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Facile and selective copper–palladium catalyzed addition of terminal alkynes to activated alkynes in water

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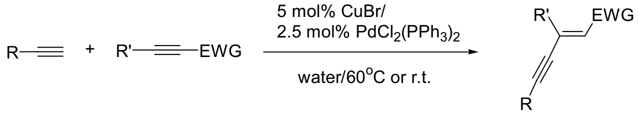
Abstract—The combination of palladium and copper catalyzes the addition of terminal alkynes to electron-deficient alkynes selectively and effectively in water without the competition of terminal alkynes' homo-coupling.

Addition reaction is an atom economical way to construct more complex structures from simpler units.[1] Recently, increased interest has been shown on the addition reaction of terminal alkynes. Most of these studies are related to the terminal alkynes' addition to compounds that involve sp^2 carbon, such as α,β-unsaturated carbonyl compound,[2] aldehydes,[3] imines,[4] nitrones.[5] On the other hand, only a very few examples on the selective addition of terminal alkynes to internal alkynes involving sp carbon have been reported,[6] possibly due to the facile competition of the homo-coupling or dimerization of the terminal alkynes.[7] Trost et al. discovered that a catalytic amount of $Pd(OAc)_2$ and triphenylphosphine in dichloroethane resulted in high yield of homo-coupling of terminal alkynes.[8] For cross-coupling of terminal alkynes to activated alkyne, a palladium catalyst involving an electron rich ligand tris(2,6-dimethoxyphenyl)phosphine (TDMPP) and an inert atmosphere are essential.[8] Since the conjugated enynes are found to be important building blocks and essential units in a variety of biologically active compounds,[9] herein we wish to report a facile and simple method to generate conjugated enynes by using a combination of Cu/Pd together with common ligand, PPh_3, in water and under an air atmosphere (Scheme 1).[10] It is noteworthy that this simple catalytic system was able to catalyze only the cross-addition of terminal alkyne to electron-deficient internal alkynes but not the homo-coupling or dimerization of the terminal alkyne.



Scheme 1.

As the salts of group 11 element are highly effective in forming acetylide from terminal acetylene,[11] we planed

Table 1. Catalysts optimization for the addition of phenylacetylene to 4-phenyl-3-butyn-2-one in water

Entry	Catalyst	Time (h), temperature: rt	Yield (%)
1	$CuCN/PdCl_2(PPh_3)_2$	48	15
2	$CuCl/PdCl_2(PPh_3)_2$	48	21
3	$CuSO_4/PdCl_2(PPh_3)_2$	48	<10[a]
4	$CuBr/PdCl_2(PPh_3)_2$	48	**63**
5	$CuI/PdCl_2(PPh_3)_2$	48	48
6	$AuBr_3/PdCl_2(PPh_3)_2$	48	ND[b]
7	$AuCl/PdCl_2(PPh_3)_2$	48	<10[a]
8	$AgBr/PdCl_2(PPh_3)_2$	48	<10[a]
9	$AgNO_3/PdCl_2(PPh_3)_2$	48	ND[b]
10	$AgCl/PdCl_2(PPh_3)_2$	48	<10[a]
11	CuBr	48	ND[b]
12	$PdCl_2(PPh_3)_2$	48	<10[a]
13	$Pd(OAc)_2/PPh_3/CuBr$	48	46
14	$Pd(OAc)_2$/TDMPP/CuBr	48	<10[a]
15	$Pd(OAc)_2$/TDMPP	48	31

[a] Determined by ^1H NMR.
[b] Not detected.

Keywords: Palladium–copper catalysis; Water; Alkyne–alkyne coupling; Enyne.

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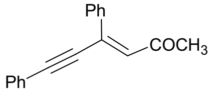
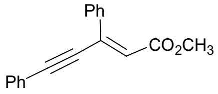
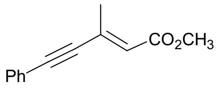
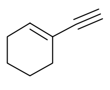
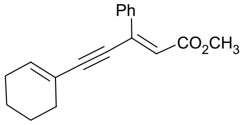
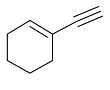
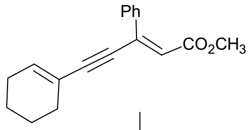
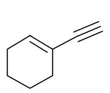
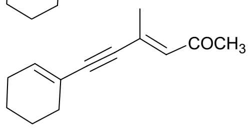
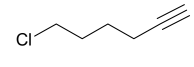
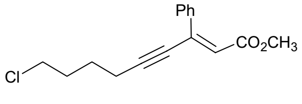
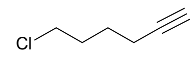
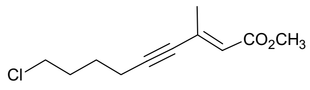
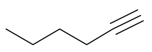
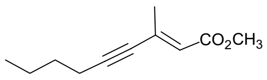
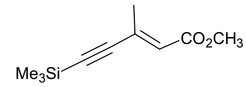
Table 2. Addition of terminal alkynes to acceptor alkynes using CuBr/PdCl$_2$(PPh$_3$)$_2$ co-catalyst in water and in toluene[a,b]

Entry	Terminal alkyne	Activated alkyne	Conditions	Product	Yield (%)
1	Ph—≡	Ph—≡—COCH$_3$	48 h/rt/water		63
2			48 h/rt/toluene		<10[c]
3			24 h/60 °C/toluene		65
4	Ph—≡	Ph—≡—CO$_2$CH$_3$	42 h/rt/water		75
5			24 h/60 °C/toluene		55
6	Ph—≡	—≡—CO$_2$CH$_3$	24 h/60 °C/water		62
7			24 h/60 °C/toluene		—
8		Ph—≡—CO$_2$CH$_3$	24 h/60 °C		56
9		Ph—≡—CO$_2$CH$_3$	30 h/60 °C		86
10		—≡—CO$_2$CH$_3$	30 h/60 °C		88
11		Ph—≡—CO$_2$CH$_3$	28 h/60 °C		74
12		—≡—CO$_2$CH$_3$	38 h/60 °C		78
13		—≡—CO$_2$CH$_3$	25 h/60 °C		48
14	Me$_3$Si—≡	—≡—CO$_2$CH$_3$	40 h/60 °C		54

[a] The reaction was conducted using 2 mmol of terminal alkyne, 1 mmol internal alkynes, 5 mol% CuBr, and 2.5 mol% PdCl$_2$(PPh$_3$)$_2$ in water or toluene at room temperature or 60 °C.

[b] Absolute configuration of the products was established by correlation with known compounds.

[c] Determined by NMR.

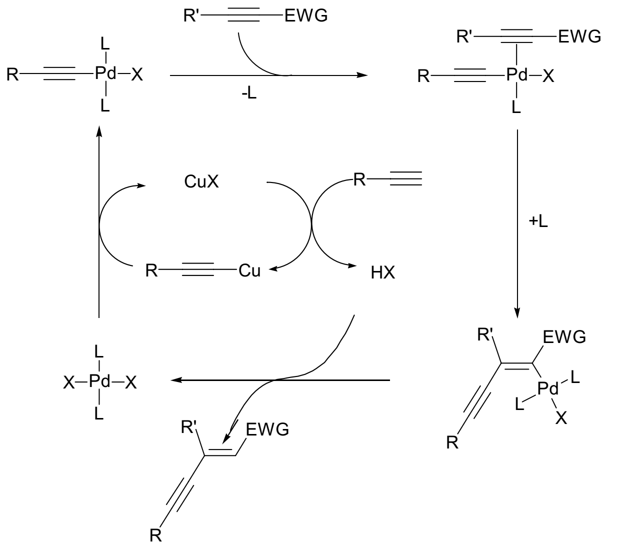
to use copper, silver, and gold salts to generate acetylide species and palladium to catalyze the addition. This would allow us to avoid using drastic catalysts that both activate the C–H bond and catalyze the addition reaction, which could also lead to the competing dimerization and homo-coupling.

Toward such a goal, a mixture of phenylacetylene (R = Ph) and 4-phenyl-3-butyn-2-one (R′ = Ph, R″ = COCH$_3$) was treated with Cu/Pd, Ag/Pd, and Au/Pd catalytic system in water at room temperature. As shown in Table 1, Cu/Pd (Table 1, entries 1–5) system provides better results than both Au/Pd (Table 1, entries 6 and 7), and Ag/Pd (Table 1, entries 8–10) systems. Among the Cu/Pd catalysts being tested, the CuBr/PdCl$_2$(PPh$_3$)$_2$ achieved the best yield of 63% (Table 1, entry 4). When CuBr alone was used as the catalyst, no desired product was detected (Table 1, entry 11), whereas with PdCl$_2$(PPh$_3$)$_2$ alone, only a small amount of the product (Table 1, entry 12) was observed. The reason for the lack of catalytic activity with either one alone is possibly that PdCl$_2$(PPh$_3$)$_2$ is not as effective as Cu(I) to form acetylide species or to activate the C–H bond of terminal alkynes; on the other hand, the Cu(I) is not as good as Pd(II) to catalyze the addition reaction.[12] Finally, we tested the phenylacetylenes' homo-coupling reaction using catalyst CuBr/PdCl$_2$(PPh$_3$)$_2$, no noticeable reaction was observed. Without the co-catalyst, ligand TDMPP appeared more effective than PPh$_3$ (Table 1, entries 12 and 15). With the co-catalyst, the Pd(II)/TMDPP/CuBr system generated more undesired by-product (Table 1, entry 14). Reaction of electron-deficient terminal alkyne, such as ethyl propiolate, with an internal alkyne methyl 2-butynoate was also examined but it did not generate the desired product under the same reactions conditions.

Subsequently, the terminal alkynes were extended from aromatic alkynes (Table 2, entries 1–7) to conjugated alkynes (Table 2, entries 8 and 9), aliphatic alkynes (Table 2, entries 11–13) and triethylsilylacetylene (Table 2, entry 14) and the activated alkynes were extended from ketone (Table 2, entries 1–3 and 8) to ester (Table 2, entries 4–7 and 9–14), from aromatic substituted alkynes (Table 2, entries 1–5, 8, 9 and 11) to aliphatic substituted alkynes (Table 2, entries 6, 7, 10 and 12–14). As shown in Table 2, the yields are from good to excellent. Toluene was also examined as solvent, however, it resulted in much lower reactivity in the reactions (Table 2, entries 1–7), possibly because water lowers the energy of the transition state. A tentative mechanism is proposed, which involves the activation of C–H bond by Cu(I) to form the copper acetylide; transmetalation between the copper intermediate with palladium generates palladium acetylide, which undergoes addition to activated alkynes (Scheme 2).

In conclusion, we have described a facile method for the synthesis of conjugated enynes from terminal alkynes and electron-deficient alkynes. The noteworthy feature of the reaction process includes: (1) the catalyst system is effective enough to catalyze the desired reaction but does not catalyze the undesired competition reaction; (2) the catalysts are common, inexpensive, and commercially available; (3) the reactions run well in water and importantly, it is actually better than toluene solvent in the reaction process; (4) the reaction procedure is easy to execute. The scope, mechanism, and synthetic application of this reaction in water are under investigation.

A general experimental procedure. A mixture of terminal alkyne (1 mmol), acceptor alkyne (0.5 mmol), CuBr (4.5 mg, 5 mol %), and Pd(II)$Cl_2(PPh_3)_2$ (9.3 mg, 2.5 mol %) in 1 mL water was stirred at room temperature or 60 °C. After the starting material was consumed as monitored by TLC, the reaction mixture was extracted with ethyl ether (3 × 10 mL). The combined organic phase was dried by anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by column chromatography (hexane–ethyl acetate = 10:1) to give the pure product.



Scheme 2. Tentative mechanism for the addition reaction.

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