Synthetic Methods

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All Kinds of Reactivity: Recent Breakthroughs in Metal-Catalyzed Alkyne Chemistry**

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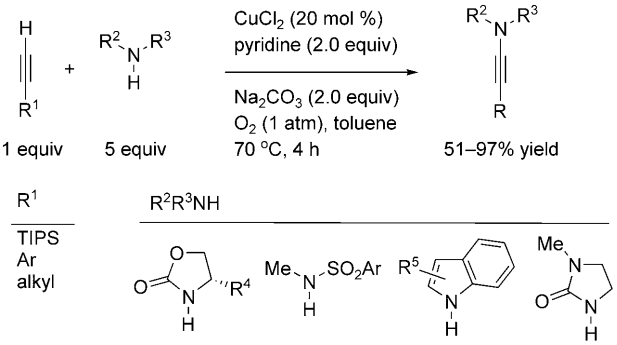
alkynes · bimetallic catalysts · homogeneous catalysis · hydrogen bonds · N ligands

Recent developments in transition-metal-catalyzed processes with alkyne substrates have enabled the synthesis of a plethora of diverse products. Simple terminal alkynes are often used to prepare more elaborate disubstituted derivatives through metal-promoted reactions. Early examples include the Glaser–Hay oxidative dimerization of alkynes[1] and the Sonogashira coupling reaction.[2] Another milestone was the catalytic asymmetric alkynylation of aldehydes developed by Carreira and co-workers to furnish highly enantioenriched propargylic alcohols.[3] Two very recent advances have broadened the range of alkynes that are readily accessible by C–N and C–C bond-forming reactions.

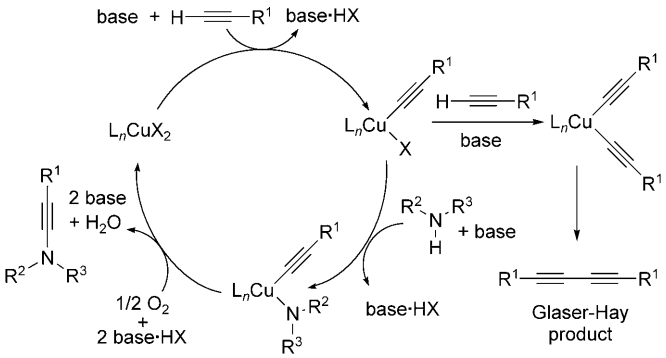
Ynamides continue to receive increasing attention as synthetic intermediates.[4] Their synthesis typically entails halogenation of terminal alkynes followed by C–N cross-coupling.[5] A recent advance from the Stahl research group described the direct amidation of terminal alkynes by copper-catalyzed C–H activation (Scheme 1).[6] Besides the high efficiency, there are two noteworthy features of this approach. First, like the Glaser–Hay oxidative dimerization of alkynes, dioxygen is used as the terminal oxidant. Second, a variety of nitrogen nucleophiles and alkynes undergo reaction to afford an array of ynamides (70–90% yield, up to 10 mmol scale).

Although the catalyst loading can probably be lowered, it may prove difficult to reduce the excess amount of amine that is required in most cases. In the proposed mechanism (Scheme 2), the alkyne and nitrogen nucleophile compete for the copper–alkynyl halide, and afford the C–C and C–N coupled products, respectively.

Another copper-catalyzed reaction involving the activation of C–H bonds, this time adjacent to a nitrogen center, was recently introduced by Zhao and Li (Scheme 3).[7] In this case, the terminal oxidant is *tert*-butyl hydroperoxide (TBHP). After C–H activation, coupling occurs with the alkyne. The analogous α-amino esters are unreactive under these conditions, thus setting the stage for chemoselective C–H functionalization (Scheme 4).



Scheme 1. Oxidative amidation of alkynes. TIPS = triisopropylsilyl.



Scheme 2. Mechanistic proposal for the C–N coupling reaction.

The selectivity observed in Scheme 4, and the minimal impact of radical inhibitors in related reactions, precludes a radical pathway for the initial cleavage of the C–H bond. A proposed mechanism involves initial coordination of the Cu^{II} center to the amino group followed by oxidation to generate an activated imine, which then undergoes copper–acetylide addition (Scheme 5). On the basis of this proposed mechanism, an asymmetric version seems plausible.

In many reactions the alkyne triple bond is not maintained in the product. Classic examples include the hydrometalation of terminal alkynes, transmetalation to zinc, and asymmetric aldehyde vinylation, as reported by Oppolzer and Radinov as

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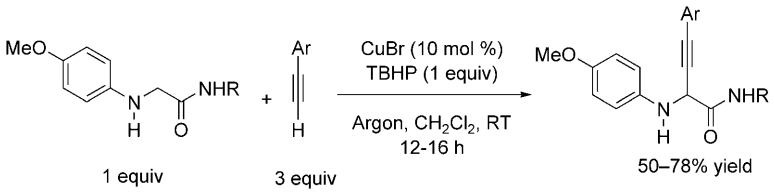
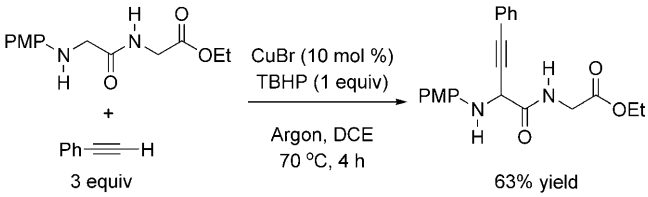
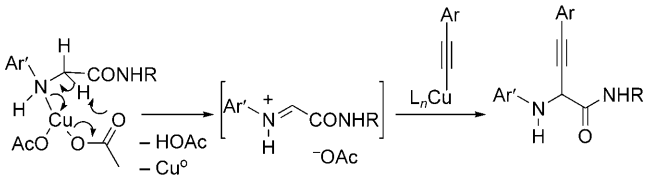


Scheme 3. Cross-dehydrogenative coupling catalyzed by copper.



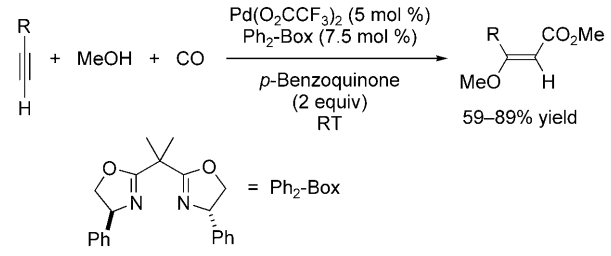
Scheme 4. Chemoselective functionalization of the terminal glycine. PMP = *p*-methoxyphenyl, DCE = 1,2-dichloroethane.



Scheme 5. A mechanistic proposal for the amine–alkyne cross-dehydrogenative coupling reaction.

well as by Wipf and Ribe.[8,9] Stoichiometric amounts of metal-based reagents are used in these reactions. The hydrogenative carbonyl vinylation developed by Krische and co-workers[10] with alkynes, hydrogen, and catalytic amounts of metal complexes will revolutionize this field.

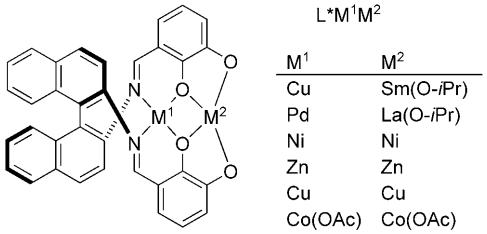
The alkoxy carbonylation of alkynes has received recent interest because of the biological activity of β-alkoxyacrylates. Although progress has been made in intramolecular alkoxy carbonylations,[11] intermolecular versions of this important transformation have been lacking.[12] However, Kato, Akita, and co-workers recently disclosed palladium-based catalysts for the intermolecular process.[13] These authors rationalized that a metal center better able to activate the alkyne π system would be more likely to accelerate the intermolecular addition of methanol to coordinated alkynes. A series of palladium sources and ligands were tested, and *rac*-Ph_2-Box/$Pd(O_2CCF_3)_2$ was found to be the most general system (Scheme 6). The catalyst works well with R = alkyl, aryl, heteroaryl, and unprotected glycosides, while disubstituted alkynes gives regioisomeric mixtures in low yields (< 50 %).



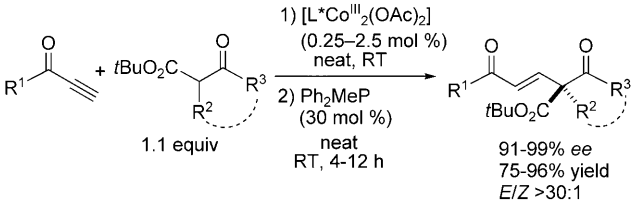
Scheme 6. Catalytic intermolecular methoxy-carbonylation of alkynes.

The mechanism envisioned begins with coordination of the alkyne and addition of methanol to generate a vinylpalladium intermediate. Insertion of CO is likely followed by methanolysis to afford the product. This method for the direct conversion of terminal alkynes into β-methoxyacrylates is likely to be synthetically very useful.

Mimicking nature's approach to catalysis by using small-molecule catalysts often leads to increased reactivity, selectivity, and even new reactions. Most enzymes contain a network of activating groups, such as metals and/or hydrogen-bond donors and acceptors that cooperate to lower the activation energies and stabilize the intermediates. One of the leading research groups in small-molecule bifunctional catalysts is that of Shibasaki who developed the pioneering Li_3(binolate)$_3$Ln (binol = 1,1′-bi-2-naphthyl) catalysts.[14] Recently Matsunaga, Shibasaki, and co-workers introduced a new class of dinuclear Schiff base catalysts (Scheme 7) that promote a variety of highly enantioselective transformations,[15,16] including additions to activated alkynes.[17]



Scheme 7. Dinuclear heterobimetallic catalysts.



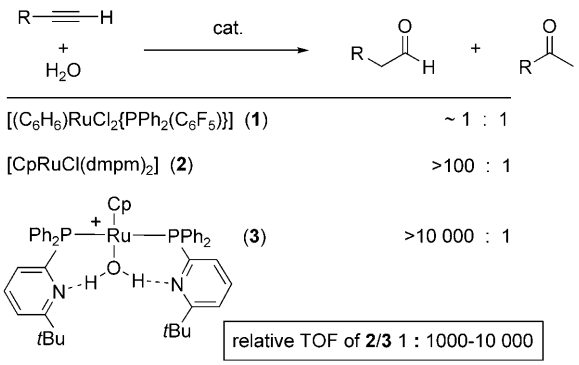
Scheme 8. Conjugate additions of β-keto esters to alkynones.

The conjugate addition of β-keto esters to alkynones[18,19] was targeted by Matsunaga, Shibasaki, and co-workers (Scheme 8).[17] Stoichiometric amounts of metal-based reagents are used in these reactions.Initially, various metals were employed as M^1 and M^2 in Scheme 7. Although the Ni_2 catalyst gave excellent results with direct Mannich-type reactions,[15,16] it was $(CoOAc)_2$ that performed best in conjugate additions.[17] Enantioselectivities ranged from 91 to 99 % with a variety of substituents R^1–R^3, including acyclic and cyclic β-keto esters (R^2,R^3 linked). Also noteworthy are the high *E*/*Z* ratios, which arise from phosphine-catalyzed isomerization. Highly enantioselective catalytic processes

conducted under solvent-free conditions, such as this, are rare.[20]

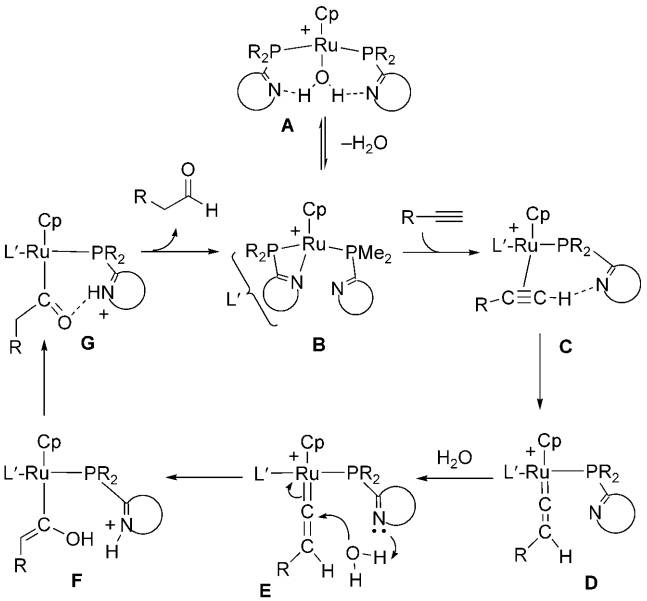
To determine if both cobalt atoms participate in the catalysis, the authors 1) used related monometallic [(salen)CoOAc] (salen = *N*,*N*′-bis(salicylidene)ethylenediamine) and 2) substituted either the inner or outer CoOAc unit in $[L^*(CoOAc)_2]$ (L^* = chiral ligand) with other metals. In each case, dramatic decreases in the enantioselectivity were observed (< 40 % *ee*). Although further studies are necessary to understand the mechanism, these experiments suggest that both cobalt centers are crucial to the enantioselectivity of the catalyst.

The same features that increase the turnover frequency (TOF) and reactivity of bifunctional catalysts also complicate mechanistic studies. Detailed mechanistic insight into bifunctional catalysts, however, is invaluable for the development of improved catalysts. Recent advances mapping how bifunctional catalysts work their magic on alkynes have recently been reported by Grotjahn et al.[21] These authors made a remarkable find: the *anti*-Markovnikov hydration of terminal alkynes was, an enzyme-like, 2.4×10^{11} faster in the presence of a ruthenium-based bifunctional catalyst than that in the absence of catalyst. Furthermore, the background reaction and acid-catalyzed hydrations favor the ketone product. In contrast, the bifunctional catalyst provides exclusively aldehyde (Scheme 9).[22]



Scheme 9. Alkyne hydration catalysts and relative turnover frequencies. Cp = C_5H_5, dmpm = bis(dimethylphosphanyl)methane.

Detailed isotopic labeling and computational studies were undertaken with **3**, which led to the proposed mechanism shown in Scheme 10. The water adduct **A** is in equilibrium with κ^2-PN complex **B**. The addition of the alkyne results in a fast reaction, and alkyne coordination is not observed. However, alkyne coordination occurs with closely related bifunctional Ru catalysts and acetylene. In this case, the acetylene coordinates to the Ru center such that both acetylenic CH protons hydrogen bond to the pyridyl nitrogen atoms of the ligands.[23] When an alkyne adds to anhydrous **B** at −40 °C, the first observed intermediate is vinylidene **D**. Reaction of this intermediate with water at 0 °C generates **G**, most likely through pyridyl-assisted addition of water to the vinylidene moiety (via **E** and **F**). When ^{15}N-labeled ligands were employed, the ^{15}N NMR spectrum of **G** recorded at −100 °C showed the pyridyl nitrogen atoms were inequivalent, with one protonated, thus giving rise to a doublet for the ^{15}NH signal in the ^1H NMR spectrum ($J_{NH} = 56.8$ Hz). Strong evidence for an NH···O_{acyl} hydrogen bond was garnered when **G** was prepared from $H^{13}C^{13}CH$ in the presence of H_2O. Once **G** had formed, treatment with D_2O caused a large isotopic perturbation of $\delta = 1.6$ ppm for the signal for the ^{13}C-labeled acyl group.[23] The remaining steps likely involve protonation of the Ru center by the pyridyl NH proton followed by reductive elimination of an aldehyde or direct protonation of the acyl group by the NH proton.



Scheme 10. A mechanistic proposal for the hydration of alkynes.

These detailed mechanistic studies have elucidated the roles of basic ligand sites, the metal center, and proton transfers in this *anti*-Markovnikov hydration of alkynes and help us understand the 1000–10000-fold increase in the reaction rate compared to those with analogous catalysts without bifunctional ligands.[24] Likewise, the bifunctional heterobimetallic catalysts developed by Shibasaki and coworkers demonstrate that Lewis acidic sites acting in concert can lead to new reactivity and excellent enantioselectivity. In combination with direct C–C and C–N oxidative coupling and methoxy carbonylation reactions, these studies represent important developments at the forefront of synthetic chemistry.

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