The Development of Catalytic Nucleophilic Additions of Terminal Alkynes in Water†

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CONSPECTUS

One of the major research endeavors in synthetic chemistry over the past two decades is the exploration of synthetic methods that work under ambient atmosphere with benign solvents, that maximize atom utilization, and that directly transform natural resources, such as renewable biomass, from their native states into useful chemical products, thus avoiding the need for protecting groups. The nucleophilic addition of terminal alkynes to various unsaturated electrophiles is a classical (textbook) reaction in organic chemistry, allowing the formation of a C−C bond while simultaneously introducing the alkyne functionality. A prerequisite of this classical reaction is the stoichiometric generation of highly reactive metal acetylides.
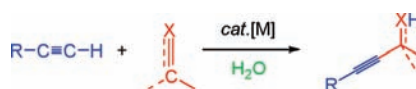
Over the past decade, our laboratory and others have been exploring an alternative, the catalytic and direct nucleophilic addition of terminal alkynes to unsaturated electrophiles in water. We found that various terminal alkynes can react efficiently with a wide range of such electrophiles in water (or organic solvent) in the presence of simple and readily available catalysts, such as copper, silver, gold, iron, palladium, and others. In this Account, we describe the development of these synthetic methods, focusing primarily on results from our laboratory.

Our studies include the following: (i) catalytic reaction of terminal alkynes with acid chloride, (ii) catalytic addition of terminal alkynes to aldehydes and ketones, (iii) catalytic addition of alkynes to C=N bonds, and (iv) catalytic conjugate additions. Most importantly, these reactions can tolerate various functional groups and, in many cases, perform better in water than in organic solvents, clearly defying classical reactivities predicated on the relative acidities of water, alcohols, and terminal alkynes. We further discuss multicomponent and enantioselective reactions that were developed.

These methods provide an alternative to the traditional requirement of separate steps in classical alkyne reactions, including the pregeneration of metal acetylides with stoichiometric, highly basic reagents and the preprotection of sensitive functional groups. Accordingly, these techniques have greatly enhanced overall synthetic efficiencies and furthered our long-term objective of developing Grignard-type reactions in water.

1. Introduction

The nucleophilic addition of metal acetylides to unsaturated electrophiles is one of the classical reactions in organic chemistry to generate functionalized alkyne products that are amenable for further transformation into a wide range of structures.[1,2] However, this classical textbook methodology requires the presynthesis of metal acetylides from terminal alkynes and highly reactive and strongly basic organometallic reagents such as alkyl Grignard reagents, alkyl lithium reagents, and metal amides (route a,

Scheme 1). Hence, such reactions are often highly sensitive toward air and water, and many functional groups cannot be tolerated under these conditions and thus require "protection". In addition, acids need to be added to quench the reaction in the end. The overall process suffers low atom economy,[3,4] often requires multiple steps and predrying of solvents, poses potential concerns for operational safety, and generates stoichiometric amounts of waste.[5]

To overcome the challenge of low atom economy associated with the classical nucleophilic addition of alkynes, Trost pioneered the

palladium-catalyzed conjugated direct addition of terminal alkynes to electron-deficient alkynes.[6] It is noteworthy that highly efficient, direct, and asymmetric conjugated additions of terminal alkynes to electron-difficient alkenes have been developed recently.[7] On the other hand, direct addition of terminal alkyne to aldehdyes was pioneered by Yamaguchi,[8] Huang,[9] and Carreira[10] by using tin, gallium and zinc as mediators or catalysts. Excellent asymmetric alkyne−aldehyde additions have been extensively developed by Carreira and many others recently.[2] For the addition of terminal alkynes to C=N bonds, Miura reported the addition of acetylene to nitrones through the initial formation of a dipolar cycloaddition,[11] while Carreira had used a Zn(II)-catalyzed process in CH_2Cl_2 for the addition of terminal alkynes to nitrones.[12] Recently, the catalytic additions of terminal alkynes to various C=N bonds have been widely studied.[13,14]

However prior to our study, such additions were very limited and generally required anhydrous conditions and an inert atmosphere. For the past two decades, we and others have been studying Barbier−Grignard-type nucleophilic additions reactions in water.[15,16] Despite tremendous successes on the subject, related reactions involving alkynyl halides never succeeded possibly due to the high strength of the sp C−X bond. Consequently, in the late 1990s with parallel research in arene−alkyne polymerizations in water,[17] we commenced an alternative strategy to explore the possibility of direct nucleophilic addition of terminal alkyne, rather than alkynyl halides, in water (route b, Scheme 1). This Account describes the development of this subject in the past decade mainly focusing on the results from our laboratory rather than a comprehensive review.

2. Relative Reactivity of Various Electrophiles

In order to understand the nature and potential of direct and catalytic nucleophilic addition of terminal alkynes, the relative reactivities of various electrophiles were considered. For convenience, we considered the reactivities in three classes: (I) carbonyl derivatives, (II) C=N bond derivatives, and (III) conjugated systems. The relative reactivities toward electrophiles are represented sequentially in Scheme 2.

**SCHEME 1.** Classical (a) and Aqueous Catalytic (b) Nucleophilic Addition of Alkynes
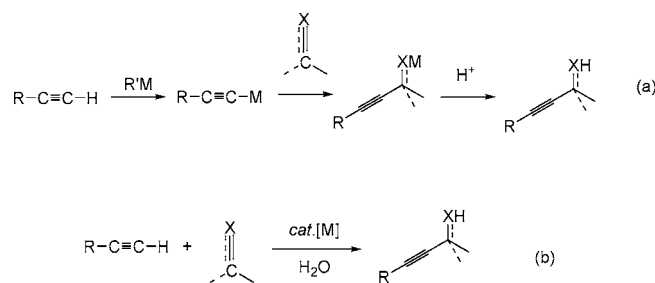
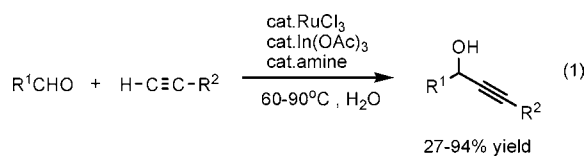**SCHEME 2.** Relative Reactivity of Three Classes of Electrophiles toward Alkynes
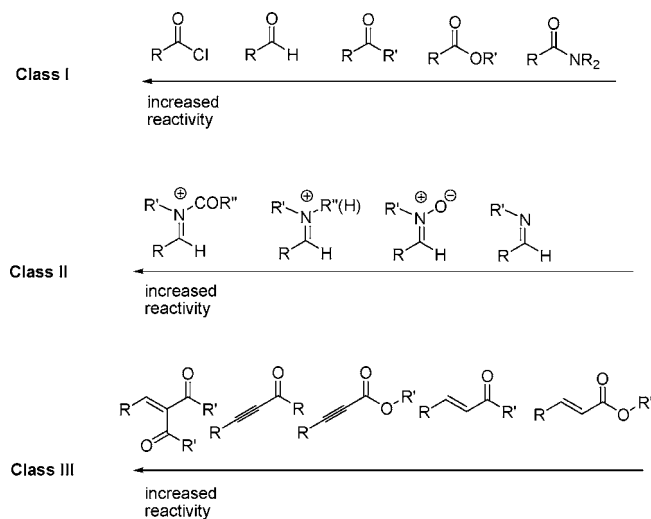
3. Direct Nucleophilic Addition of Terminal Alkynes to Carbonyl Derivatives (Class I)

Aldehydes. In order to ensure that the substrate has a reasonable reactivity and can still tolerate water, we decided to start our investigation with aldehdye−alkyne addition reactions. We speculated that since neither alkynes nor aldehydes are reactive enough, two different catalysts would be required to activate each of the reaction partners. Furthermore, the catalysts themselves must tolerate water (and possibly air). We chose $RuCl_3$ to activate alkynes based on the well-known ruthenium-catalyzed polymerization of terminal alkynes and In^{3+} to activate aldehdyes based on their water-tolerant nature.[18,19]

Indeed, we found that a direct addition of terminal alkynes to aldehydes in water proceeded successfully when a ruthenium−indium bicatalyst system was used (eq 1).[20] In this combination, the $In(OAc)_3$ presumably served in the role of a Lewis acid and activated the carbonyl, whereas the ruthenium chloride converts the alkynyl C−H bond to an alkynylruthenium intermediate. Since the metal ions can be regenerated, only a catalytic amount of the catalysts is

**SCHEME 3.** Proposed Mechanism of the Alkynylation Catalyzed by Ru/In in Water
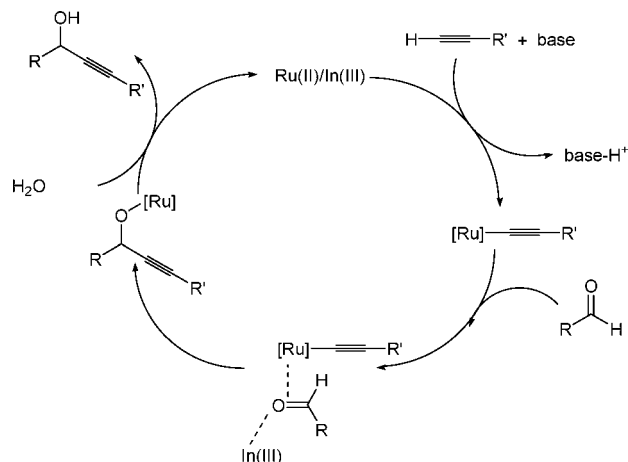
required (Scheme 3). The addition of a base improved the yield of the reaction.

$$R^1CHO + H-C\equiv C-R^2 \xrightarrow[\text{60-90°C , H}_2\text{O}]{\substack{\text{cat.RuCl}_3 \\ \text{cat.In(OAc)}_3 \\ \text{cat.amine}}} \quad (1)$$

27-94% yield

Alkynylsilver compounds are known to form readily from terminal alkynes and silver salts in water. However, simple alkynylsilver is unreactive toward aldehydes due to the strong and covalent nature of the C—Ag bond.[21] We postulated that by use of a strong coordinating and π-acidic phosphine ligand, it would serve two purposes: (1) the weakening of the C—Ag bond and (2) the increase in Lewis acidity of the [Ag] center (to coordinate and activate C=O bonds). In this way, a single metal catalyst will be enough for the reaction to occur. Indeed, a highly efficient alkynylation of aldehydes was accomplished by use of silver—phosphine complexes as catalysts in water (eq 2).[22] The reaction was dually promoted by the electron-donating (but π-acidic) phosphine ligand and water (yield 63−98%, Scheme 4). Almost no reaction was observed in toluene. A hydroxyl-containing aldehyde has been alkynylated without the need for protection (eq 3).


$$ \quad (2)$$

$$ \quad (3)$$

73%
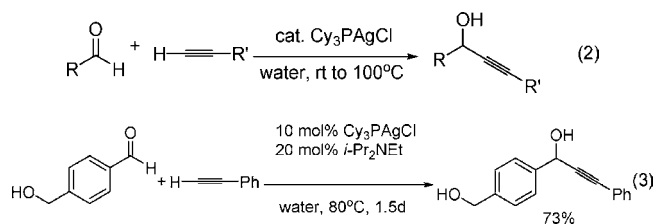
(Z)-2,3-Dihydrobenzofuran-3-ol derivatives are key intermediates for the syntheses of aurones, which have exhibited a wide

**SCHEME 4.** Proposed Mechanism of the Alkynylation Catalyzed by Silver in Water
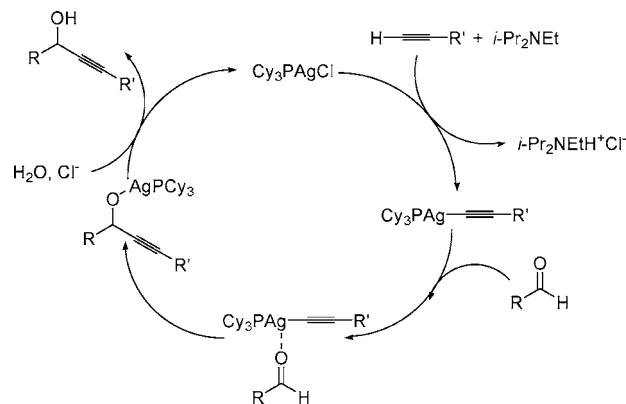
range of biological activities and have been used as antifungal agents, tyrosinase inhibitors, antioxidants, and others.[23] Among the reported methods for synthesizing aurones,[24] the gold(I)-catalyzed cyclization of 2-(1-hydroxy-3-arylprop-2-ynyl)phenols followed by oxidation of the cyclized product with MnO_2 reported very recently by Pale and co-workers provides a highly efficient route to these compounds.[25] We found that highly efficient alkynylation−cyclization of terminal alkynes with salicylaldehydes leads to substituted 2,3-dihydrobenzofuran-3-ol derives by using a Cy$_3$P−silver complex as catalyst in water. Counteranions in the silver complex proved to be the key factor to control Z/E stereoselectivity. Aurones can also be obtained effectively from the cascade reaction followed by oxidation without further purification (Scheme 5).[26]

The dihydrobenzopyran core is an important subunit of many naturally occurring heterocycles, many of which are biologically active. By using a strategy similar to the silver-catalyzed cascade reaction, we found that highly efficient alkynylation−cyclization of terminal alkynes with *ortho*-alkynylaryl aldehydes, using a gold−phosphine complex as the catalyst in water, led to the formation of 1-alkynyl-1*H*-isochromenes efficiently (eq 4). The reaction was dually promoted by an electron-donating phosphine ligand and water, as well as chelation-controlled (Scheme 6).[27] No reaction was observed with simple aromatic aldehydes, which imparts an interesting chemical selectivity. This selectivity suggested an alternative mechanism, which involves a gold-catalyzed aldehyde−alkyne cyclization followed by a acetylide addition to the resulting oxonium intermediate.[28]


$$ \quad (4)$$
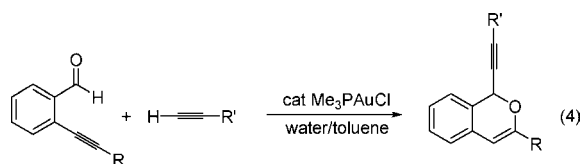
SCHEME 5. Synthesis of 2,3-Dihydrobenzofuran-3-ol and Aurone Derivatives
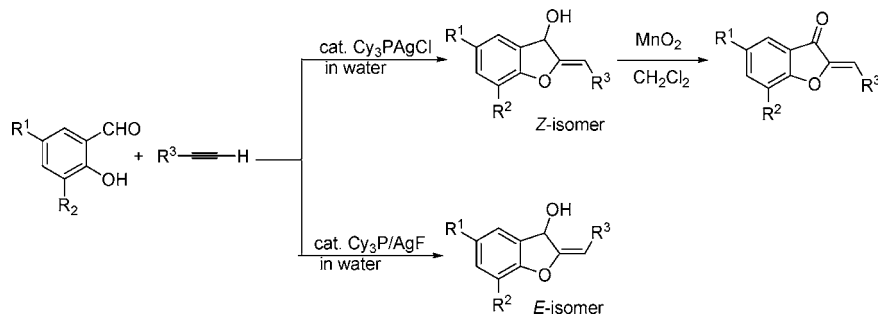
SCHEME 6. Tentative Mechanism for the Gold(I)-Catalyzed Cascade Alkynylation/Cyclization
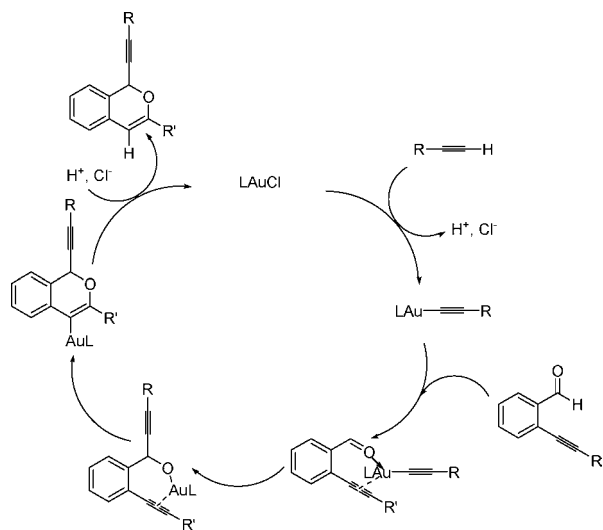
In addition to the formation of the propargyl alcohol, indium chloride catalyzed the coupling of alkynes to aldehydes to give α,β-unsaturated carbonyl compounds in water in low yields (eq 5).[29] The product may be formed via the further reaction of the propargyl alcohol.
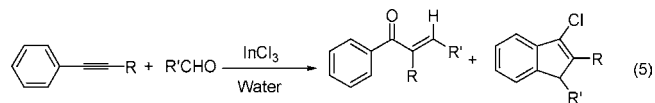

Acid Chlorides. Due to the much higher reactivity of acid chloride, we were initially quite skeptical about the possibility of performing the reaction between alkyne and acid chloride in water. Nevertheless, we were surprised to find that a highly effective direct coupling of acid chloride with terminal alkynes could be 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 6).[30] No desired product was detected when either Cu(I) or Pd(II) alone was used as the catalyst. The use of the surfactant was also necessary for the success of this transformation possibly by temporarily stabilizing the acid chlo-

ride. As an example, without a surfactant/phase-transfer reagent the yield dropped from 98% to 9%. The use of water as a solvent allowed use of inorganic bases instead of organic bases, which not only made the separation easier but also reduced the organic base waste.
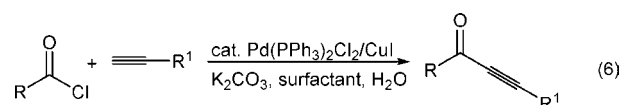

Ketones. Compared with aldehydes and imines, ketone is much less reactive for both steric and electronic reasons. One type of ketone that can overcome the electronic disadvantage is trifluoromethyl ketone. The synthesis of organofluorine compounds has attracted much interest due to their importance in biological studies.[31] We found that highly effective direct alkynylation of trifluormethyl ketone in water or in organic solvents was successful with silver as the catalyst (eq 7). Trifluoropyruvate reacted with terminal alkynes efficiently in water at room temperature.[32] By increase of the reaction temperature to 100 °C, trifluoroacetophenone could also react with phenylacetylene in water to give the alkynylation product in good yield. It is noteworthy that the reaction can be carried out under an air atmosphere, although a lower yield was obtained. The reaction in water is almost as efficient as that in common organic solvents or under neat conditions, and only a trace amount of the alkynylation product was observed when the reaction was carried out in either ethanol or methanol. The counterion also played an important role: whereas both AgI and AgBr only gave trace amounts of the desired product, an excellent yield was obtained when AgF/PCy$_3$ was employed as the catalyst. The choice of phosphine ligand is also important in this reaction: when PCy$_3$ was replaced by other phosphines, the yield decreased significantly. It is important to note that Shibasaki recently disclosed the enantioselective alkynylation of activated trifluoromethyl ketones using chiral bidentate phosphine ligand or pybox and a catalytic copper salt together with a base.[33]

$$(7)$$

93%
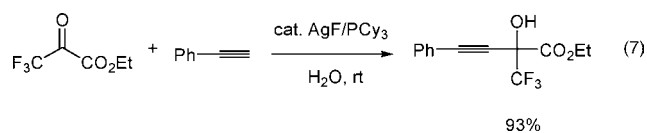
4. Addition of Terminal Alkyne to Imine, Tosylimine, Iminium Ion and Acyl Iminium Ion (Class II)

Imines. Our strategy for effecting the addition of terminal alkynes to C=N bonds is different from the one for C=O bond addition. Because simple imines are the least reactive, we decided to explore the catalytic addition of terminal alkynes to simple imines. We rationalized that the success of such a catalytic reaction will allow, essentially, the catalytic addition of terminal alkyne to all other C=N bonds. By exploiting the same dual catalytic means, in early 2001 we accomplished a highly efficient addition of acetylenes to various imines (aldehyde−alkyne−amine coupling, which we termed A[3]-coupling) by using a combined Ru/Cu catalyst in water or under neat conditions (eq 8).[34] A wide range of alkynes, aldehydes, and aromatic amines can be converted readily into synthetically useful propargyl amines efficiently in high yields. Independent from our work, Ishii[35,36] and Carreira[37,38] reported a [Ir]-catalyzed addition of trimethylsilylacetylene to imines in moderate yields under anhydrous conditions and inert atmosphere nearly at the same time. However, the reactions were limited to trimethylsilylacetylene.

$$(8)$$

R: aromatic, aliphatic
Ar: Ph
R': aromatic, aliphatic

57-95%
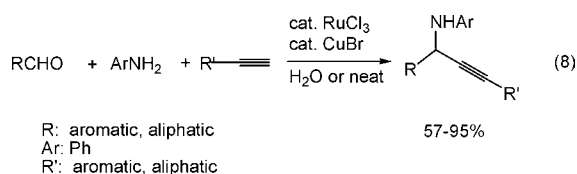
During our investigation, we noted that CuBr alone as catalyst led to only a trace amount of the product under the same reaction conditions. We thus proposed that the relatively low reactivity of the C−Cu bond provides an opportunity to activate such a bond using chiral ligands, which will lead to enantioselective alkyne−C=N bond additions. Indeed, after extensive investigation, we discovered the first enantioselective catalytic addition of terminal alkyne to C=N bonds: highly efficient asymmetric addition of alkynes to imines (we termed asymmetric aldehyde−alkyne−amine coupling or AA[3] coupling) were catalyzed by using the tridentate bis(oxazolinyl)pyridines (pybox) with Cu(OTf) in water and organic solvent (eq 9).[39] The enantioselectivity was up to 99.6% ee in organic solvent and 84% ee in water.[40] In most cases, the imines were formed *in situ* and the addition was very simple: mixing of an aldehyde, an aniline, and an alkyne with the catalyst in one

pot. Subsequently, various modifications of our reaction were reported.[13,14]

$$(9)$$

48-93% yield,
78-99% ee
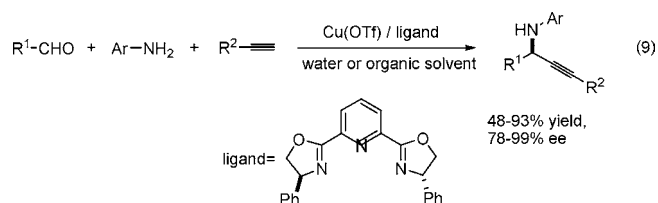
The ready access of various propargyl amines provides us opportunities for further functionalizations. For example, an efficient copper-catalyzed four-component, tandem A[3]-coupling/carboxylative cyclization between aldehydes, amines, terminal alkynes, and CO_2 in which CO_2 serves as both promoter and reagent for the facile synthesis of synthetically important oxazolidinone products was thus developed (eq 10).[41] The reaction proceeded well under neat conditions or in water; however the best yields were obtained in EtOAc and EtOH.
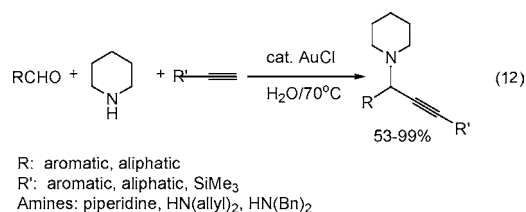

$$(10)$$
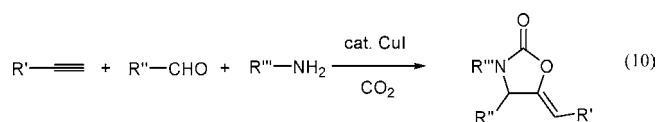
Under anhydrous conditions, a silver-catalyzed domino reaction generated polysubstituted 1,2-dihydroquinoline derivatives efficiently from alkynes and anilines (eq 11).[42]

$$(11)$$
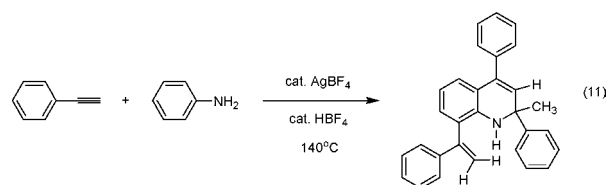
Iminium Ions. Prior to our own investigations of catalytic alkyne−imine additions, Dax and co-workers reported the use of copper as a transition metal catalyst for a solid-phase Mannich condensation of secondary amines, aldehydes, and alkynes via the formation of iminium ion.[43] A microwave-assisted reaction of terminal alkynes, amines, and formaldehyde in the presence of Cu(I) on Al_2O_3 support was reported by Pagni.[44]

Our initial success on the much more difficult addition of terminal alkyne to simple imines in water (and organic solvents) using the ruthenium/copper and chiral copper catalysts led us to explore the "less challenging" alkyne−iminium addition. The increased reactivity of iminium ions renders the opportunity of finding other catalysts for such reactions. We found that various gold salts (both Au(III) and Au(I)) can catalyze the direct coupling of aldehye, alkyne, and secondary

amines efficiently in water (eq 12).[45,46] No cocatalyst was needed for the process. Less than 1 mol % catalyst loading was enough for the A[3] coupling reaction to generate high yields of the corresponding propargyl amine products. 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 byproduct. Subsequently, Che and others developed a related reaction catalyzed by well-defined Au(I) and Au(III) catalysts in water.[47] The reaction gave very high diastereoselectivity with proline as the secondary amine.

RCHO + [piperidine] + R'——— cat. AuCl / H₂O/70°C ——→ (12)

53-99%

R: aromatic, aliphatic
R': aromatic, aliphatic, SiMe₃
Amines: piperidine, HN(allyl)₂, HN(Bn)₂

The high efficiency of gold as a catalyst for the three-component coupling of aldehydes, secondary amines, and alkynes in water led us to examine Ag catalysts for the related coupling. Initially, we focused on water-soluble silver salts. The water-soluble or partially soluble salts such as AgNO₃, Ag₂O, AgOAc, Ag₂SO₄, AgOTf, and AgBF₄ were found to catalyze the reaction of benzaldehyde, piperidine, and phenylacetylene with low conversions (ca. 25−45%) together with the formation of some carboxylic acid. The low yields were attributed to the deactivation of the silver catalyst due to its reduction to silver metal, which did not show any catalytic activity in independent experiments. AgCl, AgBr, and AgI all showed good catalytic activity for the three-component coupling, with AgI being the most effective (eq 13).[48] However, only a trace amount of product was obtained with acyclic amines (such as diallyl amine), whereas cyclic amines reacted well under these conditions. Interestingly, while both aromatic and aliphatic aldehydes were able to undergo addition to afford the corresponding propargyl amines, aromatic aldehydes had a decreased reactivity whereas aliphatic aldehydes displayed higher reactivity and cleaner reactions under the silver-catalyzed reaction conditions. The reactions proceeded well in either water or an organic solvent such as toluene and DMF. When 0.2 mol % AgI was used as a catalyst, the reaction in water generated more than 92% isolated yield of the desired product. Ionic liquid [Bmim]BF₄ is also a viable solvent for this reaction.[49] Subsequently, it was found that silver-nanoparticles and supported silver can also catalyze the A[3]-reaction efficiently under various conditions.[50] Rueping and co-workers reported the asymmetric silver-catalyzed alkyne imine

addition reaction recently though combined Bronsted acid catalysis and metal catalysis.[51]

RCHO + R'₂NH + R''——— cat. Ag(I) / H₂O ——→ (13)

53-99% yield
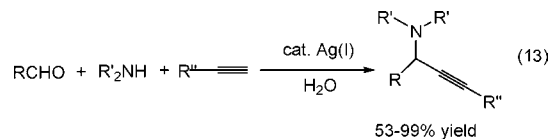
Shortly after our report on the Cu-catalyzed asymmetric addition of terminal alkynes to imines, Knochel and co-workers accomplished a highly efficient asymmetric addition of terminal alkynes to enamines catalyzed by a Cu−1-(2-diphenylphosphino-1-naphthyl)isoquinoline (QUINAP) complex (eq 14).[52] Further extensive studies show that a simple combination of secondary amine, aldehyde, and alkyne are equally successful and can be applied to a wide range of substrates.[53,54] Carreira showed that Cu−1-[2-(diphenylphosphino)-1-naphthyl]phthalazine (PINAP) as catalyst provided a higher ee.[55] Shi and co-workers found that secondary amine−aldehyde−alkyne additions can be catalyzed by CuI in water under microwave irradiation.[56] Independently, we found that the three-component addition of aldehyde, alkyne, and secondary amines can be catalyzed by CuI under solventless conditions with microwave irradiation.[57] Alper showed that such a reaction is highly effective in ionic liquids.[58] Formaldehyde as substrate for CuI-catalyzed A[3] coupling in 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.[59] The use of ultrasound is equally successful for such reactions in water.[60]
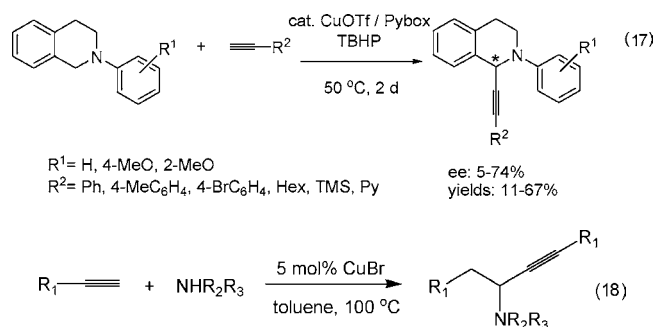
R¹CHO + H−C≡C−R² + R³NHR⁴ CuBr / ligand / toluene ——→ (14)

43-99% yield, 32-96% ee

lignad=
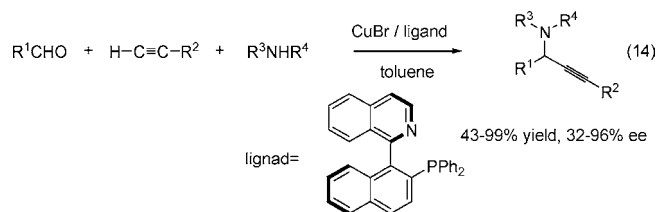
The three-component couplings of α-oxyaldehydes, alkynes, and amines in water were investigated using gold, silver, and copper catalysts (eq 15).[61] AuI was found to be the most effective catalyst in this reaction to afford propargylamines in good yields and moderate diastereoselectivities. On the other hand, silver catalysts show the best catalytic activities on noncoordinating α-alkyl-substituted aldehydes. A novel CuBr-catalyzed intermolecular decarboxylative C_{sp^3}−C_{sp^3}, C_{sp^3}−C_{sp^2}, and C_{sp^3}−C_{sp} coupling reaction using α-amino acids as starting materials under neutral

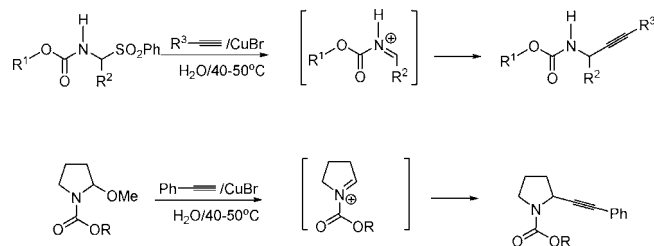conditions (eq 16) was discovered via an in situ iminium–alkyne addition.[62]

$$(15)$$

$$(16)$$
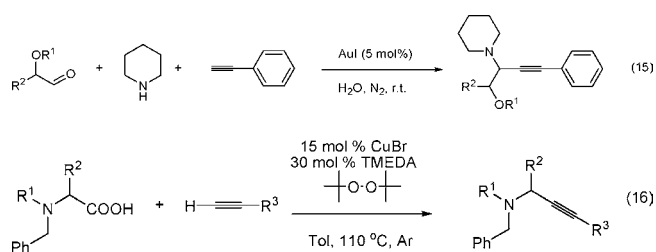
More recently, with our interest in developing cross-dehydrogenative couplings (CDC),[63] we found that α-hydrogen of amine can cross-couple with terminal alkynes, under the catalysis of CuBr via the generation of iminium intermediate in situ. The reaction can be performed in water, albeit at lower yield. Asymmetric addition of such a reaction as well as a direct addition of alkyne is also possible with the Cu(OTf)/pybox catalytic system (and to tetrahydroquinoline iminium ion with the CuBr/QUINAP system) (eq 17).[64,65] A highly efficient tandem anti-Markovnikov hydroamination and alkyne addition reaction catalyzed by Cu(I) or Cu(II) was developed. This tandem process provides a novel and simple approach to propargylamine derivatives from alkynes and amines (eq 18).[66] The alkyne iminium addition can also be catalyzed by iron.[67,68]

R[1]= H, 4-MeO, 2-MeO
R[2]= Ph, 4-MeC$_6$H$_4$, 4-BrC$_6$H$_4$, Hex, TMS, Py

ee: 5-74%
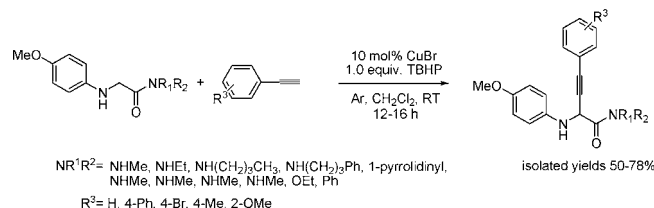yields: 11-67%

$$(17)$$

$$(18)$$

Acylimine and Acyliminium Ions. In our initial alkyne–imine addition studies, aliphatic primary amines were ineffective. We attributed the lower reactivity to the low stability toward water and the low reactivity toward carbon nucleophiles of aldimines generated from aliphatic amines, and proposed to overcome such an obstacle by using *N*-acylimine and *N*-acyliminium ions because the reactivity of the C=N bond in these compounds is greatly enhanced and their stability toward water is increased.[69] In addition, *N*-acylimine or *N*-acyliminium ion compounds can be generated conveniently in situ from a variety of methods, and the products can be modified easily for various synthetic purposes. As a proof-of-concept, one of the methods is to use amines containing a good leaving group at the α position. Indeed, we found that under ultrasonic irradiations, CuBr

SCHEME 7. Addition of Alkynes to Acylimine and Acyliminium Ions

**SCHEME 8.** Direct Alkynylation of Glycine Amides via CDC Reaction

NR[1]R[2]= NHMe, NHEt, NH(CH$_2$)$_3$CH$_3$, NH(CH$_2$)$_3$Ph, 1-pyrrolidinyl, NHMe, NHMe, NHMe, NHMe, OEt, Ph
R[3]= H, 4-Ph, 4-Br, 4-Me, 2-OMe

isolated yields 50-78%

(10–30 mol %) can catalyze the addition of terminal alkynes to both acylimine and acyliminium ions in water in moderate yields. With stoichiometric CuBr, the reaction led to good yield of the corresponding products (Scheme 7). It should be noted that this is the first reported alkyne–acylimine and alkyne–acyliminium addition reaction. Subsequently, we and others found that with similar acyliminium ions generated in situ from imines and acyl chloride under anhydrous conditions, CuBr,[70] ZnCl$_2$,[71] and AuX$_3$[72] can catalyze their alkyne addition in good yields.

Recently, in our efforts to develop novel methods for site-specific C–H functionalization of peptides, we found that CuBr can catalyze the direct C-alkynylation of α-amino acids and the N-terminus of short-chain peptides possibly via the acylimine intermediate (Scheme 8).[73,74]

Multiple and Tandem Addition of Terminal Alkynes to C=N Bonds. Using our ruthenium/copper cocatalyst system, we developed a five-component double aldehyde–alkyne–amine coupling to synthesize various dipropargyl amines from a range of simple amines, aldehydes, and alkynes in one pot under mild conditions in water under an atmosphere of air (eq 19).[75] At 60 °C, the reaction yield is slightly better in toluene than in water, whereas at room temperature, with extended reaction time, the opposite is true. The exclusion of oxygen from the reaction did not improve the yield.


$$(19)$$
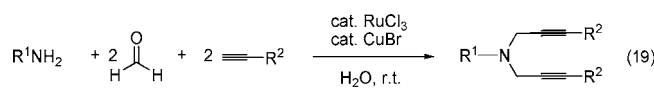
Subsequently, we found that tetrasubstituted isoindolines can be synthesized readily from three alkyne units, two aque-

ous formaldehyde units, and a primary amine in a single synthetic operation by using a combined copper/rhodium catalyst (eq 20).[76]


(20)
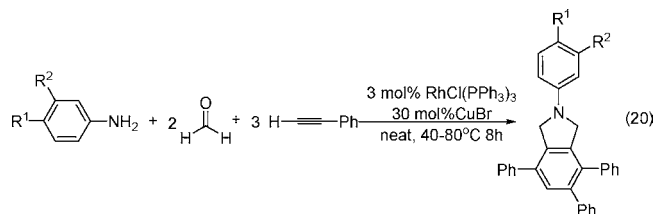
5. Direct Conjugate Addition of Terminal Alkyne (Class III)

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 electrophilic as C=N or C=O bonds. In 2003, Carreira et al. reported the first conjugate addition reaction of terminal alkynes to C=C bonds catalyzed by copper in water. The reaction only proceeded with derivatives of the Meldrum's acid in water in the presence of $Cu(OAc)_2$ and sodium ascorbate (eq 21).[77] Later, they employed copper catalyst together with chiral PINAP ligand to develop an **e**nantioselective version of this addition reaction and achieved 82−97% ee with good yields (eq 22).[78,79]


(21)

(22)
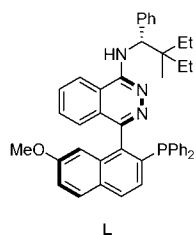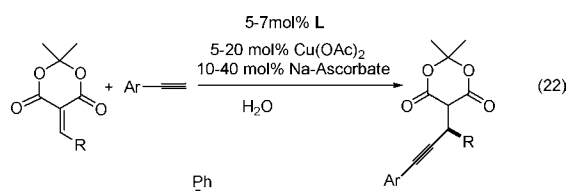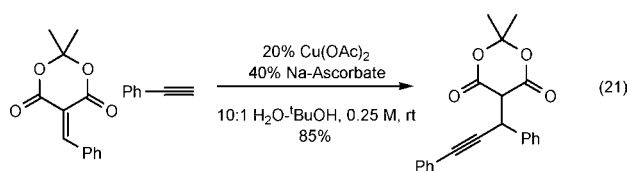
In our own studies, we found that using a combination of Cu/Pd together with PPh_3 as catalyst, the addition of terminal alkynes to electron-deficient alkynes proceeded selectively and effectively in water and under an air atmosphere without the competing homocoupling of terminal alkynes (eq 23).[80] The reaction performed in water was better than that in toluene. 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.

(23)
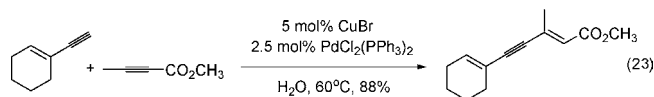
We also found that with a more electron-rich trimethylphosphine as ligand, palladium alone can catalyze the 1,4-addition of terminal alkynes to vinyl ketones in water with high yields (eq 24).[81] Chisholm et al. also reported such a reaction catalyzed by Rh metal complex $Rh(acac)(CO)_2$ (acac = acetylacetonoate) in the presence of tris(*o*-methoxyphenyl) phosphine in aqueous dioxane solutions.[82] Using highly electron-donating *N*-heterocyclic carbenes (NHCs) as ligands further increases the catalytic activity of palladium and allows the direct addition of terminal alkynes to acrylate esters in acetone (eq 25).[83]

(24)

(25)
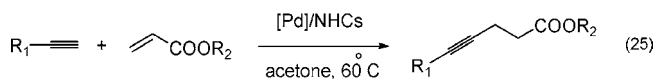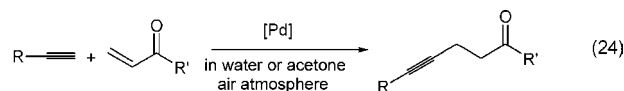
A simple and efficient method for synthesis of the γ,δ-alkynyl-β-amino acid derivatives by a copper-catalyzed three-component amine−alkyne−alkyne addition reaction was recently developed. With chiral prolinol derivatives as the amine component, excellent diastereoselectivities (up to >99:1) have been attained (eq 26).[84]

(26)
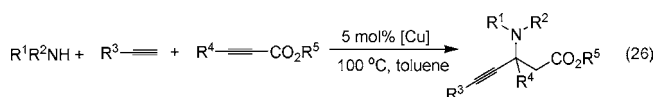
6. Conclusions

The goal of seeking more efficient and protecting-group-free synthetic methods combined with our long-term objective of developing Grignard-type reactions in water led us to explore various catalytic and direct addition of terminal alkynes to various electrophiles in water. These reactions provide an alternative to the classical alkyne reactions.

BIOGRAPHICAL INFORMATION

Chao-Jun Li received his B.S. at Zhengzhou University (1983), M.S. at the Chinese Academy of Sciences in Beijing (1988) and Ph.D. at McGill University (1992) (with T. H. Chan and D. N. Harpp). After NSERC Postdoctoral research with B. M. Trost at Stanford University, he became Assistant Professor (1994), Associate Professor (1998) and Full Professor (2000-2003) at Tulane University. In 2003, he became a Canada Research Chair (Tier I) in Organic/Green Chemistry and a Professor of Chemistry at McGill University in Canada. Currently, he serves as the Director for the CFI Facility for Green Chemistry and Green Chemicals, Co-Director (with Andre Charette) of the FQRNT Center for Green Chemistry and Catalysis, and Co-Chair (with Bernard West) of the Canadian Green Chemistry and Engineering Network. His current research efforts are focused on developing innovative and fundamentally new organic reactions that will defy conventional reactivities and have high synthetic efficiency.

FOOTNOTES

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†Dedicated to the memory of Professor Che Deji of Zhengzhou University.

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