the C—C activation process.

Control experimentation implied that the radical pathway was not involved in the C—C bond activation reaction. A putative mechanism is depicted in Scheme 1.62. The Cu(III) intermediate **II** was formed by the oxidative addition of ArX into Cu(I) complex **I**. Subsequently, with the assistance of H_2O, the C—C bond activation/cleavage occurred to generate intermediate **III** with the release



Scheme 1.62 Copper-catalyzed arylation/C—C bond activation to access to α-aryl ketones.

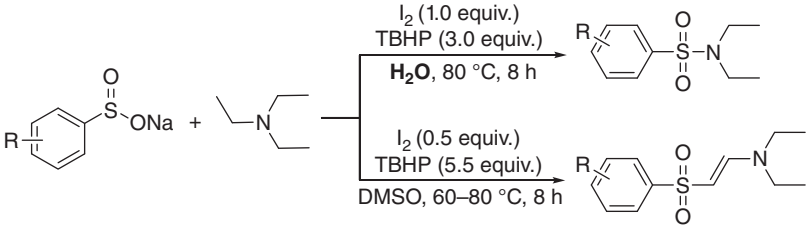


Scheme 1.63 Cu-catalyzed oxidative amidation–diketonization of terminal alkynes.

of KOAc. The following reductive elimination of intermediate **III** could produce the final product.

A Cu-catalyzed oxidative amidation–diketonization reaction of terminal alkynes via dioxygen activation leading to α-ketoamides was disclosed by Jiao and coworkers (Scheme 1.63) [79]. In this protocol, O_2 was considered as oxidant and reactant to participate in the reaction. The reaction was supposed to perform through a radical process during the dioxygen activation process, providing valuable mechanistic insights for the Cu-catalyzed oxidative coupling reactions. During the screening of the reaction conditions, it was found that the addition of excess H_2O could remarkably improve the chemical yields of the reaction, although the exact mechanism was unknown. The ^{18}O-labeled experiments suggested that both oxygen atoms of the α-ketoamide came from O_2 instead of H_2O.

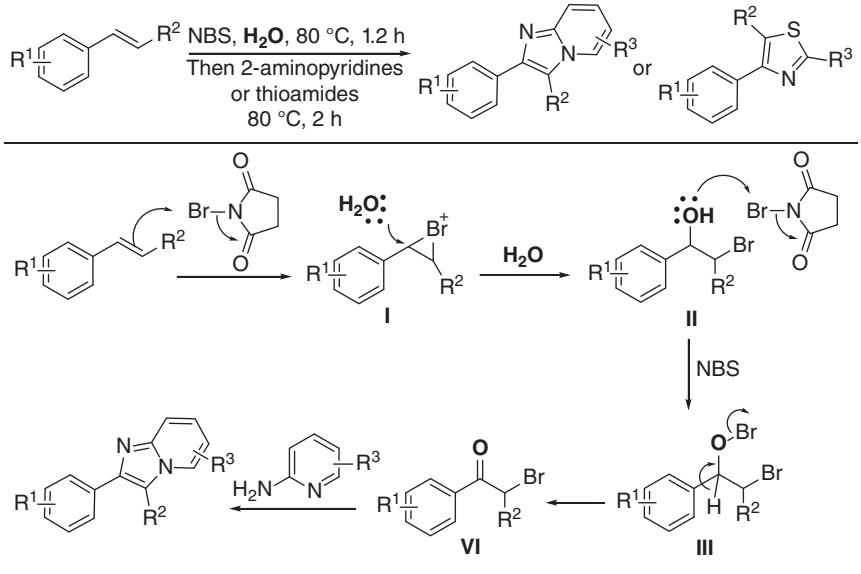
Yuan and coworkers demonstrated an I_2/TBHP-mediated coupling reaction of sodium sulfinate salts with tertiary amines for the synthesis of sulfonamides and β-arylsulfonyl enamines (Scheme 1.64) [80]. The reaction proceeded through C—N and C—H bond cleavage of tertiary amines to selective construction of two different products based on the reaction solvents. When the reaction took place



Scheme 1.64 I_2/TBHP-mediated synthesis of sulfonamides and β-arylsulfonyl enamines.

in H_2O, the H_2O could participate in the reaction to enable the C—N bond cleavage through hydrolysis of the formed imine intermediate, leading to an aldehyde and a secondary amine. Nevertheless, the enamine intermediate would be generated in the DMSO solvent case. The sulfonyl radical reacted with secondary amine or enamine intermediate to provide sulfonamide and β-arylsulfonyl enamine product, respectively.

A NBS-promoted one-pot method for the assembly of important heterocyclic scaffolds imidazopyridines or thiazoles from styrenes with 2-aminopyridines or thioamides in water was disclosed by Kshirsagar and coworkers (Scheme 1.65) [81]. In the reaction, water was not only acted as ideal solvent but also as the oxygen source for the *in situ* generation of α-bromoketones. NBS also had the dual role of being a good bromine source and oxidant. The mixed solvent system combined H_2O with other solvents (i.e. dioxane, CH_3CN, or acetone) inhibited the reaction and only H_2O as single solvent could be the best choice. Using the reaction system, various imidazo[1,2-*a*]pyridines and thiazoles were synthesized in



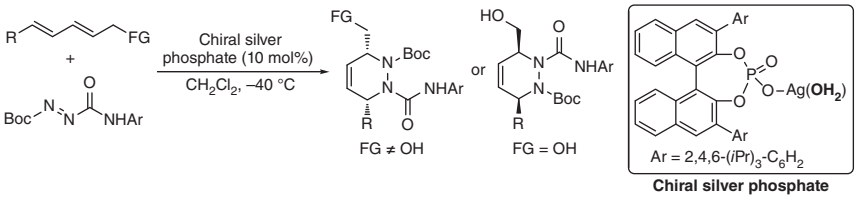
Scheme 1.65 Synthesis of substituted imidazopyridines and thiazoles from styrenes in water.

good to excellent yields by the employment of 2-aminopyridines and thioamides as the nucleophilic partners, respectively.

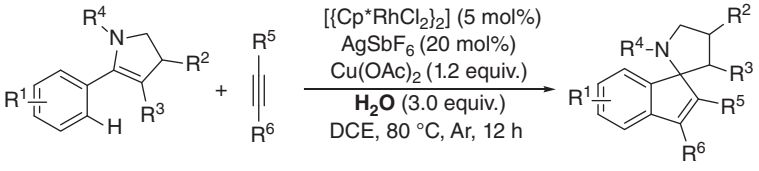
The plausible reaction pathway is shown in Scheme 1.65. The styrenes reacted with NBS to form the cyclobrominium ion **I**, which was attacked by nucleophilic H_2O to afford bromohydrin **II**. The NBS promoted oxidation of alcohol for the formation of α-bromoketone **VI**, followed by condensation with 2-aminopyridines or thioamides to lead to the corresponding heterocyclic products. The key step of the reaction lay in the conversion of styrene into phenacyl bromide mediated by NBS/H_2O system.

A chiral silver-phosphate-catalyzed asymmetric azo-HDA reaction of diazene derivatives for the highly enantioselective synthesis of piperazines was achieved by Gong, Luo, and coworkers (Scheme 1.66) [82]. Notably, in this reaction, the hydroxy group of dienes could control the regioselectivity through formation of a hydrogen bond with the oxygen of phosphate and coordination to the Ag(I) to stabilize the transition states. It was suggested that trace amounts of water in the solvent could promote the Lewis-acid-catalyzed reactions [83]. Therefore, the residual water molecule in the chiral catalyst participated in the catalysis process by coordination to silver phosphate and exerted a crucial role in the stereocontrol of the reaction, which were verified by DFT calculations.

A rhodium(III)-catalyzed [3+2] oxidative annulation of 5-aryl-2,3-dihydro-1*H*-pyrroles with internal alkynes for the regioselective synthesis of spiro[indene-1,2′-pyrrolidines] (Scheme 1.67) [84]. The reaction was assumed to involve C(sp^2)—H functionalization, the insertion of internal alkyne, and addition/protonolysis of an alkene C=C bond sequence. It should be noted that the presence of H_2O could improve the reaction yield, even though the exact role of H_2O in the reaction was elusive. Without additional H_2O enabled a longer time to complete the reaction with slightly lower reactivity. Under the



Scheme 1.66 Asymmetric hetero-Diels–Alder reaction of diazenes catalyzed by chiral silver phosphate.

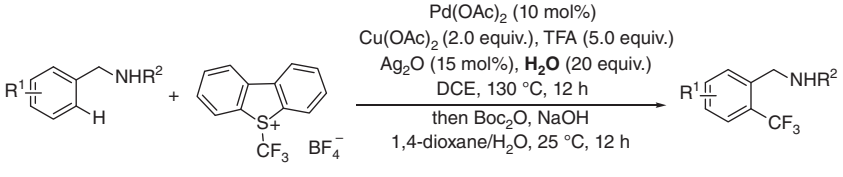


Scheme 1.67 Rh (III)-catalyzed [3+2] annulation of 5-aryl-2,3-dihydro-1*H*-pyrroles with internal alkynes.

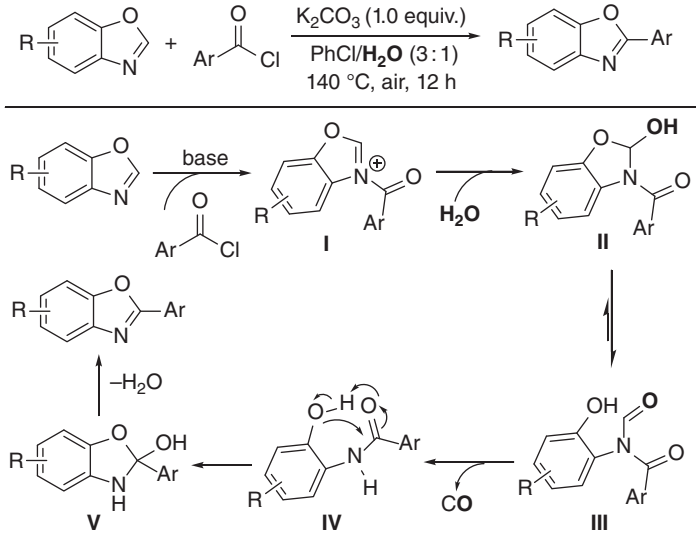
optimized conditions, a wide variety of spiro[indene-1,2′-pyrrolidine] rings were constructed with high efficiency and excellent functional-group tolerance.

A palladium-catalyzed *ortho*-trifluoromethylation of benzylamines using an electrophilic CF_3 reagent (Umemoto's trifluoromethylation reagent) was achieved by Yu and coworkers (Scheme 1.68) [85]. Other electrophilic trifluoromethylation reagents were evaluated in the reaction and inferior effect was observed. The necessity of Boc-protected benzylamine was illustrated by the fact that the excess amount of Cu salts might be coordinated with the free amine of the product, leading to the complicated products and lower yields. H_2O was identified as crucial additive since the additional water could improve the reaction yield, albeit the exact reason was elusive. The reaction provided a versatile approach for the preparation of diverse *ortho*-trifluoromethyl-substituted benzylamines.

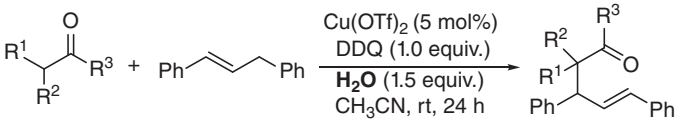
A K_2CO_3-promoted arylation of benzo[*d*]oxazoles by using acyl chloride as aryl source with the release of one molecule of CO was achieved by Cheng and coworkers (Scheme 1.69) [86]. The cosolvent H_2O had an obvious influence on the reaction's efficiency. The reaction pathway possibly underwent ring opening and closure sequence. The base mediated N-acylation of benzooxazole occurred by the reaction of benzoxazole and acyl chloride to form iminium species **I**. The



Scheme 1.68 Pd(II)-catalyzed *ortho*-trifluoromethylation of benzylamines.



Scheme 1.69 Base-promoted formal arylation of benzo[*d*]oxazoles with acyl chloride.



Scheme 1.70 Cu(II)-catalyzed CDC reaction between allylic C—H bonds and α-C—H bonds of ketones or aldehydes.

nucleophilic attack of H_2O into the iminium **I** led to the hemiacetal intermediate **II**, which could convert into intermediate **III** via the equilibrium reaction between aldehyde and hemiacetal. Subsequently, the intermediate **IV** was formed by the decarbonylation of intermediate **III**. Finally, the cyclization of intermediate **IV** and the following dehydration process provided the arylation product.

A $Cu(OTf)_2$-catalyzed dehydrogenative cross-coupling reaction of 1,3-diphenylpropene with ketones or aldehydes with DDQ as radical oxidant was developed by Huang and coworkers (Scheme 1.70) [87]. Compared with active methylene compounds, ketones or aldehydes were regarded as less reactive carbon nucleophiles. $Cu(OTf)_2$ was applied as useful Lewis acid catalyst to promote the allylic C—H alkylation, providing a facile approach to γ,δ-unsaturated ketones and aldehydes in good yields under mild conditions. It was indicated that water could promote Lewis-acid-catalyzed reactions [88], as illustrated that the addition of 1.5 equiv. of H_2O dramatically improved the yield of product. The CDC reaction possibly proceeded through a stable enol intermediate, which was generated from $Cu(OTf)_2$ promoted enolization of ketone.

1.6 Conclusions

In recent years, water, as one of the most inexpensive and environmentally benign solvents, has been extensively investigated as a versatile reagent for the rapid introduction of hydrogen atom, oxygen atom, or hydroxyl group into the target product. Furthermore, water is frequently applied as useful promoter to facilitate the reaction without a trace. Despite the tremendous accomplishments that have been achieved in this arena, this research area will remain huge space to investigate for many years. In particular, a series of new types of reaction should be designed and exploited by the utilization of water as suitable partner. It will be significant that more attention should be focused on the practical application of the transformations involving water in the future.

References

1 (a) Li, C.-J. (2005) *Chem. Rev.*, **105**, 3095–3166; (b) Li, C.-J. and Chen, L. (2006) *Chem. Soc. Rev.*, **35**, 68–82; (c) Li, C.-J. and Chan, T.-H. (2007) Comprehensive Organic Reactions in Aqueous Media, Wiley, New York;

(d) Lindström, U.M. (2007) Organic Reactions in Water: Principles, Strategies and Applications, Blackwell, Oxford, UK; (e) Chanda, A. and Fokin, V.V. (2009) *Chem. Rev.*, **109**, 725–748; (f) Butler, R.N. and Coyne, A.G. (2010) *Chem. Rev.*, **110**, 6302–6337; (g) Simon, M.-O. and Li, C.-J. (2012) *Chem. Soc. Rev.*, **41**, 1415–1427.

2 (a) Brogan, A.P., Dickerson, T.J., and Janda, K.D. (2006) *Angew. Chem.*, **118**, 8278–8280; *Angew. Chem. Int. Ed.* **2006**, 45, 8100–8102; (b) Hayashi, Y. (2006) *Angew. Chem. Int. Ed.*, **45**, 8103–8104; (c) Narayan, S., Muldoon, J., Finn, M.G., Fokin, V.V., Kolb, H.C., and Sharpless, K.B. (2005) *Angew. Chem. Int. Ed.*, **44**, 3275–3279; (d) Klijn, J.E. and Engberts, J.B.F.N. (2005) *Nature*, **435**, 746–747.

3 Roesner, S., Casatejada, J.M., Elford, T.G., Sonawane, R.P., and Aggarwal, V.K. (2011) *Org. Lett.*, **13**, 5740–5743.

4 Nave, S., Sonawane, R.P., Elford, T.G., and Aggarwal, V.K. (2010) *J. Am. Chem. Soc.*, **132**, 17096–17098.

5 Yang, Y., Tang, L., Zhang, S., Guo, X., Zha, Z., and Wang, Z. (2014) *Green Chem.*, **16**, 4106–4109.

6 Liu, Z., Liu, J., Zhang, L., Liao, P., Song, J., and Bi, X. (2014) *Angew. Chem. Int. Ed.*, **53**, 5305–5309.

7 Liu, Z., Liao, P., and Bi, X. (2014) *Org. Lett.*, **16**, 3668–3671.

8 Ning, Y., Wu, N., Yu, H., Liao, P., Li, X., and Bi, X. (2015) *Org. Lett.*, **17**, 2198–2201.

9 Taylor, S.D. and Lohani, C.R. (2016) *Org. Lett.*, **18**, 4412–4415.

10 (a) Staudinger, H. and Meyer, J. (1919) *Helv. Chim. Acta*, **2**, 635–646; (b) Staudinger, H. and Hauser, E. (1921) *Helv. Chim. Acta*, **4**, 861–886.

11 Saneyoshi, H., Ochikubo, T., Mashimo, T., Hatano, K., Ito, Y., and Abe, H. (2014) *Org. Lett.*, **16**, 30–33.

12 Lin, Q.-Y., Xu, X.-H., Zhang, K., and Qing, F.-L. (2016) *Angew. Chem. Int. Ed.*, **55**, 1479–1483.

13 Cheng, G. and Hu, Y. (2008) *J. Org. Chem.*, **73**, 4732–4735.

14 Miao, M., Cao, J., Huang, X., and Wu, L. (2013) *J. Org. Chem.*, **78**, 5999–6007.

15 Xue, C., Huang, X., Wu, S., Zhou, J., Dai, J., Fu, C., and Ma, S. (2015) *Chem. Commun.*, **51**, 17112–17115.

16 Zeng, X., Miao, C., Wang, S., Xia, C., and Sun, W. (2013) *RSC Adv.*, **3**, 9666–9669.

17 Zhang, J., Wu, D., Chen, X., Liu, Y., and Xu, Z. (2014) *J. Org. Chem.*, **79**, 4799–4808.

18 Miura, T., Biyajima, T., Fujii, T., and Murakami, M. (2012) *J. Am. Chem. Soc.*, **134**, 194–196.

19 (a) Cho, S.H., Yoo, E.J., Bae, I., and Chang, S. (2005) *J. Am. Chem. Soc.*, **127**, 16046–16047; (b) Cassidy, M.P., Raushel, J., and Fokin, V.V. (2006) *Angew. Chem. Int. Ed.*, **45**, 3154–3157.

20 (a) Smidt, J., Hafner, W., Sedlmeier, J., Jira, R., and Rüttinger, R. (1959) *Angew. Chem.*, **71**, 176–182; (b) Jira, R. (2009) *Angew. Chem. Int. Ed.*, **48**, 9034–9037; (c) Tsuji, J., Nagashima, H., and Nemoto, H. (1984) *Org. Synth.*, **62**, 9; (d) Bäckvall, J.E., Åkermark, B., and Ljunggren, S.O. (1979) *J. Am. Chem. Soc.*, **101**, 2411–2416.

21 Teo, P., Wickens, Z.K., Dong, G., and Grubbs, R.H. (2012) *Org. Lett.*, **14**, 3237–3239.
22 Chen, H., Jiang, H., Cai, C., Dong, J., and Fu, W. (2011) *Org. Lett.*, **13**, 992–994.
23 Zhang, G., Hu, X., Chiang, C.-W., Yi, H., Pei, P., Singh, A.K., and Lei, A. (2016) *J. Am. Chem. Soc.*, **138**, 12037–12040.
24 Xia, Z. and Zhu, Q. (2013) *Org. Lett.*, **15**, 4110–4113.
25 Kaicharla, T., Thangaraj, M., and Biju, A.T. (2014) *Org. Lett.*, **16**, 1728–1731.
26 Rigby, J.H. and Laurent, S. (1998) *J. Org. Chem.*, **63**, 6742–6744.
27 Wan, J.-C., Huang, J.-M., Jhan, Y.-H., and Hsieh, J.-C. (2013) *Org. Lett.*, **15**, 2742–2745.
28 Reddy, M.C. and Jeganmohan, M. (2014) *Org. Lett.*, **16**, 4866–4869.
29 Sakthivel, K. and Srinivasan, K. (2014) *Org. Biomol. Chem.*, **12**, 6440–6446.
30 (a) Sydner, H.R. and Elston, C.T. (1954) *J. Am. Chem. Soc.*, **76**, 3039–3040; (b) Hauser, C.R. and Eby, C.J. (1957) *J. Am. Chem. Soc.*, **79**, 725–727; (c) Kornblum, N. and Singaram, S. (1979) *J. Org. Chem.*, **44**, 4727–4729.
31 (a) Kukushkin, V.Y. and Pombeiro, A.J.L. (2005) *Inorg. Chim. Acta*, **358**, 1–21; (b) Kukushkin, V.Y. and Pombeiro, A.J.L. (2002) *Chem. Rev.*, **102**, 1771–1802; (c) Ahmed, T.J., Knapp, S.M.M., and Tyler, D.R. (2011) *Coord. Chem. Rev.*, **255**, 949–974; (d) Kobayashi, M., Nagasawa, T., and Yamada, H. (1992) *Trends Biotechnol.*, **10**, 402–408; (e) Ghaffar, T. and Parkins, A.W. (1995) *Tetrahedron Lett.*, **36**, 8657–8660; (f) Murahashi, S.-I. and Takaya, H. (2000) *Acc. Chem. Res.*, **33**, 225–233; (g) Goto, A., Endo, K., and Saito, S. (2008) *Angew. Chem. Int. Ed.*, **47**, 3607–3609; (h) Ramón, R.S., Marion, N., and Nolan, S.P. (2009) *Chem. – Eur. J*, **15**, 8695–8697; (i) Crestani, M.G., Arévalo, A., and García, J.J. (2006) *Adv. Synth. Catal.*, **348**, 732–742; (j) Thallaj, N.K., Przybilla, J., Welter, R., and Mandon, D. (2008) *J. Am. Chem. Soc.*, **130**, 2414–2415; (k) Li, Z., Wang, L., and Zhou, X. (2012) *Adv. Synth. Catal.*, **354**, 584–588.
32 Xin, X., Xiang, D., Yang, J., Zhang, Q., Zhou, F., and Dong, D. (2013) *J. Org. Chem.*, **78**, 11956–11961.
33 Uetake, Y., Uwamori, M., and Nakada, M. (2015) *J. Org. Chem.*, **80**, 1735–1745.
34 Yang, D., Huang, B., Wei, W., Li, J., Lin, G., Liu, Y., Ding, J., Sun, P., and Wang, H. (2016) *Green Chem.* doi: 10.1039/c6gc01403h
35 Aruri, H., Singh, U., Kumar, S., Kushwaha, M., Gupta, A.P., Vishwakarma, R.A., and Singh, P.P. (2016) *Org. Lett.*, **18**, 3638–3641.
36 Guo, R., Zhang, Z., Shi, F., and Tang, P. (2016) *Org. Lett.*, **18**, 1008–1011.
37 Li, X., Che, X., Chen, G.-H., Zhang, J., Yan, J.-L., Zhang, Y.-F., Zhang, L.-S., Hsu, C.-P., Gao, Y.G., and Shi, Z.-J. (2016) *Org. Lett.*, **18**, 1234–1237.
38 Huang, R., Chang, X., Li, J., and Wang, C.-J. (2016) *J. Am. Chem. Soc.*, **138**, 3998–4001.
39 Chen, M., Peng, J., Mao, T., and Huang, J. (2014) *Org. Lett.*, **16**, 6286–6289.
40 Kucherov, M. (1881) *Chem. Ber.*, **14**, 1540–1542.
41 (a) Trost, B.M. (1991) *Science*, **254**, 1471–1477; (b) Hintermann, L. and Labonne, A. (2007) *Synthesis*, 1121–1150; (c) Casado, R., Contel, M., Laguna, M., Romero, P., and Sanz, S. (2003) *J. Am. Chem. Soc.*, **125**, 11925–11935; (d) Yang, D., Huang, J., and Liu, B. (2010) *Eur. J. Org. Chem.*, 4185–4188.

42 (a) Abu Sohel, S.M. and Liu, R.-S. (2009) *Chem. Soc. Rev.*, **38**, 2269–2281; (b) Trost, B.M., Brown, R.E., and Toste, F.D. (2000) *J. Am. Chem. Soc.*, **122**, 5877–5878; (c) Trost, B.M. and Rudd, M.T. (2005) *J. Am. Chem. Soc.*, **127**, 4763–4776; (d) Das, A., Chang, H.-K., Yang, C.-H., and Liu, R.-S. (2008) *Org. Lett.*, **10**, 4061–4064.

43 Marioon, N., Ramón, R.S., and Nolan, S.P. (2009) *J. Am. Chem. Soc.*, **131**, 448–449.

44 Ying, J. and Pu, L. (2016) *J. Org. Chem.*, **81**, 8135–8141.

45 (a) Fukuda, Y. and Utimoto, K. (1991) *J. Org. Chem.*, **56**, 3729–3731; (b) Wang, W., Xu, B., and Hammond, G.B. (2009) *J. Org. Chem.*, **74**, 1640–1643.

46 Mukherjee, A. and Liu, R.-S. (2011) *Org. Lett.*, **13**, 660–663.

47 Tang, X.-B., Song, R.-J., Wu, C.-Y., Wang, Z.-Q., Liu, Y., Huang, X.-C., Xie, Y.-X., and Li, J.-H. (2011) *Chem. Sci.*, **2**, 2131–2134.

48 Ling, F., Li, Z., Zheng, C., Liu, X., and Ma, C. (2014) *J. Am. Chem. Soc.*, **136**, 10914–10917.

49 Ling, F., Wan, Y., Wang, D., and Ma, C. (2016) *J. Org. Chem.*, **81**, 2770–2781.

50 Wang, Z.-Q., Zhang, W.-W., Gong, L.-B., Tang, R.-Y., Yang, X.-H., Liu, Y., and Li, J.-H. (2011) *Angew. Chem. Int. Ed.*, **50**, 8968–8973.

51 Tang, B.-X., Zhang, Y.-H., Song, R.-J., Tang, D.-J., Deng, G.-B., Wang, Z.-Q., Xie, Y.-X., Xia, Y.-Z., and Li, J.-H. (2012) *J. Org. Chem.*, **77**, 2837–2849.

52 Appel, T.R., Yehia, N.A.M., Baumeister, U., Hartung, H., Kluge, R., Ströhl, D., and Fanghänel, E. (2003) *Eur. J. Org. Chem.*, 47–53.

53 Deng, G.-B., Zhang, J.-L., Liu, Y.-Y., Liu, B., Yang, X.-H., and Li, J.-H. (2014) *Chem. Commun.*, **51**, 1886–1888.

54 Liu, Y., Zhang, J.-L., Song, R.-J., Qian, P.-C., and Li, J.-H. (2014) *Angew. Chem. Int. Ed.*, **53**, 9017–9020.

55 Gao, P., Li, H.-X., Hao, X.-H., Jin, D.-P., Chen, D.-Q., Yan, X.-B., Wu, X.-X., Song, X.-R., Liu, X.-Y., and Liang, Y.-M. (2014) *Org. Lett.*, **16**, 6298–6301.

56 Yang, X.-H., Ouyang, X.-H., Wei, W.-T., Song, R.-J., and Li, J.-H. (2015) *Adv. Synth. Catal.*, **357**, 1161–1166.

57 Hu, M., Liu, B., Ouyang, X.-H., Song, R.-J., and Li, J.-H. (2015) *Adv. Synth. Catal.*, **357**, 3332–3340.

58 Yang, X.-H., Song, R.-J., and Li, J.-H. (2015) *Adv. Synth. Catal.*, **357**, 3849–3856.

59 Liu, B., Song, R.-J., Ouyang, X.-H., Li, Y., Hu, M., and Li, J.-H. (2015) *Chem. Commun.*, **51**, 12819–12822.

60 Li, D.Y., Chen, H.J., and Liu, P.N. (2016) *Angew. Chem. Int. Ed.*, **55**, 373–377.

61 Guo, Z., Shi, T., Jiang, J., Yang, L., and Hu, W. (2009) *Org. Biomol. Chem.*, **7**, 5028–5033.

62 (a) Guo, X., Huang, H., Yang, L., and Hu, W. (2007) *Org. Lett.*, **9**, 4721–4723; (b) Zhu, S.-F., Chen, C., Cai, Y., and Zhou, Q.-L. (2008) *Angew. Chem. Int. Ed.*, **47**, 932–934.

63 Mukerjee, P., Abid, M., and Schroeder, F.C. (2010) *Org. Lett.*, **12**, 3986–3989.

64 Lin, R., Ding, S., Shi, Z., and Jiao, N. (2011) *Org. Lett.*, **13**, 4498–4501.

65 (a) Ma, S., Wei, Q., and Wang, H. (2000) *Org. Lett.*, **2**, 3893–3895; (b) Ma, S., Ren, H., and Wei, Q. (2003) *J. Am. Chem. Soc.*, **125**, 4817–4830; (c) Guo, H., Qian, R., Guo, Y., and Ma, S. (2008) *J. Org. Chem.*, **73**, 7934–7938.

66 Su, C., Cao, J., Huang, X., Wu, L., and Huang, X. (2011) *Chem. – Eur. J.*, **17**, 1579–1585.

67 Mohite, A.R. and Bhat, R.G. (2013) *Org. Lett.*, **15**, 4564–4567.

68 Shen, H., Fu, J., Gong, J., and Yang, Z. (2014) *Org. Lett.*, **16**, 5588–5591.

69 Matsuda, T. and Sakurai, Y. (2014) *J. Org. Chem.*, **79**, 2739–2745.

70 Dong, G., Teo, P., Wickens, Z.K., and Grubbs, R.H. (2011) *Science*, **333**, 1609–1612.

71 Tomita, R., Mantani, K., Hamasaki, A., Ishida, T., and Tokunaga, M. (2014) *Chem. – Eur. J.*, **20**, 9914–9917.

72 Roy, T., Baviskar, D.R., and Biju, A.T. (2015) *J. Org. Chem.*, **80**, 11131–11137.

73 Yang, C., Zhang, X., Zhang-Negrerie, D., Du, Y., and Zhao, K. (2015) *J. Org. Chem.*, **80**, 5320–5328.

74 Kindt, S., Wicht, K., and Heinrich, M.R. (2016) *Angew. Chem. Int. Ed.*, **55**, 8744–8747.

75 Hu, J., Lan, T., Sun, Y., Chen, H., Yao, J., and Rao, Y. (2015) *Chem. Commun.*, **51**, 14929–14932.

76 Chen, Z., Yang, W., Xu, L., Zhang, L., Miao, M., and Ren, H. (2013) *Eur. J. Org. Chem.*, 7411–7420.

77 Yang, Y., Zhou, M.-B., Ouyang, X.-H., Pi, R., Song, R.-J., and Li, J.-H. (2015) *Angew. Chem. Int. Ed.*, **54**, 6595–6599.

78 He, C., Guo, S., Huang, L., and Lei, A. (2010) *J. Am. Chem. Soc.*, **132**, 8273–8275.

79 Zhang, C. and Jiao, N. (2010) *J. Am. Chem. Soc.*, **132**, 28–29.

80 Lai, J., Chang, L., and Yuan, G. (2016) *Org. Lett.*, **18**, 3194–3197.

81 Shinde, M.H. and Kshirsagar, U.A. (2016) *Green Chem.*, **18**, 1455–1458.

82 Liu, B., Liu, T.-Y., Luo, S.-W., and Gong, L.-Z. (2014) *Org. Lett.*, **16**, 6164–6167.

83 Hollis, T.K. and Bosnich, B. (1995) *J. Am. Chem. Soc.*, **117**, 4570–4581.

84 Zhou, M.-B., Pi, R., Hu, M., Yang, Y., Song, R.-J., Xia, Y., and Li, J.-H. (2014) *Angew. Chem. Int. Ed.*, **53**, 11338–11341.

85 Miura, M., Feng, C.-G., Ma, S., and Yu, J.-Q. (2013) *Org. Lett.*, **15**, 5258–5261.

86 Wang, L., Ren, X., Yu, J., Jiang, Y., and Cheng, J. (2013) *J. Org. Chem.*, **78**, 12076–12081.

87 Huang, X.-F., Salman, M., and Huang, Z.-Z. (2014) *Chem. – Eur. J.*, **20**, 6618–6621.

88 (a) Kobayashi, S. and Manabe, K. (2002) *Acc. Chem. Res.*, **35**, 209–217; (b) Manabe, K. and Kobayashi, S. (2002) *Chem. – Eur. J.*, **8**, 4094–4101.