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Catalyzed Reactions of Alkynes in Water

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Abstract: This review summarizes the catalytic organic reactions of alkynes in aqueous media. The aqueous version of the alkyne reactions gives new reactivities, is environmentally friendly, and has broard applications in all areas of chemistry and materials science.

Keywords: catalytic; cyclization; green chemistry; terminal alkynes; triple bonds; water

1 Introduction

Over the last decade, growing interest has been devoted to the use of water as a solvent for organic reactions. It is reflected by the fact that papers and reviews[1–23] on this topic have been published at an increasing rate since 1993 when the first comprehensive review on this topic was published.[24] A recent significant development in this area is the development of unique reactivities of organic compounds "on-water" by Sharpless and co-workers.[25] The strong interest in water as a solvent is partially attributed to developments in "green" chemistry. In addition, water has offered many other advantages. Hydrophobic effects enable water to increase rates and sometimes enhance reaction selectivities. The low solubility of oxygen gas in water can facilitate air-sensitive catalytic organic reactions. Furthermore, since enzymatic processes in nature must occur in an aqueous environment, the development of organic reactions in water may be helpful to understand chemistry in living systems and may have potential applications in biotechnologies.

The reaction behavior of alkynes is one of the most interesting and useful subjects in organic chemistry due to its wide applications in all areas of chemistry and materials science. In the last ten years, the growing interest on this subject has become even more pronounced.[26–32] Reactions of alkynes have been mainly carried out in organic solvents, possibly due to the concerns of a competing hydration reaction of alkynes in water. However, the potential use of water as a solvent for reactions of alkynes has not escaped the attention of chemists. Over the last several years, increasing numbers of reactions of alkynes in water have been reported. Those reactions in water have been shown to be similar to or even more efficient than those reactions in organic solvents. This article is the first general review to summarize the reactions of alkynes in water.

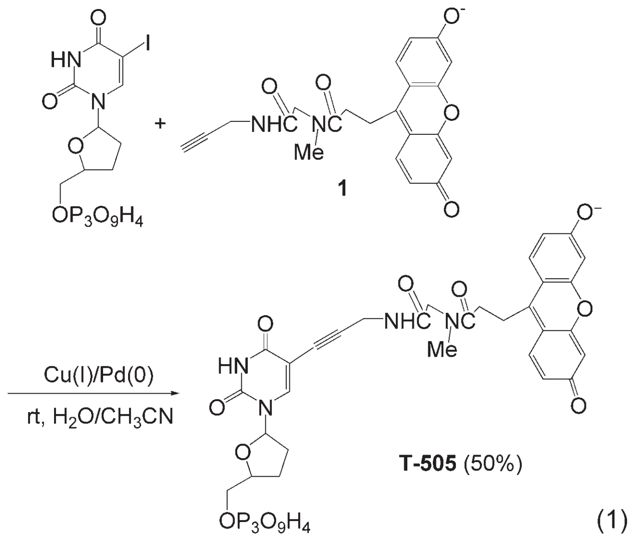
Liang Chen was born in 1977 in Fujian, China. He received his Bachelor degree from Nanjing University, China. Thereafter, he spent two years in working with Professor Xiao-rong Wang at the State Key Laboratory of Pollution Control & Resource Reuse in Nanjing, China. In 2005, he obtained his PhD under the supervision of Professor C.-J. Li at Tulane University, New Orleans, for the development of catalytic reactions of *sp*-C–H bonds in water. Currently, he is working with Professor Xu in the School of Dentistry at Louisiana State University Health Sciences Center, New Orleans, for the development of novel dental materials.

Chao-Jun Li (born in 1963) received his BSc at Zhengzhou University (1983), MS at the Chinese Academy of Sciences in Beijing (1988) and Ph.D. at McGill University (1992, under the direction of T. H. Chan and D. N. Harpp). He spent 1992–1994 as a NSERC Postdoctoral Fellow in Barry M. Trost's laboratory at Stanford University (US), and became an Assistant Professor at Tulane University (US) in 1994. He was promoted to Associate Professor with tenure in 1998 and Full Professor in 2000. In 2003, he became a Canada Research Chair (Tier I) in Green Chemistry and a Professor of Chemistry at McGill University in Canada. While at Tulane University, Li received a (US) NSF Career Award (1997), the 2001 (US) Presidential Green Chemistry Challenge Award (academic category), a Faculty Research Award by the Faculty of Arts and Sciences at Tulane (2002), and was named as an Innovator Award by the Business Association of New Orleans (2002). He was an Eli Lilly Teaching Fellow in 1995 and a Japan Society for the Promotion of Science (Senior) Fellow in 2002. He was a visiting professor (with Robert G. Bergman) at University of California at Berkeley (2002). Li is currently the Associate Editor for Americas for the journal *Green Chemistry* (since 2005), an International Advisory Board Member of *Chemistry World* (since 2005), a consulting editor for McGraw-Hill's *Encyclopedia of Sciences and Technologies* (since 2002) and McGraw-Hill's *Year Book of Sciences and Technologies* (since 2002), and is on the Editorial Advisory Boards of *Letters in Organic Chemistry* (since 2004) and *Mini Reviews in Organic Chemistry* (since 2004). He serves as the Coordinator of the Canadian Green Chemistry Network (since 2005). His current research efforts are to develop green chemistry for organic synthesis based upon innovative and fundamentally new organic reactions that will defy conventional reactivities and possess high "atom-efficiency". He has published over 190 original research papers and reviews and authored (together with T. H. Chan) a book "*Organic Reactions in Aqueous Media*" (John Wiley, **1997**). He has given over 140 invited and plenary lectures worldwide. He is widely recognized for the development of Grignard-type reactions in water, transition-metal catalysis in air and water, alkyne-aldehyde-amine coupling (A^3 coupling), asymmetric alkyne-aldehyde-amine coupling (AA^3-coupling), and cross-dehydrogenative-coupling (CDC) reactions.

2 Reaction of *sp* Carbon-Hydrogen Bonds

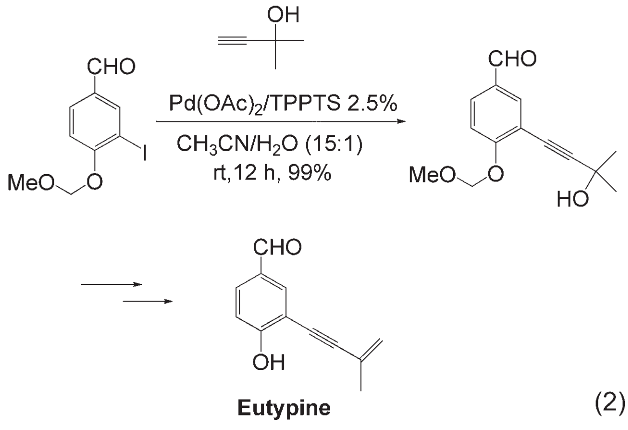
2.1 Reaction with Halides

The catalytic coupling of terminal alkynes with organic halides is one of the most general and reliable methods for the synthesis of complex alkynes. The most widely used method is the Sonogashira reaction, which was originally reported in 1975,[33,34] using a combination of copper and palladium catalysts. Notably, these reactions have been utilized for the chemical modification of biomolecules in aqueous media recently. In 1990, Casalnuovo and co-workers reported that unprotected iodonucleosides, iodonucleotides, and iodoamino acids underwent coupling with acetylenes catalyzed by water-soluble Pd(0) complexes Pd[$PPh_2(m\text{-}C_6H_4SO_3M)]_3$ ($M = Na^+$, K^+) in aqueous media (a mixture of CH_3CN and water).[35] They also provided an alternative synthesis of T-505, part of a family of chain-terminating nucleotide reagents used in automated DNA sequencing and labeling, from the coupling reaction of 5-iododideoxyuridine 5′-triphosphate with the unprotected fluorescein dye **1** in aqueous media [Eq. (1)]. At the same time, Bumagin and co-workers reported $Pd(PPh_2C_6H_4SO_3Na\text{-}m)_2Cl_2$, Ph_3P, and CuI as an effective catalytic system for Sonogashira reactions of propargyl alcohol, prop-2-yn-1-ol, with aryl iodides in aqueous media.[36] Two years later, this water-soluble Pd(0) complex prepared *in situ* from $Pd(OAc)_2[P(m\text{-}C_6H_4SO_3Na)]_3$ was reported as an efficient catalyst for Sonogashira cross-coupling reactions of terminal alkynes with iodoaromatic compounds without a copper(I) promoter under mild conditions in aqueous medium.[37]



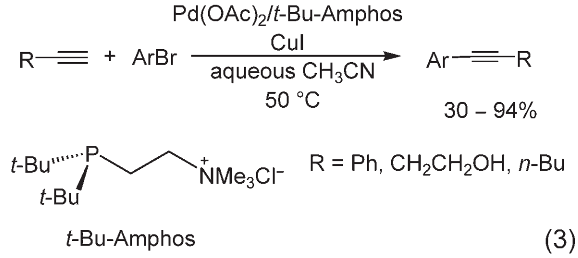
(1)

Later in 1995, Amatore et al. reported an efficient Sonogashira coupling catalyzed by $Pd(OAc)_2[P(m\text{-}C_6H_4SO_3Na)]_3$ (TPPTS) in aqueous media ($CH_3CN/H_2O = 15/1$).[38] They applied this methodology as the key step to the synthesis of eutypine, an antibacterial substance isolated from the culture medium of *Eutypa lata* [Eq. (2)]. They also demonstrated through a series of kinetic and ^{31}P NMR experiments that a mixture of $Pd(OAc)_2$ and TPPTS afforded a palladium(0) complex spontaneously. Beside TPPTS, the $[P(m\text{-}C_6H_4CO_2Li)]_3$ (*m*-TPPTC) ligand with a higher basicity also works for the Pd-catalyzed copper-free Sonogashira reaction in aqueous media.[39] Another example of copper-free coupling in water under aerobic conditions has been reported recently with $PdCl_2$ as a catalyst.[40]



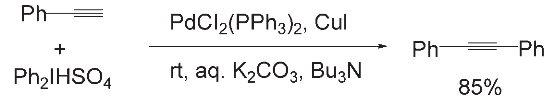
(2)

Compared to TPPTS, the sterically demanding, water-soluble alkylphosphines ligand *t*-Bu-Amphos, in combination with palladium(II) salts were found to be significantly more active for aqueous Sonogashira reactions of unactivated aryl bromides with alkynes [Eq. (3)].[41]



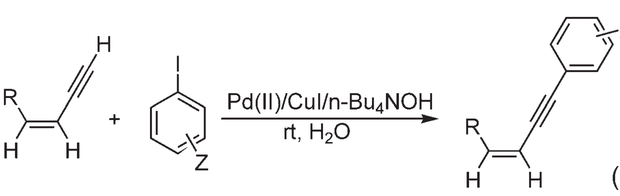
(3)

Palladium catalysts with water-insoluble ligands are also effective for Sonogashira couplings in aqueous media. Bumagin et al. reported a coupling of terminal acetylenes with iodoarenes in aqueous media in the presence of 10 mol% Bu_3N under very mild conditions using $PdCl_2(PPh_3)_2$ and CuI as catalyst precursor without the need of a water-soluble phosphine ligand. They also reported the coupling of terminal acetylenes with more reactive diaryliodonium salts under the same conditions [Eq. (4)].[42]



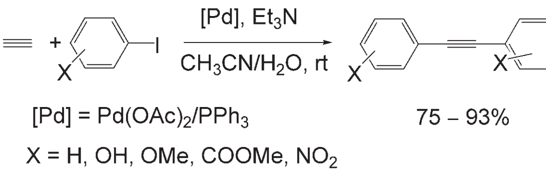
(4)

At the same time, Sinou et al. reported a palladium-catalyzed coupling reaction of terminal alkynes with aryl halides at room temperature in the presence of a quaternary ammonium salt and a base in acetonitrile-water solution, without the need of cuprous iodide.[43] After that, the combination of $Pd(PPh_3)_4$/CuI was reported to be an effective catalyst system for the Sonogashira reaction in water without the need of any additives,[44] and the use of $PdCl_2(PPh_3)$/CuI with aqueous ammonia is successful for the reaction of aryl iodides and terminal alkynes bearing an azobenzene group.[45,46] This Pd/Cu system in aqueous nBu_4NOH has also proved to be effective for enyne substrates [Eq. (5)].[47]



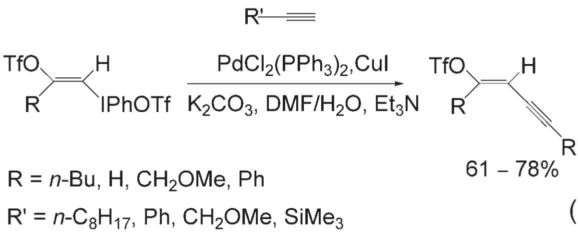
(5)

Li and co-workers found that a mixture of acetonitrile and water is a highly efficient medium for the palladium-catalyzed bis-coupling of acetylene gas with aryl iodides. Both water-soluble $Pd(OAc)_2[P(m\text{-}C_6H_4SO_3Na)_3]_2$ and water-insoluble $Pd(OAc)_2(PPh_3)_2$ are effective catalysts for this transformation [Eq. (6)].[48]



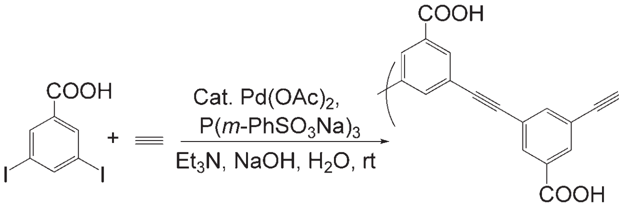
(6)

When organic salts are used as a coupling reagent, water is a preferred reaction medium. Pirguliyev et al. developed a novel stereoselective coupling of terminal alkynes with alkenyliodonium salts in aqueous media. The reaction of (*E*)-[β-(trifluoromethanemlfonyloxy)-l-alkenyl](phenyl)iodonium trifluoromethanesulfonate with terminal alkynes in the presence of catalytic amounts of dichloro(triphenylphosphine)palladium(II) and CuI in aqueous medium proceeded stereospecifically to give the corresponding enynes in good yields [Eq. (7)].[49]



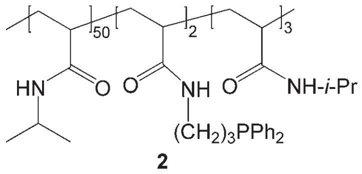
(7)

The aqueous Sonogashira coupling could be used in polymer synthesis. Li et al. have developed a palladium-catalyzed copolymerization of 3,5-diiodobenzoic acid with acetylene gas in a basic aqueous medium, giving a high molecular weight (~60,000) phenylethynylene polymer [Eq. (8)].[50] The polymer has a high thermostability, is soluble in basic solutions and could be switched from soluble to hydrogel states reversibly by changing the pH in water.

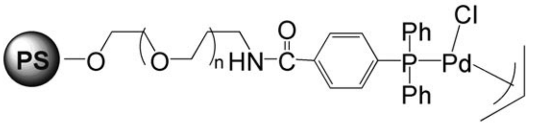


(8)

Polymer-bound palladium catalysts were also used in the Sonogashira reaction in water. Bergbreiter et al. developed an effective polymer-bound Pd(0)-phosphine catalyst for the coupling of terminal alkynes with aryl halides in CH_3CN/H_2O under mild conditions. The polymer-bound Pd(0)-phosphine catalyst was made by ligand exchange of $Pd(0)(dba)_2$ with a phosphine ligand **2**, which is based on a water-soluble polymer poly(*N*-isopropyl)aerylamide (PNIPAM) (Scheme 1).[51] Later, Xia et al. reported a polyethylene glycol-supported palladium-catalyzed Sonogashira reaction.[52] Uozumi et al. explored an efficient copper-free Sonogashira reaction in water catalyzed by an amphiphilic resin-supported palladium-phosphine complexes(Scheme 2), which was prepared on polystyrene-poly(ethylene glycol) graft co-polymer (1% DVB cross-linked) beads (PS-PEG).[53]

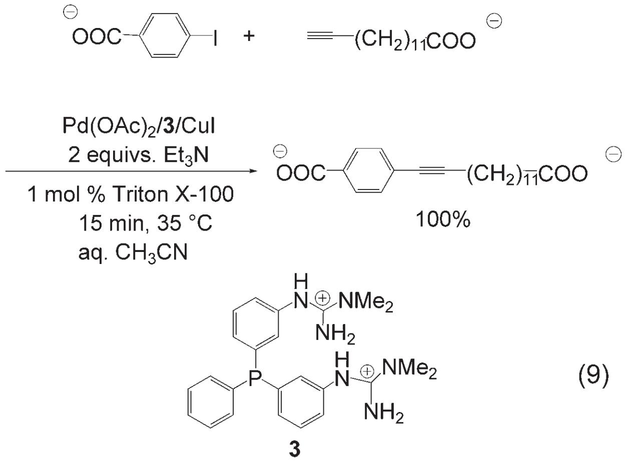


Scheme 1.



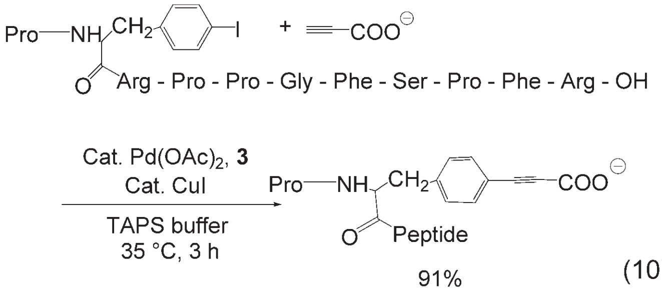
Scheme 2.

Aqueous media are necessary for most biological processes where substrate anions are usually formed by the action of base. Schmidtchen et al. found that a palladium catalyst with guanidino phosphine **3**, a water-soluble ligand, is more effective than $[P(m\text{-}C_6H_4SO_3Na)]_3$ (TPPTS) for the coupling reaction between anionic substrates in aqueous media [Eq.(9)].[54] They applied the reaction to the regiose-



(9)

lective C–C coupling of free and unprotected peptides.[55] For example, the coupling of an unprotected Pro(p-I-Phe)-bradykinin with propiolic acid in aqueous (3-[tris(hydroxymethyl)methylamino]-1-propanesulfonic acid (TAPS) buffer (pH 8.3) at 35 °C gave a 91% yield of the target product after 3 h [Eq. (10)]. The coupling of biotinylglutamoylpropargylamide, a water-soluble biotin derivative, with Pro(p-I-Phe)-bradykinin in aqueous TAPS buffer (pH 8.3) at 35 °C gave 75% yield of target product after 4 h [Eq. (11)]. It has been shown that the specific protection of functional groups in the protein was not necessary.



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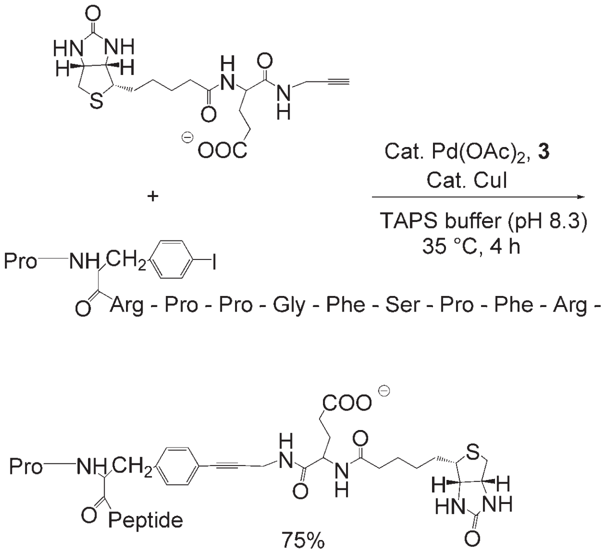
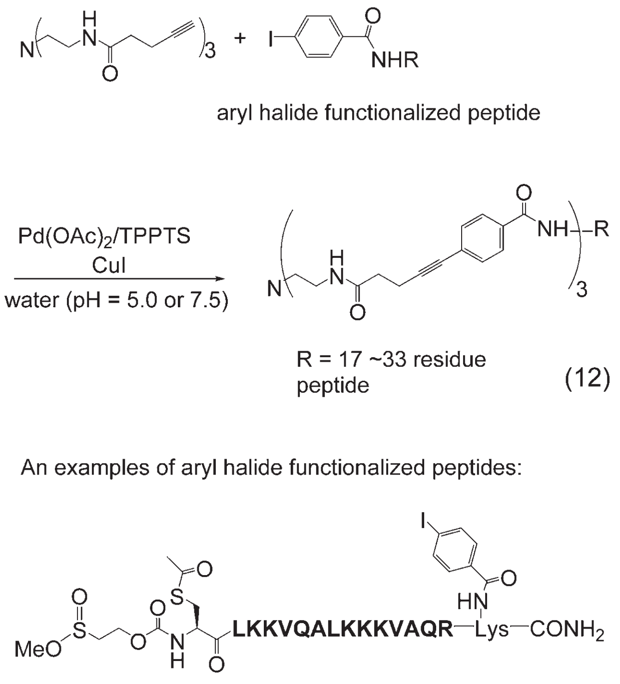


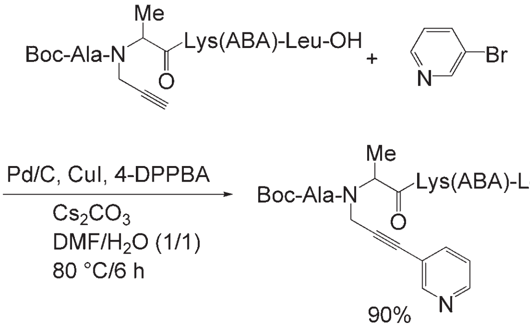
(11)

Later, Ghadiri et al. reported a tri-coupling of highly charged peptides (−6 to +9) of considerable length (from 17 to 33 residues) with a trialkyne by using a Pd(0) catalyst under both acidic (pH 5.0) and basic (pH 7.5) conditions in water, giving protein-sized structures (12,000 mol wt) efficiently [Eq. (12)].[56] These peptides, containing amines, carboxylates, guanidines, hydroxy groups, and thiol esters do not have to be protected during the reaction. However, free thiols, thioethers, and bipyridyl moieties were shown to be non-compatible, perhaps because these functional groups serve as competing ligands for palladium as well as copper.



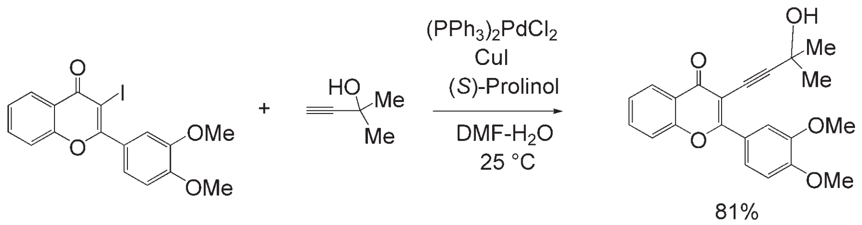
(12)

Palladium/charcoal could also serve a catalyst for the Sonogashira reaction. Cosford et al. and later Pal et al. reported efficient coupling reactions of alkynes with aryl and heteroaryl substrates using a Pd/C-CuI-PPh_3 catalyst in aqueous media.[57,58] Recently, Granja et al. used palladium/carbon associated with 4-diphenylphosphinobenzoic acid (4-DPPBA) or triphenylphosphine ligand to catalyze such a reaction in aqueous DMF [Eq. (13)].[59]



(13)

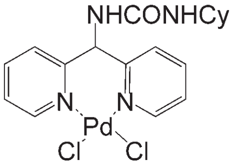
Wang et al. reported an efficient cross-coupling of terminal alkynes with aromatic iodides or bromides in the presence of Pd/C, potassium fluoride, cuprous iodide and triphenylphosphine in aqueous media (THF/H_2O, v/v, 3/1) at 60 °C.[60] The palladium powder was easily recovered and was effective for six consecutive runs with no significant loss of catalytic activity.



(14)

Recently, Pal et al. found that (*S*)-prolinol could facilitate the coupling reaction of terminal alkynes with 3-iodoflavone *via* palladium-copper catalysis in aqueous DMF, which afforded a mild and convenient method for the synthesis of 3-alkynyl-substituted flavones of potential biological interest [Eq. (14)]. They also investigated the coupling reaction of a more frequently used aryl halide such as iodobenzene with terminal alkynes at room temperature in water without any co-solvent. Iodobenzene was found to have good miscibility with water in the presence of prolinol and the reaction was completed within 30 min affording the desired product in a good yield.[61]

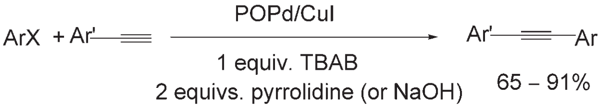
Besides the phosphine ligands, nitrogen ligands are also effective. Recently, a new palladium catalyst with a nitrogen ligand, 2,2′-dipyridylmethylamine-based palladium complexes (Scheme 3), has been developed as an efficient catalyst for Sonogashira coupling in aqueous media. It has been shown that the coupling of aryl iodides or bromides with terminal alkynes proceeded smoothly in the presence of pyrrolidine and tetrabutylammonium acetate (TBAB) at 100 °C in water.[62,63] However, the reactions were shown to be faster in NMP solvent than in water under the reaction conditions.



Scheme 3.

Palladium-phosphinous acid (POPd) was also reported as an effective catalyst for Sonogashira cross-coupling reaction of aryl alkynes with aryl iodides, bromides or chlorides in water [Eq. (15)].[64]

With further developments in palladium chemistry, the catalytic couplings of unactivated aryl chlorides have become possible. Recently, Buchwald and coworkers disclosed that a catalyst system based on [$PdCl_2(CH_3CN)_2$] and a sulfonated phosphine ligand provided an excellent reactivity in the copper-free Sonogashira coupling of aryl chlorides with alkynes in aqueous media [Eq. (16)].[65]



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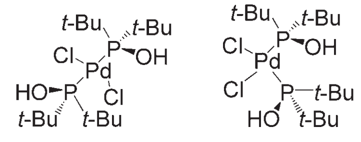
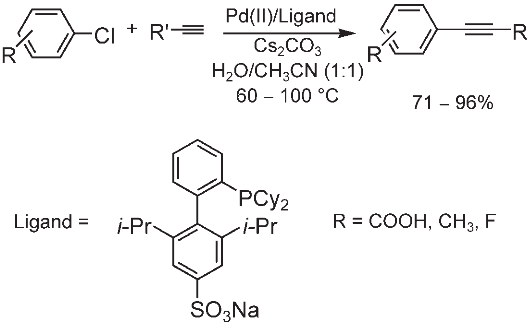
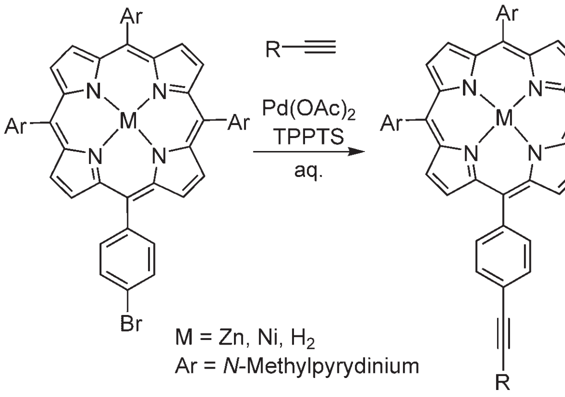


POPd



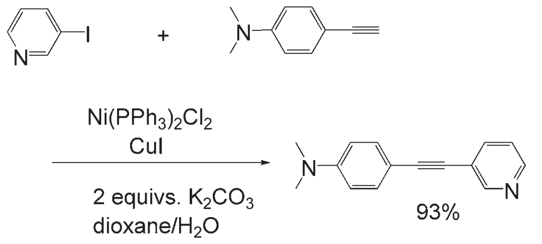
(16)

A recent interesting example of a palladium-catalyzed Sonogashira reaction is the coupling reaction of cationic porphyrins with alkynes in aqueous solution [Eq.(17)].[66]



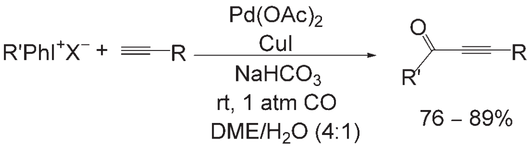
(17)

Beside palladium catalysts, nickel was also found to be an effective catalyst for the Sonogashira reaction in aqueous media. Recently, Beletskaya et al. developed a $Ni(PPh_3)_2Cl_2/CuI$-catalyzed Sonogashira coupling reaction of terminal acetylenes with aryl iodides in aqueous dioxane with high yields [Eq. (18)].[67]



(18)

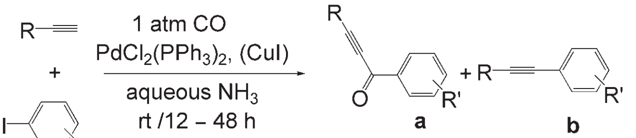
Carbonylative Sonogashira couplings are important methods to construct conjugated ynones. Aqueous media were found to be effective for carbonylative Sonogashira couplings of terminal alkynes. Kang et al. have found that iodonium salts can readily undergo the carbonylative coupling with terminal alkynes in the presence of Pd/Cu catalysts and 1 atmosphere pressure of carbon monoxide in aqueous media at room temperature, generating the expected α,β-acetylenic ketone products [Eq.(19)].[68] In the cases of terminal arylalkynes as substrates, a palladium or copper catalyst alone was also effective.



(19)

R' = Ph, 4-MeOC$_6$H$_4$, 2-thienyl, (*E*)-PhCH=CH
R = Ph, Bu
X = BF$_4$, OTs

Recently, Mori et al. reported an efficient carbonylative coupling of phenylacetylene with aryl iodide in the presence of $PdCl_2(PPh_3)_2/(CuI)$ in aqueous ammonia and CO (1 atm) to give the corresponding conjugated alkynyl ketone in good yields at room temperature without forming the non-carbonylative coupling product [Eq. (20)].[69] They found that aqueous ammonia (in a mixture of 2 mL water and 3 mL tetrahydrofuran) is much more effective for such a coupling reaction than the use of an excess of tertiary amine as a solvent. For example, treatment of phenylacetylene with 4-methoxy-1-iodobenzene in the presence of 1 mol% $PdCl_2(PPh_3)_2$ at room temperature under an ambient pressure of carbon monoxide in tertiary amine gave the carbonylative coupling product in only 11% yield. In contrast, when the reaction solvent was changed to 2 mL of aqueous ammonia (0.5 M) solution together with 3 mL of THF, the carbonylative coupling product was obtained in 72% yield. Later, Yang and co-workers reported a copper free version of the carbonylative coupling.[70]

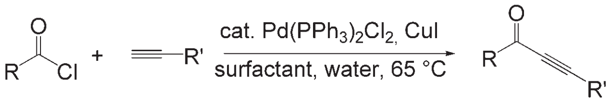


(20)

without CuI:
R = aromatic
R' = H, OMe, Me, COMe, Cl
a: 50 – 81%
b: 0 – 7%

with CuI:
R = aliphatic
R' = Me, NH$_2$, COMe, Cl
a: 55 – 78%
b: 0 – 5%

Acid chlorides are highly water sensitive, therefore a cross-coupling reaction of a terminal alkyne with acid chloride in aqueous media had not been reported until recently. In 2004, Li et al. developed a highly effective direct coupling of acid chlorides with terminal alkynes catalyzed by $PdCl_2(PPh_3)_2/CuI$ together with a catalytic amount of sodium lauryl sulfate as the surfactant and K_2CO_3 as the base to produce ynones with up to 99% yield in water [Eq. (21)].[71] No desired product was detected when either Cu(I) alone or Pd(II) alone was used as the catalyst. The use of surfactant was also necessary for the success of this transformation, possibly by temporarily stabilizing the acid chloride. As an example, without a surfactant/phase-transfer reagent the yield dropped from 98% to 9%. The use of water as a solvent allowed the use of inorganic bases instead of organic bases, which not only made the separation easier but also reduced the organic base pollutants.



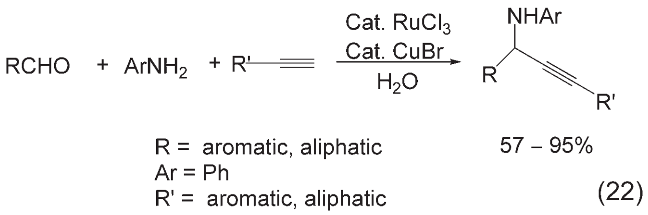
R = aromatic
R' = aromatic, aliphatic

51 – 99% (21)

2.2 Reaction with Imines

The direct addition of terminal alkynes to imines is a very important reaction since it generates propargylamines which are key reaction intermediates and show a broad range of biological activities. In 2002, Li et al. reported the first catalytic addition of acetylenes to various imines or acyliminium ions (A^3 coupling of aldehyde-alkyne-amine) *via* C–H activation by a Ru/Cu catalyst or CuBr alone in water under mild conditions [Eq. (22)].[72]

Later, Li and co-workers developed a gold catalyzed A^3 coupling reaction in water [Eq. (23)].[73] No



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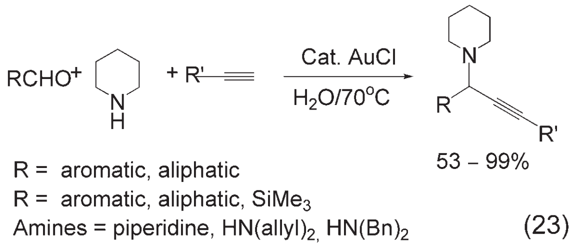
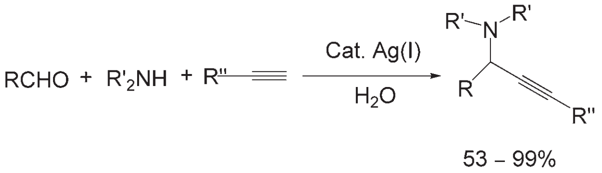


(23)

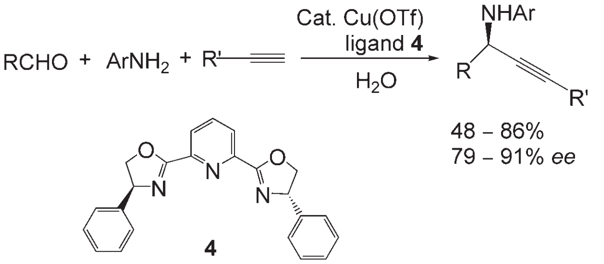
co-catalyst was needed for the process. Less than 1% of catalyst loading was enough for the A^3 coupling reaction to generate high yields of the corresponding propargylamine products. Solvents significantly affected the reaction. Water was shown to be the best solvent for the process, giving almost quantitative yields of the desired products in most cases. Organic solvents, such as THF, toluene and DMF, gave low conversions and more by-products.

Beside the copper and gold catalysts, Li et al. also found that Ag(I) salts, such as AgCl, AgBr, and AgI showed good catalytic activities for the A^3 coupling in water [Eq. (24)].[74] Compared to the reactions catalyzed by gold and copper catalysts, the silver-catalyzed reactions displayed higher reactivity and cleaner reactions for aliphatic aldehydes.



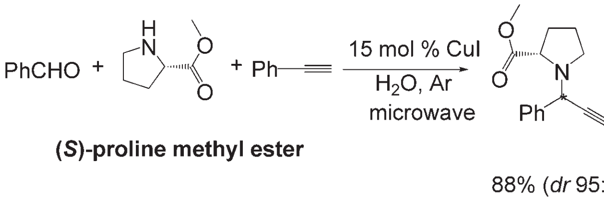
(24)

Li et al. subsequently extended the A^3 coupling to the first asymmetric coupling of alkynes, aldehydes and amines (AA^3) catalyzed by a chiral Cu(I)-bis(oxazolinyl)pyridine (pybox) complex in water. They observed that Cu(I) alone could provide the desired product in low conversions and thus postulated that the low catalytic activity when using Cu(I) alone could be due to the strong C–Cu bond of copper acetylides. They conceived that the addition of a strongly coordinating and electron-rich ligand may weaken the strong C–Cu bond. Therefore, in order to get the enantioselective addition products, they tried Cu(I) catalysts with several chiral bis(oxazolinyl) ligands in their reaction in water. Finally they found that the use of the **4**-Cu(OTf) complex afforded the corresponding (+)-propargylamine products with both a high reactivity and enantioselectivity (48–86% yields and 78–91% *ee* in water and up to 99.5% *ee* in organic solvent) [Eq. (25)].[75–77]



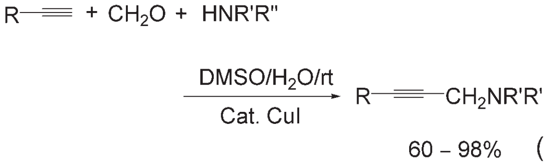
(25)

Microwave irradiation is particularly efficient on liquid water as it is highly dielectric. Tu et al. found that the A^3 coupling can be catalyzed by CuI alone under microwave irradiation in water. Using (*S*)-proline methyl ester as a chiral amine source, they were able to generate a pure chiral propargylamine [Eq. (26)].[78] An ultrasound-assisted version of A^3 coupling also has been shown to be highly effective in the presence of CuI as the catalyst in water at an ambient temperature.[79]



(26)

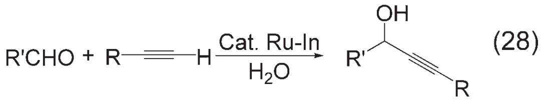
Formaldehyde as substrates for CuI-catalyzed A^3 coupling in an aqueous solution has been reported recently. It was shown that a variety of substrates such as aromatic, aliphatic and silylated acetylenes as well as alkynols, and secondary amines, could survive the reaction [Eq. (27)].[80]



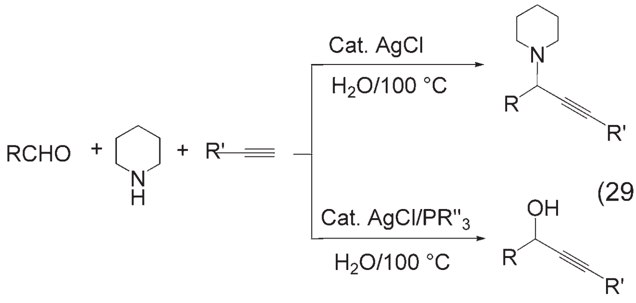
(27)

2.3 Reaction with Carbonyl Compounds

Propargylic alcohols are versatile building blocks in organic synthesis. Their traditional synthesis involves the alkynylation of ketones and aldehydes using a stoichiometric amount of organometallic reagents such as Grignard reagents or alkyllithiums in an anhydrous organic solvent. Such reactions have recently been replaced by a catalytic system in water. Li and co-workers found an effective addition reaction of phenylacetylene to aldehydes in aqueous solution *via* C–H activation catalyzed by a bimetallic Ru-In catalytic system [Eq. (28)].[81,82]

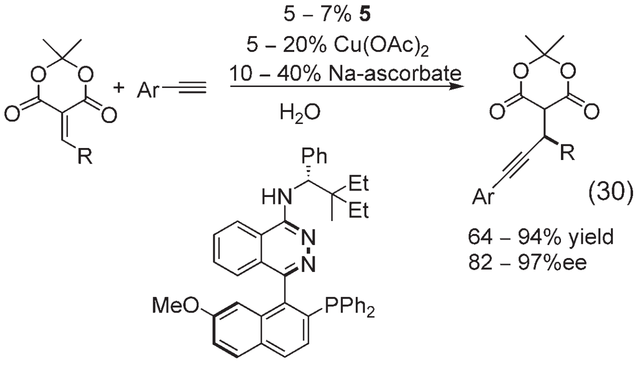


Later, Li and co-workers found that silver complexes, such as Cy_3PAgCl, were also a choice of catalyst for the addition of terminal alkynes to aldehydes.[83] Interestingly, the phosphine ligand served as a remarkable chemo-switch for the reaction of aldehydes with alkynes in the presence of amines in water. In the presence of a phosphine ligand, silver catalyzed exclusive aldehyde-alkyne coupling, whereas exclusive aldehyde-alkyne-amine (A^3) coupling occurred in the absence of phosphine [Eq. (29)].



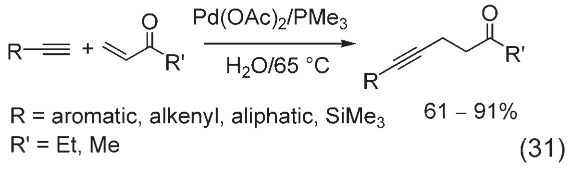
2.4 Conjugate Addition

Conjugate addition of terminal alkynes to C=C double bonds in water has only been explored recently, possibly because C=C double bonds are not as good electrophiles as C=N or C=O bonds. In 2003, Carreira et al. reported the first conjugate addition reaction of terminal alkynes to C=C bond catalyzed by copper in water. The reaction only proceeded with derivatives of Meldrum's acid in water in the presence of $Cu(OAc)_2$ and sodium ascorbate [Eq. (30)].[84] The Cu(II) salts were reduced to Cu(I) salts in the presence of sodium ascorbate, and thus would not lead to a facile generation of Cu(I)-alkynylide which participates in oxidative acetylide coupling. Later, they employed a copper catalyst together with the chiral PINAP ligand **5** to develop an **e**nantioselective version of this addition reaction and achieved 82–97% *ee* of products with useful yields [Eq. (30)].[85]

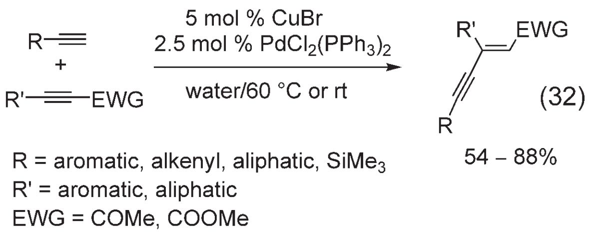


5

Li et al. reported the first palladium-catalyzed 1,4-addition of terminal alkynes to vinyl ketones in water with high yields [Eq. (31)].[86] Chisholm et al. also reported such a reaction catalyzed by the Rh metal complex $Rh(acac)(CO)_2$ (acac = acetylacetonate) in the presence of tris(*o*-methoxyphenyl)phosphine in aqueous dioxane solutions.[87]



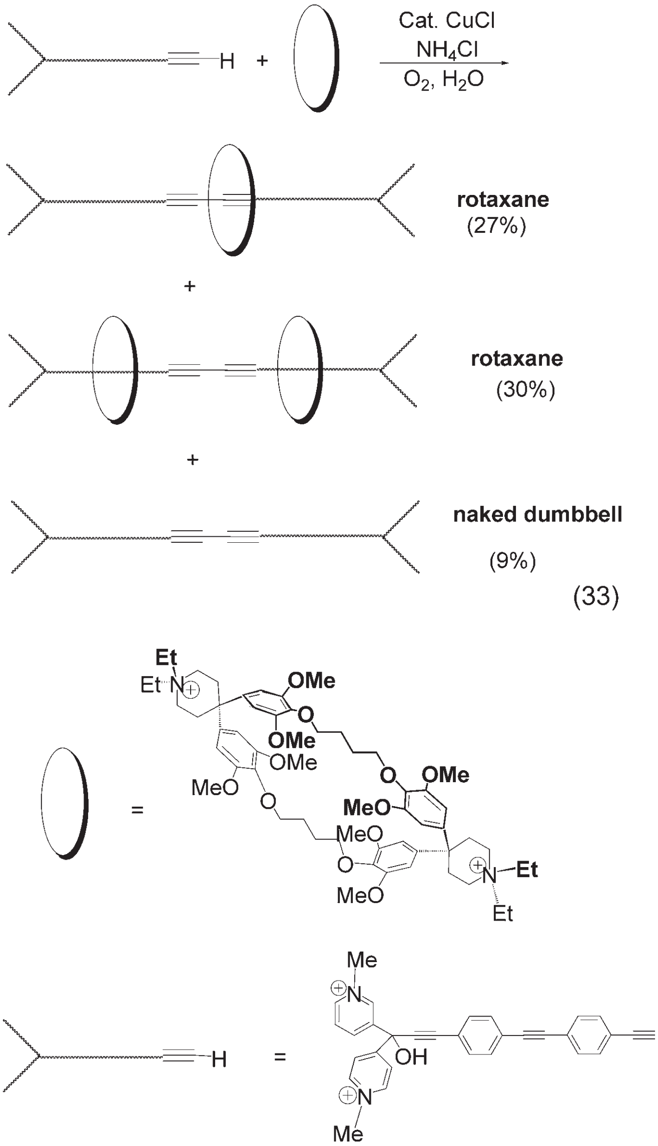
The conjugated addition of *sp* C–H bonds to carbon-carbon triple bonds is an important way to synthesize conjugated enynes which are important building blocks and essential units in a variety of biologically active compounds. Recently Li et al. reported a facile and simple method to generate conjugated enynes by using a combination of Cu/Pd together with PPh_3, in water and under an air atmosphere [Eq. (32)].They found that the reaction run in water is better than that in toluene.[88] For example, an addition of phenylacetylene to 4-phenyl-3-butyn-2-one at room temperature in water gave 63% yield of the desired enyne product. In contrast, it gave less than 10% of the enyne product at room temperature in toluene.



2.5 Alkyne-Alkyne Coupling

Alkyne-alkyne coupling is one of the most powerful methods to synthesize di- and oligoacetylene moieties, and has been widely used in the synthesis of natural products, pharmaceuticals, supramolecules, carbon-rich and all-carbon scaffoldings. Two types of alkyne-alkyne couplings have been intensively studied: one is the Glaser homocoupling and the other one is the Cadiot–Chodkiewicz heterocoupling.[89]

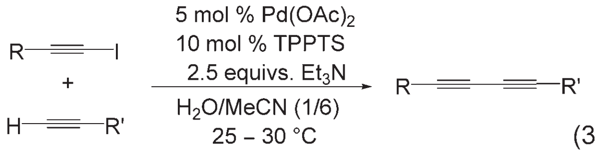
Since 1869 when Glaser found that copper(I) phenylacetylide underwent oxidative dimerization to diphenylacetylene in air, numerous modifications of the reaction conditions have been reported. Recently, Anderson et al. used the hydrophobic effect to direct water-soluble rotaxane formation *via* a Glaser reaction in water, in which the Glaser coupling of the stopper terminal alkyne and the macrocyclic cyclophane in H_2O gave a product mixture of 2 rotaxanes and 1 naked dumbbell [Eq. (33)].[90]



(33)

It also has been reported that oxidative self-coupling of terminal alkynes occurred smoothly in the presence of a phase transfer reagent n-Bu_4NBr, allyl bromide, and a catalytic amount of $Pd(dba)_2$ in the aqueous $NaOH$-CH_2Cl_2 biphasic system.[91] An $NiCl_2$ catalyst was found to be effective for the Glaser coupling in hot water (200 °C).[92] A Cu(I)Cl-catalyzed Glaser coupling reaction of terminal alkynes without bases under near-critical water has also been reported recently.[93]

As a development of the oxidative homocoupling reaction, in 1955, Chodkiewicz and Cadiot explored a Cu(I)-catalyzed heterocoupling reaction of terminal alkynes with 1-bromoalkyne in the presence of an amine in aqueous medium to produce the expected products. Recently, Amatore et al. developed an aqueous cross-coupling reaction of terminal alkynes with 1-iodoalkynes using a water-soluble Pd(0) catalyst prepared *in situ* from $Pd(OAc)_2$ and sulfonated triphenylphosphine $P(C_6H_4\text{-}m\text{-}SO_3Na)_3$ (TPPTS) without a Cu(I) promoter, giving diynes in moderate yields (43–65 %) [Eq. (34)].[94]

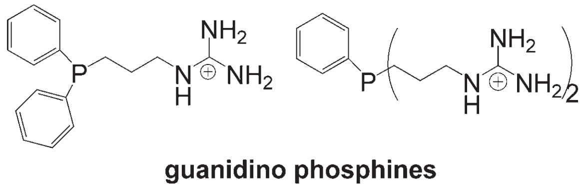


(34)

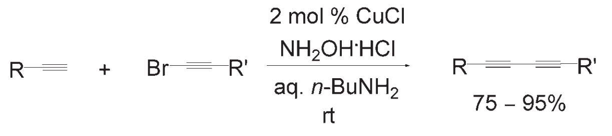
$R = CH_3(CH_2)_3$,	$R' = C(CH_3)_2(OH)$	60%
$R = (CH_3)_3Si$,	$R' = CH(OH)(CH_2)_4CH_3$	43%
$R = (CH_3)_3Si$,	$R' = C(CH_3)_2(OH)$	57%
$R = CEt_2NH_2$,	$R' = CH(OH)(CH_2)_4CH_3$	65%

Compared to anionic phosphine ligand TPPTS, cationic phosphine ligands containing the hydrophilic guanidinium moiety (Scheme 4) associated with palladium catalysts were found to be effective for the heterocoupling reaction of terminal alkynes with 1-haloalkyne but were less efficient than TPPTS.[95]

Recently, Marino et al. have reported a Cadiot–Chodkiewicz cross-coupling reaction of bulky trialkylsilyl-protected alkynes with 1-bromoalkynes in aqueous amine to form a variety of unsymmetrical diynes in good yields (75–95 %) [Eq.(35)].[96]



Scheme 4.

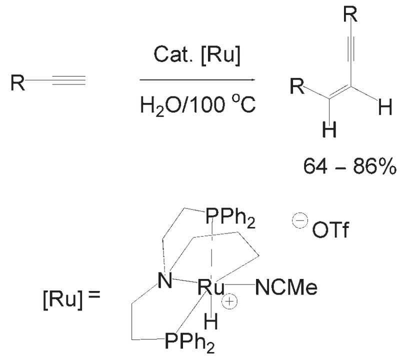


(35)

R = TES, TBS, TIPS
R' = $C(CH_3)_2(OH)$, CH_2OH, CH_2NMe_2, $CH_2CH_2CH_3$, $(CH_3)C{=}CH_2CH_2OH$, 1-cyclohexenyl

TES = triethylsilyl, TBS = *tert*-butyldimethylsilyl, TIPS = triisopropylsilyl

Beside the oxidative alkyne-alkyne coupling reactions, a ruthenium-catalyzed non-oxidative dimerization of terminal alkynes has been reported recently. It was shown that $[RuH(CH_3CN)(NP_3)]OTf$ effectively catalyzed the dimerization of both aliphatic and aromatic alkynes to give (*Z*)-enynes in high regio- and stereoselectivity in aqueous medium [Eq. (36)].[97]



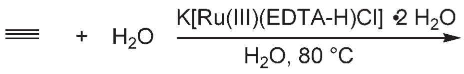
(36)

3 Reaction of Carbon-Carbon Triple Bonds

Reaction of the carbon-carbon triple bond is the most extensively used transformation of alkynes, which generates many useful alkenyl organic compounds such as vinyl halides, ketones, and nitrogen- and oxygen-containing products.

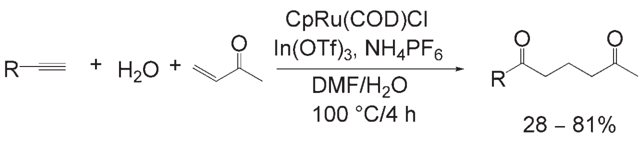
3.1 Hydration

The hydration of acetylenes, which usually gives aldehydes or ketones, has been widely used in industry for a long time. In 1990, Taqui Khan et al. reported a water-soluble complex, $K[Ru(III)(EDTA\text{-}H)Cl]\cdot 2\,H_2O$, catalyzed hydration of acetylene to give acetaldehyde cleanly [Eq. (37)].[98]



(37)

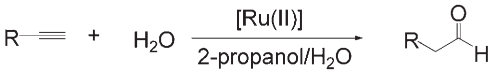
Recently, on the basis of the Markovnikov addition of water to alkynes, Trost et al. developed a three-component addition reaction of terminal alkynes, water, and methyl vinyl ketone, affording 1,5-diketones in DMF/water in the presence of ruthenium and indium catalysts [Eq. (38)].[99] Ruthenium complexes alone, such as $[RuCl_2(\eta^6\text{-arene})\text{-}\{P(CH_2OH)_3\}]$, have also been reported to be effective catalysts for hydrations of terminal alkynes in water to give ketone products.[100]



R = $HO(CH_2)_3$, $NC(CH_2)_3$, $Boc(CH_2)_3$, $MeO(CH_2)_3$, Me_2COH, 1-hydroxycyclohexyl, *trans*-2-hydroxycyclohexylmethyl

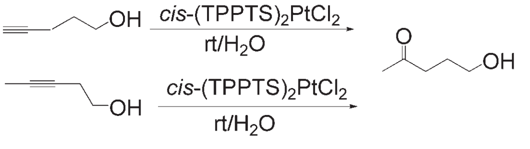
(38)

Hydration of alkynes usually follows the Markovnikov's rule to form the corresponding ketone compounds. In contrast, it has been recently reported that the reaction can regioselectively form aldehydes in aqueous alcoholic media (a mixture of water and 2-propanol) by catalysis of ruthenium(II) complexes, such as $[RuCl_2(\eta^6\text{-}C_6H_6)\{PPh_2(C_6F_5)\}]$,[101] and $[Ru(\eta^5\text{-}C_9H_7)Cl(PPh_3)_2]$ [Eq. (39)].[102]



(39)

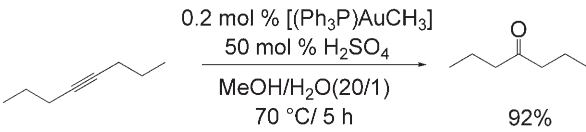
More recently, Atwood et al. developed a platinum complex having a water-soluble, bidentate phosphine ligand, *cis*-$(TPPTS)_2PtCl_2$ [TPPTS = tris(sodium *m*-benzenesulfonate)phosphine], as an effective hydration catalyst for the water-soluble alkynes 4-pentyn-1-ol and 3-pentyn-1-ol [Eq. (40)]. Both substrates gave the same product, 5-hydroxy-2-pentanone, as a result of Markovnikov hydration and a regioselective hydration, respectively.[103]



(40)

It has also been reported that Pt-catalyzed hydration of various aliphatic and aromatic alkynes under phase transfer conditions in $(CHCl_2)_2/H_2O$ in the presence of Aliquat 336 gave the Markovnikov product, mixtures of two ketones, or ketones with the carbonyl group away from the bulky side.[104] A hydrophobic, low-loading and alkylated polystyrene-supported sulfonic acid (LL-ALPS-SO_3H) has also been developed for the hydration of terminal alkynes in pure water to give ketone products.[105]

Recently, various gold catalysts have been developed in organic synthesis. Organometallic Au(III) complexes were found to be effective for catalyzing the hydration of terminal alkynes in water.[106] Beside terminal alkynes, the hydration of internal alkynes in water has also been reported by the use of Au(I) catalysts [Eq. (41)].[107] It was shown that $(Ph_3P)AuCH_3$ together with an acid catalyst was highly efficient in the hydration of a wide range of alkynes with high turnover frequencies in aqueous methanol. The new process is a valuable alternative to the Wacker oxidation in organic synthesis.

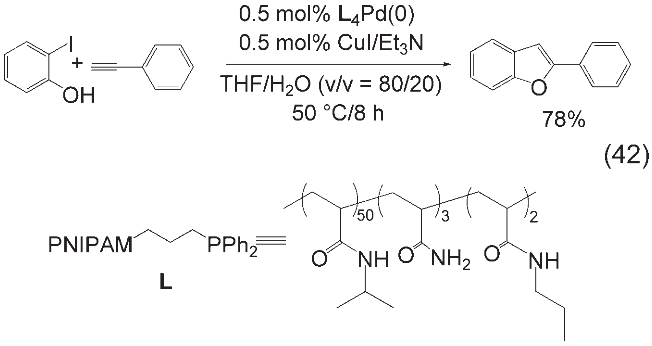


(41)

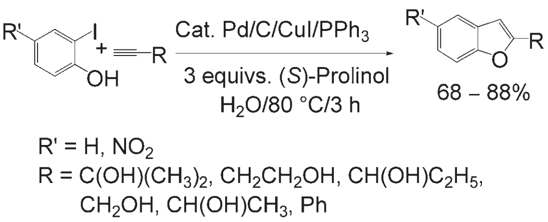
3.2 Hydroalkoxylation

The hydroalkoxylation of alkynes, or the addition of alcohol to alkynes, is a fundamental reaction in organic chemistry which allows the preparation of enol ethers and a variety of oxygen-containing heterocycles, such as furan, pyran, benzofuran derivatives. Recently, the reactions have been developed by the use of water as a solvent.

Bergbreiter et al. found that a linear poly-(*N*-isopropylacrylamide) (PNIPAM) polymer exhibited inverse temperature solubility in water, that is, soluble in cold water but insoluble in hot water. They used it in the preparation of a recoverable homogenous palladium catalyst.[108] The PNIPAM-bound Pd(0) catalyst was effective for the reaction of 2-iodophenol with phenylacetylene in aqueous THF media to give the target product benzofuran [Eq. (42)]. This catalyst can be recovered by simply heating the water solution or by adding a poor solvent like hexane (in aqueous THF). They have shown that this catalyst could be reused up to 15 times with only a very modest loss of activity. Later, Uozumi et al. showed that an amphiphilic polystyrene-poly(ethylene glycol) (PS-PEG) resin-supported palladium-phosphine complex could also effect this reaction in water.[53]



Pal et al. explored an efficient Pd/C-catalyzed reaction of 2-iodophenols with terminal alkynes in water without the use of any organic co-solvents in the presence of PPh_3, CuI and prolinol to give expected benzofuran products [Eq. (43) and Eq. (44)].[109] Hydroxy groups are tolerated during these reactions. The use of prolinol as a base afforded better yields of the products than did the use of triethylamine (a common organic base), possibly due to its better miscibility with water.



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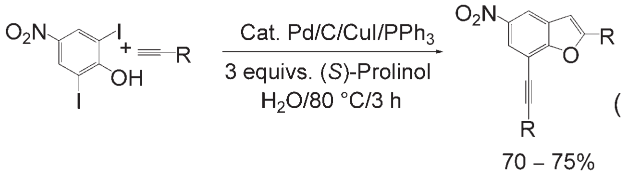
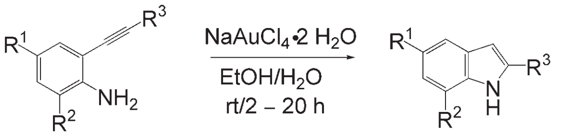


(44)

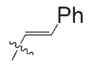
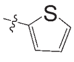
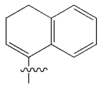
3.3 Hydroamination

The hydroamination of alkynes offers a straight-forward route for the preparation of a variety of amines, enamines and imines. The annulation of alkynes with amines, which affords N-containing heterocycle compounds, particularly, has attracted the chemist's attention. Numerous methods have appeared in the literature for this process.

Recently, Marinelli et al. have reported an Au(III)-catalyzed hydroamination of alkynes in aqueous media ($EtOH/H_2O$) in which the annulation of 2-alkynylanilines gave indole derivatives in good yields [Eq. (45)].[110] However, in some cases, raising the amount of water in the EtOH-water mixture resulted in a less satisfactory yield of the target products, perhaps due to the decreasing solubility of the starting materials. Later, Hiroya et al. developed a copper(II) salts-catalyzed cyclization reaction of 2-ethynylaniline

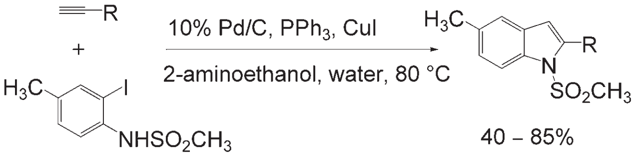


(45)

R^1	R^2	R^3	EtOH/H_2O	Yield [%]
H	H	Ph	50/5	82
H	H	*n*-Bu	95/5	74
H	H		50/50	75
H	H		50/50	90
Cl	Cl	*p*-C_6H_4OMe	95/5	77
Cl	Cl		50/50	75

derivatives to indoles in a mixture of H_2O and MeOH in the presence of 1-ethylpiperidine at room temperature.[111]

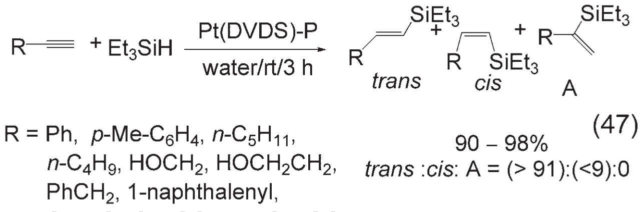
Pal et al. reported a one-pot tandem Pd/C-catalyzed coupling of terminal alkynes with *N*-substituted iodoanilines in water to form 2-akyl-/aryl-substituted indoles [Eq. (46)].[112]



R = aromatic, aliphatic (46)

3.4 Hydrometalation

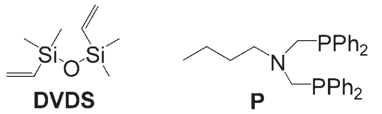
The hydrometalation, such as hydrosilylation, hydrostannylation and hydrogermylation, of alkynes is an important process to generate various reaction intermediates in organic synthesis. Recently, some examples of the hydrosilytation of alkynes have been carried out in aqueous media. Li et al. developed a highly regio- and stereoselective Pt(DVDS)-P-catalyzed hydrosilylation of terminal alkynes in water at room temperature, giving 100% stereoselectivities (*trans*) in most cases [Eq. (47)].[113] It is worth noting that a hydroxy group on the substrate does not need to be protected before hydrosilylation.



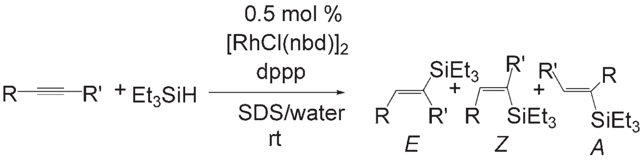
(47)

R = Ph, *p*-Me-C_6H_4, *n*-C_5H_{11}, *n*-C_4H_9, $HOCH_2$, $HOCH_2CH_2$, $PhCH_2$, 1-naphthalenyl, $CH_2{=}CHCH_2OCH_2$, $PhCH_2OCH_2$ — 90 – 98%, *trans* :*cis*: A = (> 91):(<9):0

R = $SiMe_3$ — 92%, *trans*:*cis*:A = 35:65:0



Cationic rhodium catalysts are found to be effective for the regio- and stereoselective hydrosilylation of alkynes in aqueous media. Recently Oshima et al. developed a rhodium-catalyzed hydrosilylation of alkynes in an aqueous micellar system. A combination of $[RhCl(nbd)]_2$ and bis(diphenylphosphino)propane (dppp) was shown to be effective for the (*E*)-selective hydrosilylation in the presence of sodium dodecyl sulfate (SDS), an anionic surfactant, in water [Eq. (48)].[114] An anionic surfactant is essential for this (*E*)-selective hydrosilylation, possibly because anionic micelles are helpful for the formation of a cationic rhodium species *via* dissociation of the Rh−Cl bond. For example, Triton X-100, a neutral surfactant, gave non-stereoselective hydrosilylation. Methyltrioctylammonium chloride, a cationic surfactant, resulted in none of the hydrosilylation products. They also have shown that the selectivity can be switched from *E* to *Z* in the presence of sodium iodide.



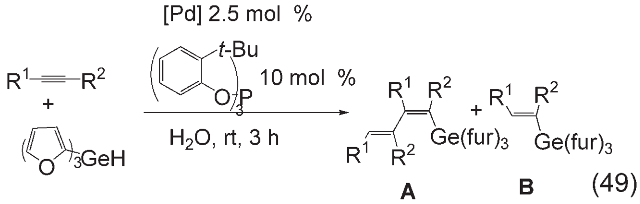
(48)

R' = H
R = aromatic, aliphatic, $SiMe_3$
E: 35 – 87%
Z: < 2%
A: < 5%

R (= R'): Ph, Et
E: 53 – 66%
Z: 0
A: 0

In the presence of 1 equiv. **NaI**:
R' = H
R = aromatic, aliphatic
E: 5 – 21%
Z: 50 – 70%
A: < 2%

They also have reported a Pd-catalyzed hydrogermylation of alkynes in water, providing mixtures of dienylgermanes and alkenylgermanes efficiently, with the dienylgermanes as major products in most cases [Eq. (49)].[115] It is worth noting that the reaction in water proceeded much faster than in organic solvents or under neat conditions. In addition, in an aqueous system, the catalyst loading could be as low as 0.0025



(49)

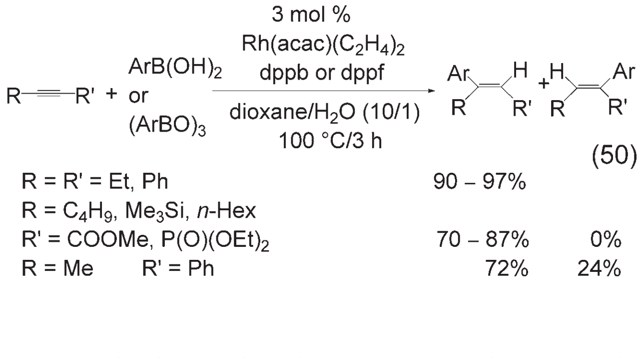
R^1	R^2	A	B
Me_3Si	H	60	40
$CH_2{=}C(Me)$	H	70	27
$HOCH_2$	H	68	-
t-Bu	H	25	71
n-C_6H_3	H	91	-
Me	Me	70	27

mol%. Interestingly, addition of surfactants such as sodium dodecyl sulfate, Triton X-100, or methyltrioctylammonium chloride, decreased the reaction rates.

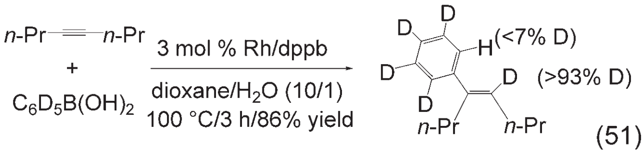
In addition, Li et al. recently developed an efficient rhodium-catalyzed hydrostannylation of terminal alkynes in water, providing tandem hydrostannylation/conjugate addition products stereoselectively.[116]

3.5 Arylation

The arylation of alkynes *via* addition of arylboronic acids to alkynes represents an attractive strategy in organic synthesis. The first addition of arylboronic acids to alkynes in aqueous media catalyzed by rhodium was reported by Hayashi et al.[117] They found that a rhodium catalyst associated with a chelating bisphosphine ligand such as 1,4-bis(diphenylphosphino)-butane (dppb) and 1,1′-bis(diphenylphosphino)ferrocene (dppf) was highly effective for the arylation of alkynes with arylboronic acids in aqueous media (dioxane/water = 10/1), to give the target products with high *syn*-selectivity [Eq. (50)]. Triphenylcyclotriboroxane can also be used as the source of aryl groups. The arylation of unsymmetrical alkynes, such as 1-phenylpropyne, gave mixtures of *E* and *Z* isomers. However, unsymmetrical alkynes substituted with an ester or phosphonate group afforded the desired products in high regio- and *syn*-selectivities. Surprisingly, isotope experiments showed that the hydrogen on the vinylic carbon did not come from water, but came from the phenyl group of boronic acid, perhaps due to a 1,4-shift of rhodium from a 2-aryl-1-alkenylrhodium to a 2-alkenylarylrhodium intermediate [Eq. (51)].

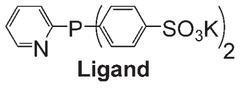


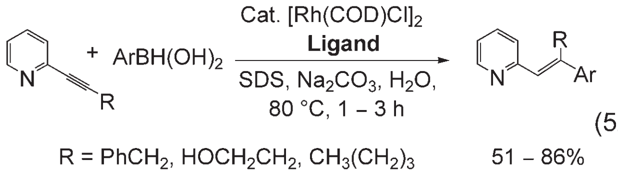
(50)



(51)

Lautens et al. explored a new water-soluble ligand, which has a pyridyl phosphine moiety [Eqs. (52–55)].[118,119] $[Rh(COD)Cl]_2$ together with this ligand was effective for the addition of arylboronic acids to 2-alkynylpyridine compounds in the presence of sodium dodecyl sulfate (SDS) in water. The reaction was also effective for alkynes with a triple bond one carbon away from the pyridyl group. No reaction oc-





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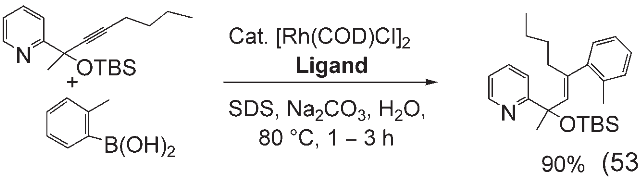
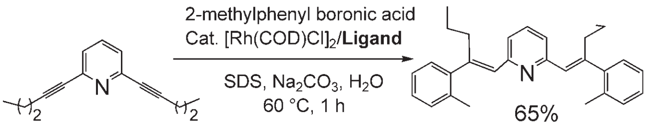


(53)

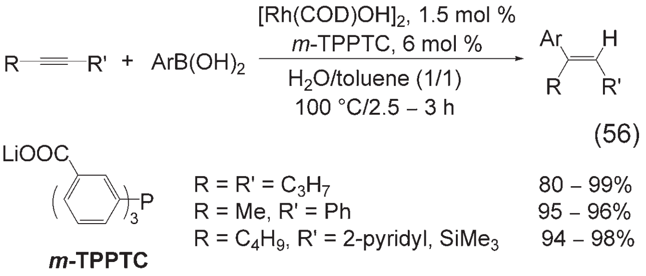


(54)

(55)

curred for the alkynes substituted other than at the *ortho* position of pyridine, possibly because this reaction involves a chelation-controlled process.

Biphasic systems were found to have unique effects for the selectivity of the addition of arylboronic acids to alkynes. It was found that the use of [Rh(COD)OH]$_2$ associated with the water-soluble ligand *m*-TPPTC was highly effective for such a reaction in the biphasic water/toluene system [Eq. (56)].[120,121]



(56)

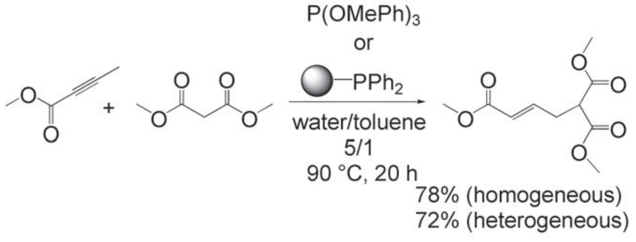
R = R' = C$_3$H$_7$ 80 – 99%
R = Me, R' = Ph 95 – 96%
R = C$_4$H$_9$, R' = 2-pyridyl, SiMe$_3$ 94 – 98%

***m*-TPPTC**

The reaction was completely stereo- and regioselectivitive. In addition, the catalyst did not lose any activity after being reused 4 times.

3.6 Alkylation

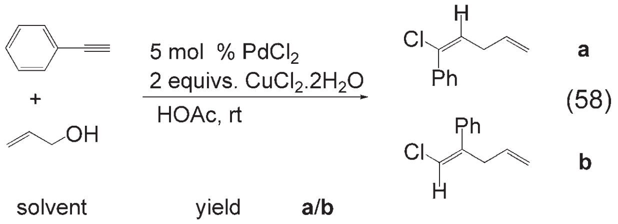
Recently, Li et al. developed a variant of Trost's γ-addition of malonate to 2-alkynoates in water catalyzed by phosphines.[122] They demonstrated that the polymer-supported triphenylphosphine as a catalyst efficiently catalyzed the addition and was easily recycled [Eq. (57)].



78% (homogeneous)
72% (heterogeneous)

(57)

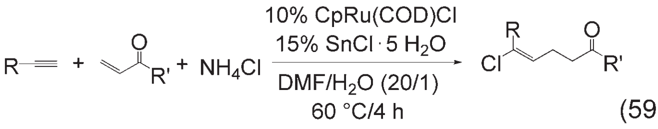
More recently, Jiang et al. reported a palladium-catalyzed allylation of alkynes by the direct use of allyl alcohol as the allylating agent in an aqueous solution.[123] The process provided a new highly stereo- and regioselective method to construct 1,4-dienes. It was shown that this reaction was more efficient and selective in aqueous media than in organic solvents. For example, the allylation of phenylacetylene in allyl alcohol solvent gave two isomers with the combined yield of 63% and a low regioselectivity (**a**/**b** = 63/37), whereas in aqueous HOAc, it furnished almost exclusively isomer **a** in 87% yield [Eq. (58)].



(58)

solvent	yield	a/b
allyl alcohol	63%	63/37
HOAc/H$_2$O (1/1)	87%	99/1

Trost et al. investigated a ruthenium-catalyzed, three-component coupling of an alkyne, an enone, and halide ion to form *E*- or *Z*-vinyl halides. In the presence of cyclopentadienylruthenium(II)(cyclooctadiene) chloride as a catalyst and stannic chloride pentahydrate as a co-catalyst, solvents are the key factor to affect the isomer selectivity. In most cases, polar solvents favored the formation of the *E*-isomer, and less polar solvents favored formation of the *Z*-isomer. The mixture of DMF/water proved to be the optimal solvent for the formation of *E*-vinyl chlorides [Eq. (59)].[124]

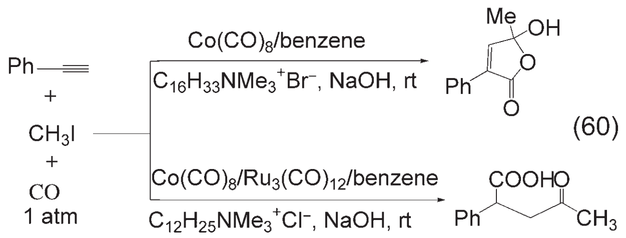


(59)

3.7 Carbonylation

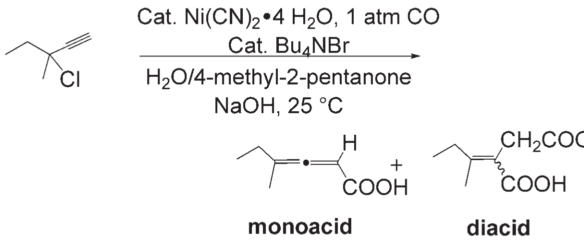
The carbonylation of alkynes is a convenient method to synthesize various carbonyl compounds. Alper et al. found that the carbonylation of terminal alkynes could be carried out in aqueous media in the presence of 1 atm CO by a cobalt catalyst, affording 2-butenolide products. They also reported this reaction catalyzed by a cobalt complex and a ruthenium complex to give γ-keto acids [Eq. (60)].[125]

Recently, it has been reported that the nickel-catalyzed carbonylation of α-haloalkynes with carbon



(60)

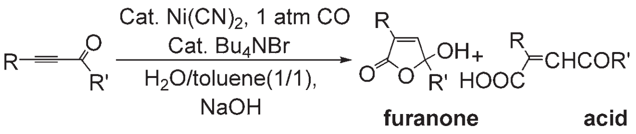
monoxide under phase-transfer conditions gave either allenic monoacids or unsaturated diacids. It was shown that the carbonylation afforded monoacids first, and then gave diacids with high stereoselectivity [Eq. (61)].[126,127]



(61)

1 hour : 94% (overall yield) *mono-*:*di-* = 87/13 (*E*/*Z* = 5/95)
48 hours: 96% (overall yield) *mono-*:*di-* = 0 /100 (*E*/*Z* = 9/91)

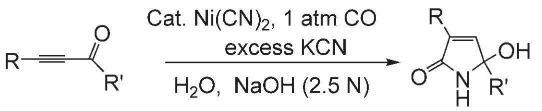
The nickel-catalyzed carbonylation of α-ketoalkynes under phase-transfer conditions has been reported by Arzoumanian et al.[128] The carbonylation gave either furanones or unsaturated carboxylic acids depending on the substituents of the substrates [Eq. (62)].They also reported a nickel-catalyzed cyanation



(62)

R = Ph, R' = Me: 78% (overall yield) *fu-*:*acid* = 100/0
R = Ph, R' = CMe_3: 35% (overall yield) *fu-*:*acid* = 41/59
R = C_4H_9, R' = Me: 53% (overall yield) *fu-*:*acid* = 0/100
R = C_4H_9, R' = CMe_3: 67% (overall yield) *fu-*:*acid* = 0/100

of α- ketoalkynes with KCN in water, affording unsaturated hydroxylactams [Eq. (63)].[129]

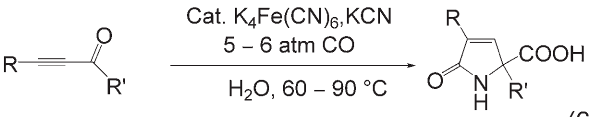


(63)

R = n-C_4H_9, Ph
R' = Me, Et, n-C_3H_7, n-C_4H_9 50 – 77%

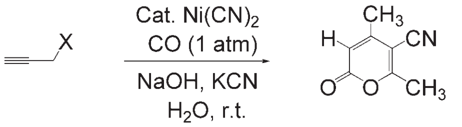
Later, Rosas et al. reported a potassium ferrocyanide-catalyzed carbonylation in the presence of KCN and CO in water, affording carboxylactams [Eq. (64)].[130]

They also developed a nickel-catalyzed cascade conversion of propargyl halides and propargyl alcohols into pyrones in water, which involves a carbonylation by CO and a cyanation by KCN [Eq. (65)].[131]



(64)

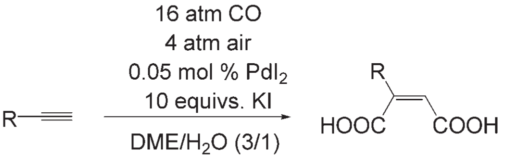
R = n-C_4H_9, Ph
R' = Et, n-C_3H_7, n-C_4H_9 73 – 82%



(65)

X = Br 86%
X = Cl 63%
X = OH 47%

Recently, Gabriele et al. explored a facile synthesis of maleic acids by palladium-catalyzed oxidative carbonylation of terminal alkynes in aqueous DME (1,2-dimethoxyethane) [Eq. (66)].[132]



20 – 71%

(66)

R = Ph, 4-MeC_4H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, n-Bu, t-Bu

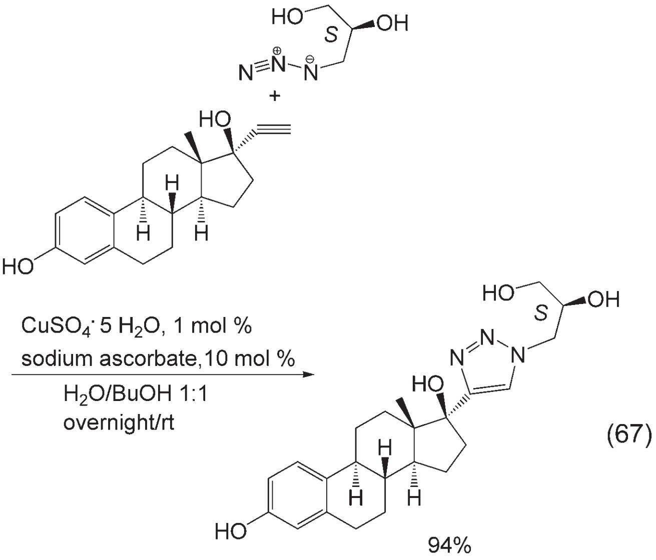
3.8 Other Reactions

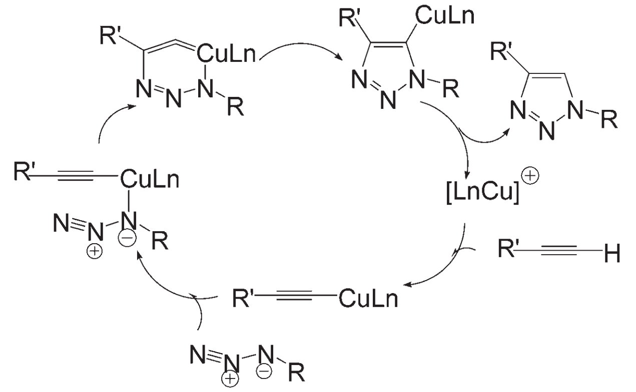
Beside the reactions surveyed above, there are other catalytic reactions of alkyne carbon-carbon bonds in water reported. Derien et al. reported a synthesis of γ,δ-unsaturated acetals and aldehydes *via* a ruthenium-catalyzed coupling of allyl alcohols with alkynes in water.[133] The indium-catalyzed addition reaction of Ph_2Se_2 or Ph_2S_2 with alkynes in aqueous media has also been reported.[134] It has also been found that the Pd(0)-catalyzed Kharasch reaction of alkynes could be enhanced by the use of a water as a solvent.[135]

4 Cyclization

4.1 [3+2] 1,3-Dipolar Cyclization

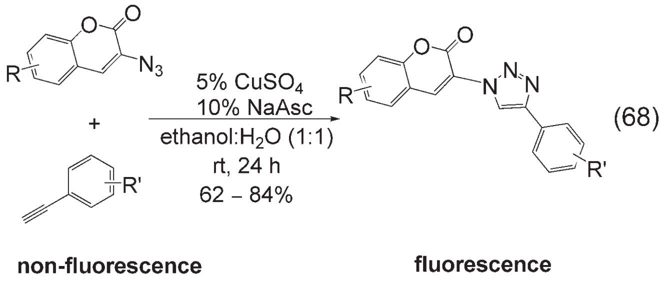
Recently, the [3+2] cyclization between alkynes and azides has been intensively studied. The strong interest in this field is not only because the triazole products obtained from the reaction show a broad range of biological activities, but also due to the reaction's high efficiency, termed "click chemistry" by Sharpless and co-workers.[136] In 2002, Sharpless et al. developed a Cu(I)-catalyzed [3+2] cycloaddition of alkynes and azides for the synthesis of 1,4-disubstituted 1,2,3-triazoles in excellent yields and near perfect regioselectivity in aqueous media (a mixture of water and alcohol) or water without co-solvent [Eq. (67)].[137] It has been shown that various unprotected functional groups did not interfere. The Cu(I) catalyst was generated *in situ* through reduction of Cu(II) by sodium ascorbate. They proposed a mechanism involving a regioselective ligation of Cu(I) to azide (Scheme 5). Based on this reaction, they subsequently developed an efficient click chemistry route to synthesize a variety of triazole dendrimers in water.[138]



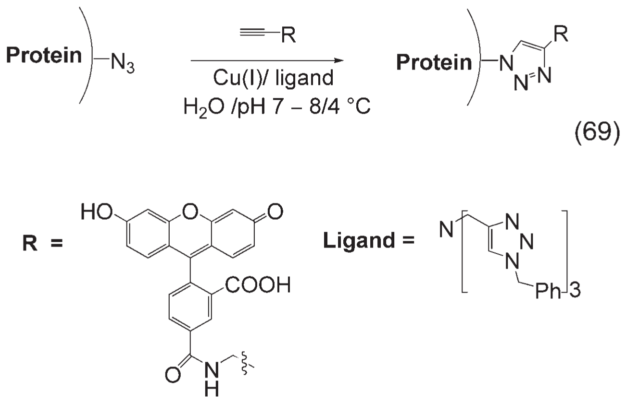


Scheme 5.

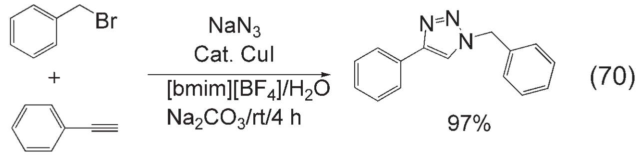
With the copper(I)-catalyzed 1,3-dipolar cycloaddition reaction, Wang et al. developed a facile route for the synthesis of fluorescent 1,2,3-triazole products from non-fluorescent 3-azidocoumarins and terminal alkynes in aqueous solution [Eq. (68)].[139]



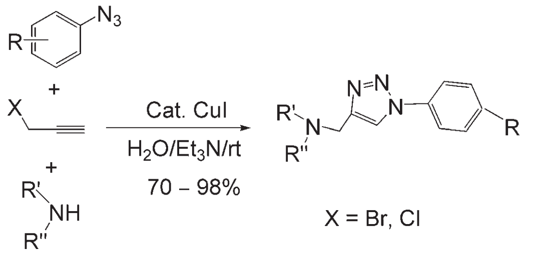
It is challenging to incorporate functional groups into biological molecules by organic synthesis since a large protein structure has numerous sensitive groups. Recently, Finn, Sharpless and co-workers applied the Cu(I)-catalyzed azide-alkyne [3+2] cycloaddition, which was rapid and highly selective at room temperature, to biological molecules. They utilized cowpea mosaic virus (CPMV) as the protein component which is a structurally rigid assembly of 60 identical copies of a two-protein for their studies. They demonstrated that [3+2] cycloaddition occurred quantitatively towards the triazole product in the presence of tris(triazolyl)amine (as a ligand), which protected the virus from Cu-triazole-induced disassembly, and the Cu(I) catalyst which was generated *in situ* through the reduction of Cu(II)$SO_4 \cdot 5\,H_2O$ by using Cu wire or a water-soluble reducing agent of tris(carboxyethyl)-phosphine (TCEP) [Eq. (69)].[140]



A Cu(I)-catalyzed three-component reaction of halides, sodium azide and alkynes has been reported by Liang et al. [Eq. (70)].The reaction was carried out in a mixture of the ionic liquid [bmim][BF_4] and water to form 1,4-disubstituted 1,2,3-triazoles efficiently.[141]

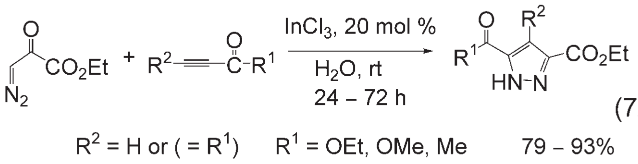


They also reported a three-component reaction of azides, propargyl halides and amines, to form (1-substituted-1*H*-1,2,3-triazol-4-ylmethyl)-dialkylamines based on the Cu(I)-catalyzed reaction in water [Eq. (71)].[142]

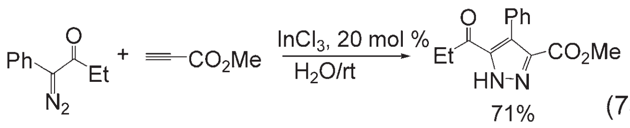


(71)

In addition, other types of [3+2] 1,3-dipolar cycloadditions in water have been reported recently. One of the examples is the cycloaddition of diazo compounds with alkynes, to synthesize pyrazoles that are known to show many biological activities. Li et al. reported the first intermolecular 1,3-dipolar cycloaddition of diazocarbonyl compounds with alkynes catalyzed by $InCl_3$ in water. It has been found that the reaction proceeded by a domino 1,3-dipolar cycloaddition-hydrogen (alkyl or aryl) migration [Eqs. (72–74)].[143] It is worth mentioning that the use of water as a solvent not only enables one to reuse the $InCl_3$ catalyst but also plays a crucial role in this reaction. For example, $InCl_3$ was shown to be reused for two additional times for the reaction of ethyl diazoacetate and propiolate in water without loss of catalytic activity (yields, 87%, 89%, and 90% for the first, second and third runs, respectively). In contrast, this reaction in the organic solvents CH_2Cl_2 or benzene (the common solvent for diazo chemistry) gave only a trace amount of the target product.



(72)



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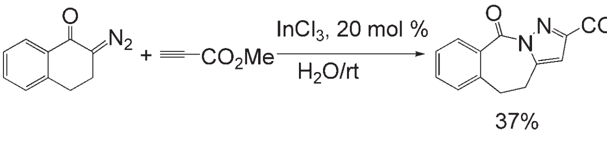
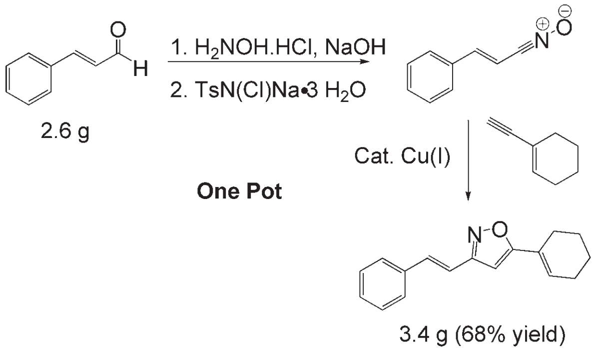


(74)

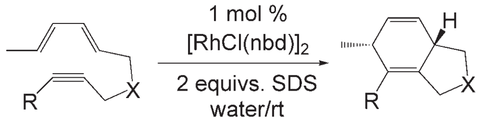
Another example is a Cu(I) catalyzed-cycloaddition of nitrile oxides to acetylenes in water reported recently. It was shown that a regioselective copper(I)-catalyzed cycloaddition reaction between *in situ* generated nitrile oxides and terminal alkynes *via* a one-pot, three-step procedure, afforded 3,5-disubstituted isoxazoles in good yields in water [Eq. (75)].[144]



(75)

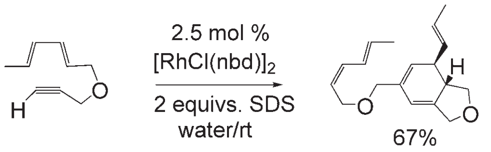
4.2 [4+2] Cyclization

Oshima et al. explored a cationic rhodium-catalyzed intramolecular [4+2] annulation of 1,3-dien-8-ynes in water in the presence of sodium dodecyl sulfate (SDS), an anionic surfactant [Eq. (76)].[145] In contrast, when the substrate 1,3-dien-8-yne is a terminal alkyne, the reaction provided an intermolecular [2+2+2] product [Eq. (77)]. In water, a reactive cationic rhodium species was formed by dissociation of the Rh–Cl bond in the presence of SDS. The SDS forms negatively charged micelles, which would concentrate



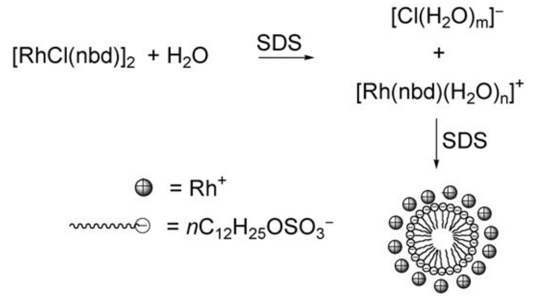
(76)

R = CH_2OH,	X = O,	93%
R = CH_2OBn,	X = O,	97%
R = $SiMe_3$,	X = O,	99%
R = CH_3,	X = NBn,	95%
R = Ph,	X = $CH(COOEt)_2$,	71%



(77)

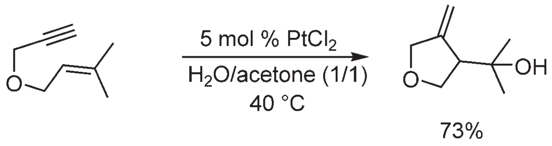
the cationic rhodium species to facilitate the reaction [Eq. (78)].



(78)

4.3 Enyne Cyclization

In the presence of $PtCl_2$ as a catalyst, 1-en-6-ynes were reacted with water in an aqueous acetone solution to give carbocycles with hydroxy functional groups at the side chain [Eqs. (79–81)].[146]



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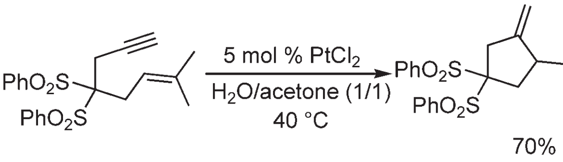
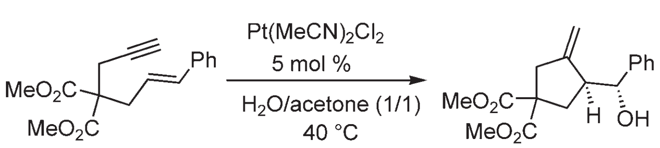


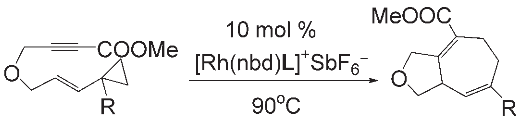
(80)



95% (81)

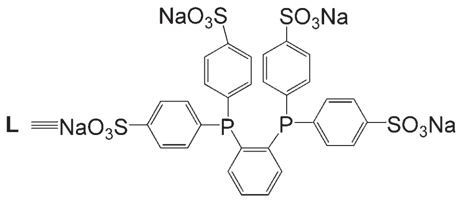
It was shown that the *trans* addition of the electrophile derived from the alkyne and the nucleophile to the double bond of the enyne formed the C–C and C–O bonds stereoselectively and simultaneously. It was found that a cyclopropyl platinacarbene complex was the key intermediate in the process based on density functional theory (DFT) calculations.

A rhodium catalyst associated with a new water-soluble bidentate phosphine ligand was shown to be highly effective for [5+2] enyne cyclization in water, giving a 7-membered ring product [Eq. (82)]. The water soluble catalyst was reused for 8 times without any significant loss in catalytic activity.[147]



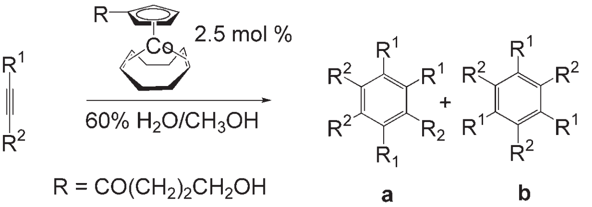
(82)

R = Me (H_2O solvent , 12 h) 80%
R = H (20% MeOH/H_2O, 1.5 h) 79%



4.4 [2+2+2] Cyclotrimerization

Alkyne cyclotrimerization is an important synthetic methodology since aromatic rings are key units for many pharmaceutical, biological, and polymer molecules. Numerous cyclotrimerization reactions in organic solvents have been reported using (cyclopentadienyl)cobalt dicarbonyl [$CpCo(CO)_2$], whereas no CpCo catalysis in aqueous solutions had been reported until recently. One problem for aqueous catalysis is that with $CpCo(CO)_2$ in aqueous media it is difficult to substitute the CO ligands, possibly due to the strong back-bonding enhanced by the highly dielectric water. Recently, Sigman et al. successfully developed a new, water-soluble cobalt catalyst, CpCo-η^4-cyclooctadiene, to catalyze alkyne cyclotrimerization in water at an elevated temperature [Eq. (83)]. Protection of alkyne functional groups, such as amine, hydroxy, ketone, ester, and carboxylic acid, was not required in this aqueous [2+2+2] cyclotrimerization chemistry.[148]

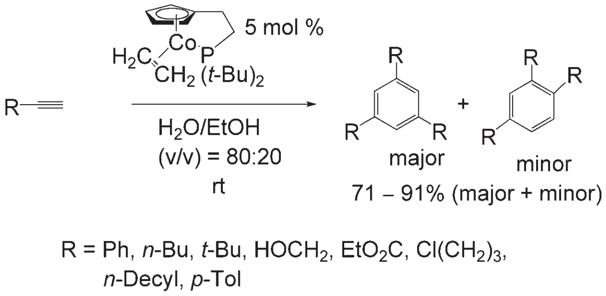


(83)

R = $CO(CH_2)_2CH_2OH$

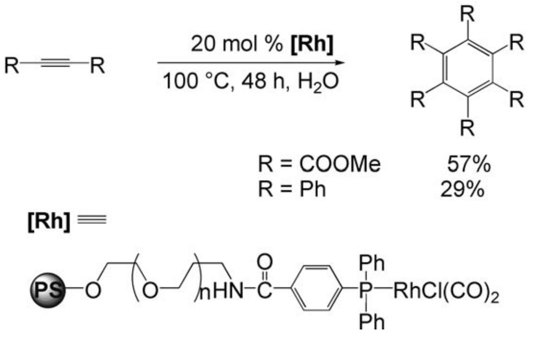
R^1	R^2	Yield [%]	a/b
H	COMe	44	0/44
H	COOMe	67	47/20
H	CH_2OH	85	62/23
H	CH_2NHCH_3	73	47/26
H	$(CH_2)_2COOH$	56	36/20

Later, Yong et al. developed a cobalt-catalyzed [2+2+2] cyclotrimerization of terminal alkynes in good yields in aqueous media (80/20 mixture of water and ethanol) at room temperature. They employed a cyclopentadienylcobalt complex bearing a pendant phosphine ligand as a catalyst [Eq. (84)]. The cyclotrimerization of internal alkynes resulted in lower yields and required an elevated temperature, most likely due to steric interactions. For example, cyclotrimerization of 2,5-dimethyl-3-hexyne gave hexaisopropylbenzene in 51% yield, and the reaction of diphenylethyne resulted in 47% yield of hexaphenylbenzene.[149]



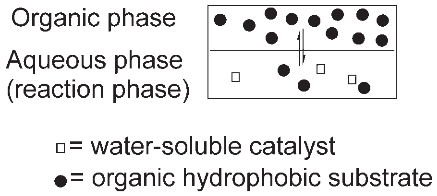
(84)

Rhodium has also been reported as a catalyst for [2+2+2] alkyne cycloaddition in water. Uozumi et al. studied an amphiphilic resin-supported rhodium-phosphine complex, which was prepared on polystyrene-poly(ethylene glycol) graft co-polymer (1% DVB cross-linked) beads (PS-PEG) [Eq. (85)]. The immobilized rhodium catalyst was effective for the [2+2+2] cycloaddition of internal alkynes in water, although the product yields were not satisfactory.[150]



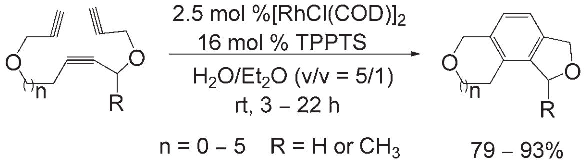
(85)

Rhodium was reported as a highly effective catalyst for an intramolecular [2+2+2] cyclotrimerization in an aqueous-organic biphasic system. It has been shown that the use of a biphasic system could control the concentration of an organic hydrophobic substrate in the aqueous phase (Scheme 6) and thus increase the reaction selectivity. The intramolecular cyclization for the synthesis of medium- and large-sized ring systems usually requires a slow addition process or highly diluted reaction conditions to prevent intermolecular side reactions.



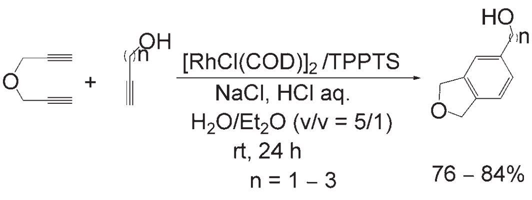
Scheme 6.

However, the process of slow addition is time-consuming and the highly diluted reaction conditions not only waste large quantities of solvent but also lower the reaction rate. Kinoshita et al. has successfully developed an intramolecular [2+2+2] cyclotrimerization in an aqueous-organic biphasic system catalyzed by a water-soluble rhodium catalyst, which was prepared *in situ* from $[RhCl(COD)]_2$ and tris(sodium *m*-benzenesulfonate)phosphine (TPPTS) [Eq. (86)].[151]

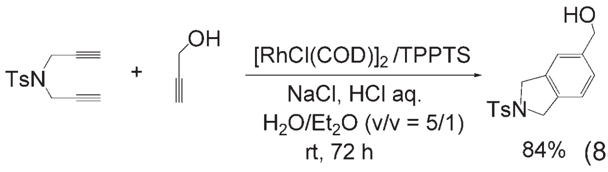


(86)

A selective [2+2+2] cross-annulation between hydrophobic diynes, such as 1,6-diyne, and hydrophilic alkynes, such as alkynols, has also been achieved in good yields [Eqs. (87 and 88)].



(87)



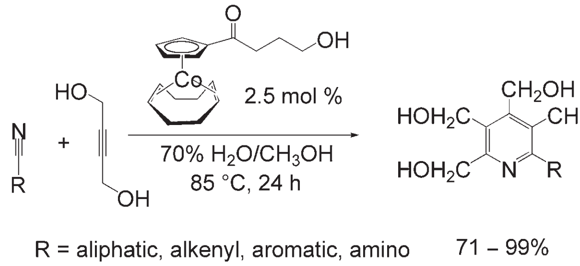
(88)

The low efficiency due to highly diluted conditions was possibly compensated by water accelerating the Diels–Alder type cycloaddition.[152] It was shown that medium and large rings were obtained in excellent yields with only trace amounts of polymeric compounds, and no dimerization products were detected in the reaction mixture.

Palladium has also been reported as an effective catalyst for [2+2+2] alkyne cyclotrimerization in water. Both aryl- and alkylalkynes underwent cyclotrimerization to afford the corresponding products regioselectivity in high yields in the presence of $PdCl_2$, $CuCl_2$ and CO_2 in water at room temperature.[153] For example, the cyclotrimerization of terminal alkynes gave symmetric benzenes and 1-phenylpropyne gave 1,3,5-triphenyl-2,4,6-trimethylbenzene. However, alkynes with bulky substrates such as *tert*-butylacetylene gave a dimerization product.

4.5 Hetero-[2+2+2] Cyclotrimerization

Hetero-[2+2+2] cyclotrimerization is a powerful synthetic methodology that has been elegantly exploited in organic solvents for the synthesis of complex heterocyclic aromatic molecules. Recently, Fatland et al. developed an aqueous alkyne-nitrile cyclotrimerization of one nitrile with two alkynes for the synthesis of highly functionalized pyridines by a water-soluble cobalt(I) catalyst [Eq. (89)]. It has been shown that the reaction was chemospecific and several different functional groups were well incorporated in this transformation without being protected, such as alcohols, ketones, and amines.[154]

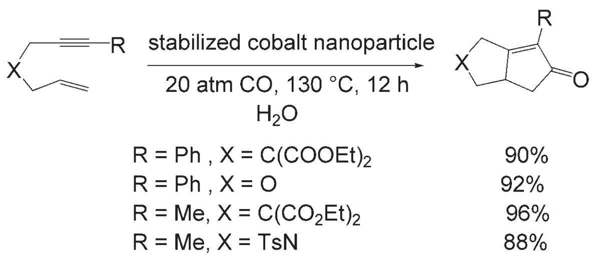


(89)

Additionally, photocatalyzed [2+2+2] alkyne or alkyne-nitrile cyclotrimerization in water[155–157] and cyclotrimerization in supercritical H_2O[158,159] have been reported in recent years.

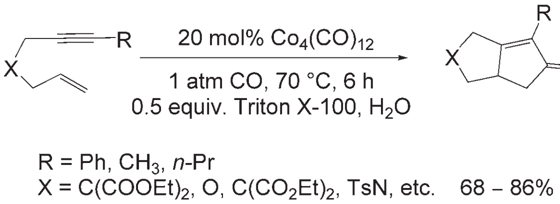
4.6 Pauson–Khand-Type Reaction

The Pauson–Khand reaction (PKR) is an efficient method to synthesize cyclopentenones. Recently, this reaction has been studied in aqueous medium. Chung et al. successfully developed an intramolecular Pauson–Khand reaction in water without any co-solvents by using aqueous colloidal cobalt nanoparticles as catalysts, which were prepared by reducing an aqueous solution of cobalt acetate containing sodium dodecyl sulfate (SDS) surfactant [Eq. (90)].[160] The cobalt nanoparticles could be reused for 8 times without any loss of catalytic activity.

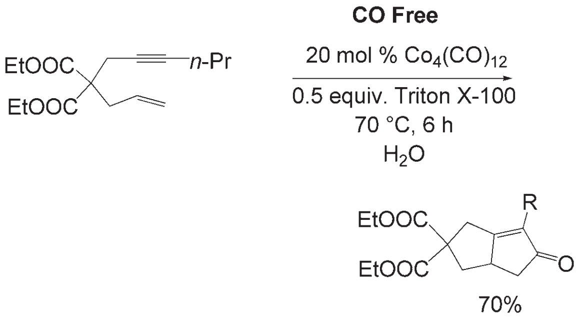


(90)

Later, Krafft et al. demonstrated a $Co_4(CO)_{12}$-catalyzed PK-type reaction in a water-Triton® X-100 medium.[161,162] It has been shown that only 1 atm CO was required for the process [Eq. (91)] and even in the absence of CO, the reaction still furnished the desired products, albeit with slightly decreased yields [Eq. (92)].

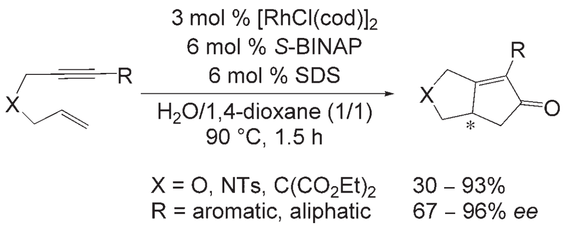


(91)



(92)

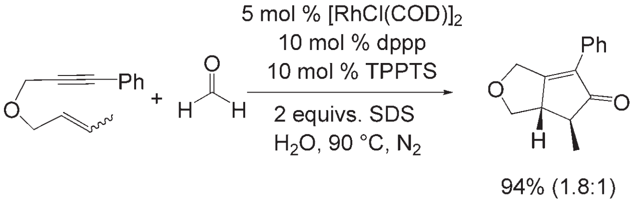
Chung et al. reported the first rhodium-(*S*)-BINAP complex-catalyzed enantioselective Pauson–Khand reaction in aqueous media [Eq. (93)].[163] The chiral rhodium catalyst was easily prepared *in situ*. It was shown that the reaction was accelerated by a surfac-



(93)

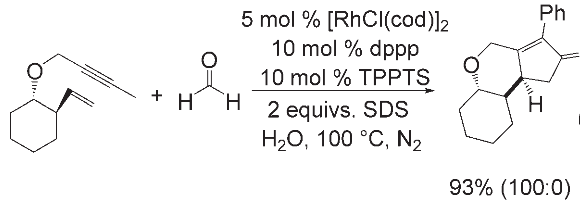
tant, and under 1 atm of CO at 90 °C, the PK-type products were achieved with up to 96% *ee*.

Recently, Morimoto, Kakiuchi and co-workers employed formaldehyde as a water-soluble source of carbon monoxide for the PK-type reaction. The use of low-cost formaldehyde as the source of carbon monoxide offered a more convenient and safer PK-type reaction than the conventional processes.[164] With a rhodium catalyst associated with the ligand dppp [1,3 bis(diphenylphosphanyl)propane], and a water-soluble ligand TPPTS (triphenylphosphane-3,3′,3″-trisulfonic acid trisodium salt), reactions of enynes with formaldehyde gave asymmetric products with high yields in aqueous solution [Eqs. (94 and 95)].



94% (1.8:1)

dppp = 1,3-bis(diphenylphosphanyl)propane (94)
SDS = sodium dodecyl sulfate
TPPTS = triphenylphosphane-3,3',3''-trisulfonic acid trisodium salt
COD = cyclooctadiene



(95)

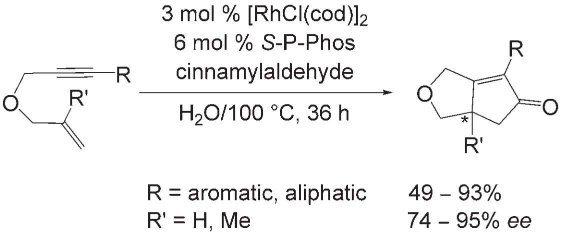
93% (100:0)

The chiral ligand tolBINAP [2,2′-bis(di-*p*-tolylphosphino)-1,1′-binaphthyl] together with [RhCl(COD)]$_2$/TPPTS was also shown to be effective for the asymmetric PK-type reaction in water.[165]

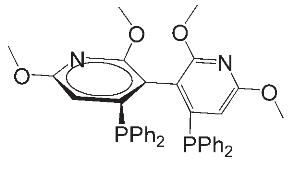
Kwong, Chan, and co-workers also developed a rhodium-catalyzed asymmetric aqueous Pauson–Khand-type reaction.[166] It was shown that a chiral atropisomeric dipyridyldiphosphane ligand (*S*-P-Phos) was highly effective for this process, transforming various enynes into the corresponding bicyclic cyclopentenones in good yield and enantiomeric excess (up to 95% *ee*) [Eq. (96)].

4.7 Other Cyclizations

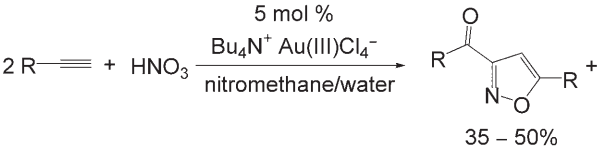
Isoxazole, an important compound in medicinal and agricultural chemistry, could be synthesized *via* a gold(III)-catalyzed [2+2+1] cyclization of terminal alkynes and nitric acid [Eq. (97)].[167] Terminal alkynes bearing alkyl, aryl, alkoxy, and carboxylate groups all survived in this process. Additionally, nitromethane/water proved to be a unique biphasic system for promoting this reaction.



(96)

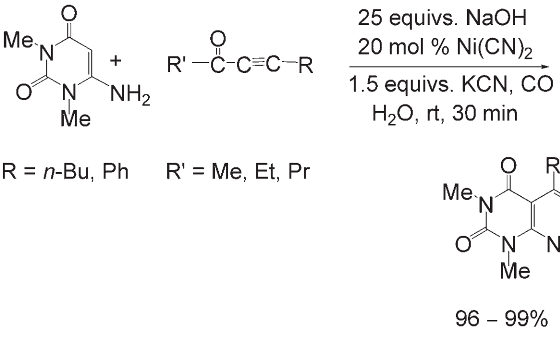


***S*-P-Phos**



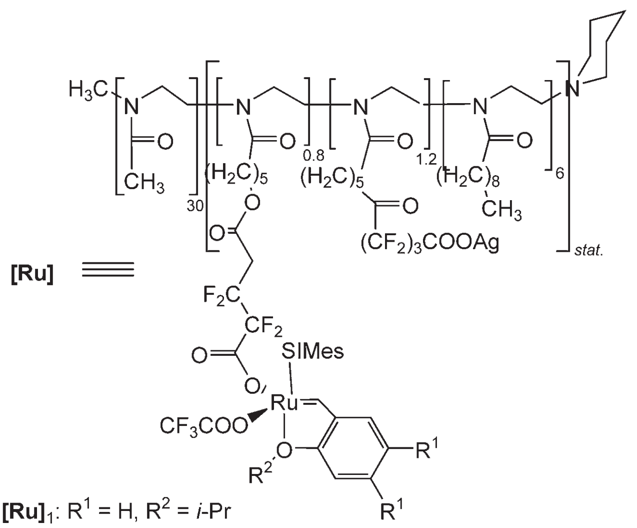
(97)

It has been reported that nickel-catalyzed reactions of 6-amino-1,3-dimethyluracil with ynones gave substituted 2,4-dioxopyrido[2,3-*d*]pyrimidine derivatives, which have potential pharmacological and biological activities, in quantitative yields at room temperature in water [Eq. (98)].[168]

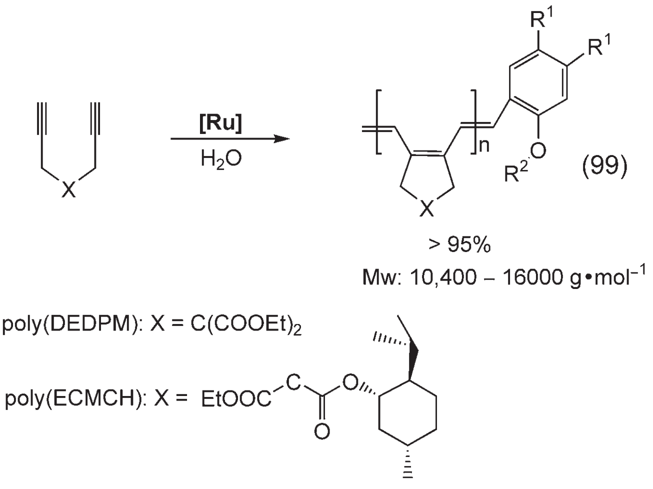


(98)

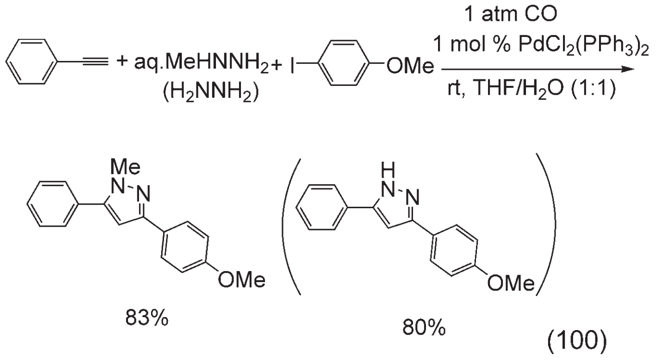
Poly(acetylene) has been widely used in different fields such as organic light-emitting diodes (OLEDS), solar cells, and lasers, etc. The synthesis of poly(acetylene)s in water is very attractive for many industrial applications, since they can form a stable aqueous dispersion which can be directly deposited on suitable supports. Recently, Buchmeiser et al. explored a synthesis of poly(acetylene) in water catalyzed by a poly(2-oxazoline)-immobilized ruthenium catalyst which tolerated water.[169] The polymerization of the diethyl dipropargylmalonate (DEDPM) and chiral 4-



[Ru]$_1$: R^1 = H, R^2 = *i*-Pr
[Ru]$_2$: R^1 = OMe, R^2 = Me
SIMes = 1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazolin-2-ylidene



(ethoxycarbonyl)-4-(1*S*,2*R*,5*S*)-(+)-menthoxycarbonyl-1,6-heptadiyne (ECMCH) gave quantitative yields of the expected polymers, respectively, with molecular weights ranging from 10,000–16,000 g mol^{-1} [Eq. (99)]. The immobilization of the Ru catalyst separated the product from the catalyst and provided Ru-free poly(acetylene)s.



A four-component coupling of a terminal alkyne, hydrazine, carbon monoxide, and an aryl iodide was reported by Mori et al. recently.[170] It was shown that the reaction proceeded at room temperature and an ambient pressure of carbon monoxide in an aqueous solvent to furnish pyrazole derivatives in the presence of a palladium catalyst [Eq. (100)].

5 Conclusion

As both catalytic reaction of alkynes and water-based organic synthesis have been experiencing most intensive studies in recent years, research on the aqueous reactions of alkynes has also been explored recently. This article gives the first general review of catalyzed alkyne reaction in aqueous media. The use of water as a solvent for reactions of alkynes has numerous advantages in terms of reaction efficiency and selectivity or economical and environmental concerns. More and more highly efficient aqueous alkyne reactions have been developed and many of them have been applied to materials science and other areas of chemistry such as peptide chemistry, synthetic chemistry, and medicinal chemistry. More and more new results on this subject are emerging.

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