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A New Multicomponent Multicatalyst Reaction (MC)^{2}R: Chemoselective Cycloaddition and Latent Catalyst Activation for the Synthesis of Fully Substituted 1,2,3-Triazoles

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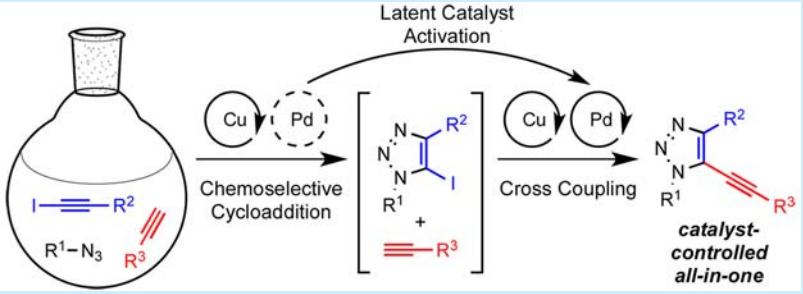
Supporting Information

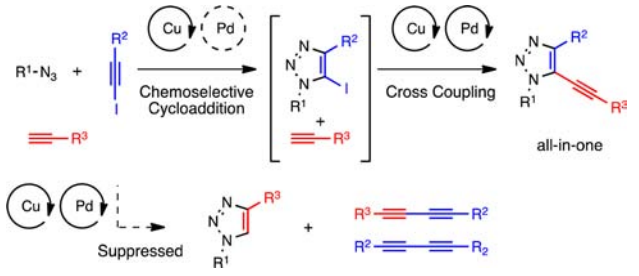


ABSTRACT: A multicomponent multicatalyst reaction (MC)^{2}R for constructing fully substituted 1,2,3-triazoles is reported. An application of chemoselectivity and latent catalysis in a sequence of multicatalytic reactions confers control over a number of undesired processes, where all of the reagents coexist in the same reaction vessel. The sequence of a chemoselective copper-catalyzed azide alkyne cycloaddition followed by a palladium/copper-catalyzed Sonogashira cross-coupling afforded 1,2,3-triazoles regioselectively with good to high yields and a broad scope.

When a number of substrates are placed in a single reaction vessel containing several catalysts, the selective and orderly assembly of these components is challenging but necessary if a single product is to emerge. The role of metal catalysts is to ensure that desired reactions occur in a specific order so as to minimize "off-path" or "parasitic" processes. As a result, significant a research effort has been invested in the development of switchable or latent catalysis based on heat,[1] light,[2] or mechanical[3] stimuli to gain temporal control. In seeking to achieve subtle catalyst control in more complex reaction sequences, we have studied the use of multiple catalysts that confer chemoselectivity and latent activation in multicomponent reactions,[4] where closely related reactants coexist with a number of possible interfering processes (Scheme 1).

We now report a copper-catalyzed cycloaddition of an organic azide with two closely related alkyne species with differential rates of reactivity affording remarkable chemoselectivity. The resulting cycloadduct, an iodotriazole, is stable under the reaction conditions at room temperature. Upon heating the reaction mixture, the latent Pd catalyst is activated, promoting a Pd/Cu cocatalyzed Sonogashira reaction to provide a fully substituted triazole. We demonstrate the importance of the choice of catalysts in providing the chemoselectivity and latent activation that led to temporal control and the minimization of interfering processes in the reaction pathway.

Scheme 1. Chemoselectivity and Latent Catalyst Activation Enabled (MC)^{2}R



Based on our strategy, we accessed two modes of copper catalysis in the direct synthesis of fully substituted 1,2,3-triazoles. These important motifs are used in a wide range of applications, including medicinal chemistry, crop science, materials, and bioconjugation.[5] Preexisting methods that accessed these fully substituted triazoles were limited by selectivity and scope. For example, Fokin and co-workers[6] reported a regioselective ruthenium-catalyzed azide alkyne cycloaddition (RuAAC) of internal alkynes that contained directing groups or an electronic bias. Other approaches include one-pot copper-catalyzed azide alkyne cycloaddition

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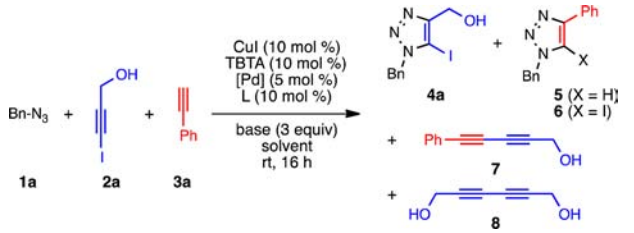
(CuAAC) of terminal alkynes followed by copper-catalyzed C−H arylation[7] or CuAAC followed by an oxidative alkynylation, incorporating 2 equiv of an alkyne.[8] Recently, Xu and co-workers reported the one-pot synthesis of 5-aryl-1,2,3-triazoles using a stoichiometric Cu and Pd catalyst by transmetalation between a copper-triazolide and a Pd-aryl species.[9] Conversely, the $(MC)^2R$ provided a divergent and regioselective synthesis with alkyne differentiation, affording products with good to high yields.

The recent study of the CuAAC indicated that the CuAAC with iodoalkynes may proceed via a different activation pathway from that with terminal alkynes.[10] Furthermore, the reactivity of iodoalkynes toward CuAAC exceeds that of terminal alkynes.[10a] We observed a chemoselective copper-catalyzed formation of 5-iodotriazole **4a** from benzyl azide **1a** and a mixture of iodoalkyne **2a** in the presence of phenyl acetylene **3a** in an equimolar ratio in THF (Table 1, entry 1).

Table 1. Competition Studies of the CuAAC for Iodoalkynes in the Presence of Terminal Alkynes and Pd[a]

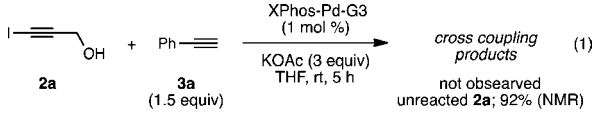


entry	solvent	[Pd]/L	base	yield[b] (%) (**4a**:**5**:**6**:**7**:**8**)
1	THF	–	–	91:0:9:3:0
2	dioxane	–	–	80:0:16:0:0
3	toluene	–	–	36:0:0:32:n.d.[c]
4	THF	–	Et_3N	76:0:23:1:1
5	THF	–	KOAc	81:0:8:0:<1
6	THF	$Pd(OAc)_2$	KOAc	2:0:0:8:17
7	THF	Pd_2dba_3	KOAc	<1:9:1:3:31
8	THF	$Pd(OAc)_2$/XPhos	KOAc	4:10:1:4:n.d.[c]
9	THF	XPhos-Pd-G3	KOAc	66:7:7:8:2

[a]Representative reaction procedure: in a 2 dram vial under an argon atmosphere, benzyl azide **1a** (0.2 mmol), iodoalkyne **2a** (1 equiv), and phenyl acetylene **3a** (1 equiv) were dissolved in THF. CuI (10 mol %) and TBTA (10 mol %) were added, followed by the addition of additives as indicated. The mixture was stirred for 16 h. [b]Yields were determined via ^1H NMR spectroscopy of the crude mixture using 1,3,5-trimethoxybenzene as the internal standard. [c]Not determined. TBTA = Tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine. XPhos-Pd-G3 = (2-Dicyclohexylphosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl)[2-(2′-amino-1,1′-biphenyl)]palladium(II) methanesulfonate.

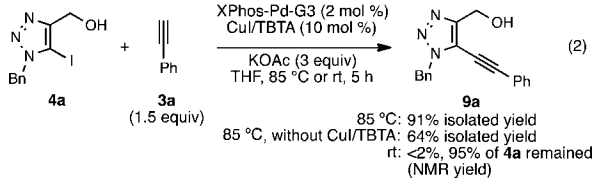
However, the chemoselectivity deteriorated in dioxane, and 5-iodotriazole **6** was formed either through a σ-metathesis of a copper-triazolide with a iodoalkyne **2a** or via CuAAC with *in situ* generated iodoethynylbenzene (entry 2).[10a,b] We observed a significant amount of diyne **7** in toluene by the copper-catalyzed Cadiot−Chodkiewicz cross-coupling (entry 3).[11] The addition of a base also affected the selectivity of the CuAAC, and KOAc gave better selectivity than Et_3N (entry 4 and 5). The palladium catalyst and added ligand played an important role in the reaction outcome. For example, with the use of $Pd(OAc)_2$ or Pd_2dba_3, we observed diyne **8** as a major product formed by the Cu/Pd catalyzed homocoupling of iodoalkyne (entries 6 and 7).[12] Parasitic reactions that formed diyne **7** and **8** would reduce the maximum possible yield of the final product even if diynes do not undergo the CuAAC. Finally, we found the use of palladacycle precatalyst developed by the Buchwald group was important in restoring reactivity for the formation of iodotriazole **4a** (entry 9).

XPhos-Pd-G3 releases the active monoligated Pd^0 catalysts in the presence of base.[13] Catalyst activation could occur with carbonate bases as low as room temperature. However, with a weaker base such as KOAc, the precatalyst remained inactive.[14] When subjecting the iodoalkyne to the XPhos-Pd-G3 in the presence of KOAc and excess phenyl acetylene, we did not observe any diyne cross-coupling product (eq 1).



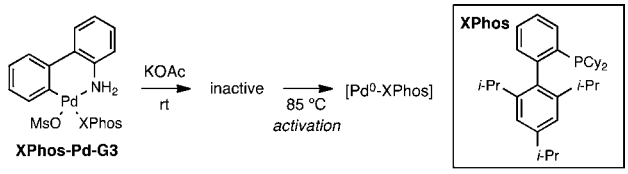
However, by using a $Pd(OAc)_2$/XPhos system instead of the precatalyst, a decomposition of iodoalkyne was observed. The inactive precatalyst prevented possible interference of the chemoselective CuAAC and further enforced the desired reaction pathway.

Concurrently, we sought conditions for the Cu/Pd-catalyzed Sonogashira cross-coupling of iodotriazole **4a** with phenyl acetylene. While a number of conditions have been reported,[15] we also observed this transformation was possible using the palladium catalyst XPhos-Pd-G3 at 85 °C (eq 2).[16]



The use of CuI in combination with the precatalyst was important in affording high yields.[17] In contrast, we observed a negligible amount of **9a** and 95% of unreacted **4a** by ^1H NMR analysis, when the same reaction was performed at room temperature. The use of KOAc as a weak base allowed us to control the release of the active Pd^0 catalysts by elevating the temperature (Scheme 2).

Scheme 2. Latent Activation of the Palladacycle Precatalyst



We next optimized the "all-in-one" process (Table 2; see Table S2 for full optimizations). Heating the reaction mixture from the outset, we observed a 30% yield of the desired product **9a** at 85 °C with 1.5 equiv of phenyl acetylene (entry 1).[18] Having demonstrated the latent catalyst activation approach, we subsequently used room temperature followed by heating at 85 °C. From the optimization results, we found the reaction could be conducted at a lower catalyst loading and the optimal reaction time for the CuAAC was found to be 4 h. Under optimized conditions, we were able to access the desired $(MC)^2R$ product **9a** in 73% yield (entry 2). The

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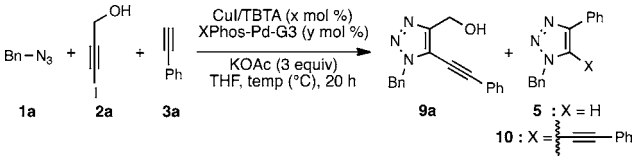
Table 2. Optimization of the "All-in-One" $(MC)^2R$[a]



				yield[b] (%)		
entry	x	y	temp (°C)	**9a**	**5**	**10**
1	10	2	85	30	14	3
2	5	1	rt (4 h) then 85	73[c]	4	6
3[d]	5	1	rt (4 h)	1	5	0

[a]Representative reaction procedure: in a microwave vial under an argon atmosphere, CuI, TBTA, XPhos-Pd-G3, and KOAc were added, followed by the addition of iodoalkyne (0.2 mmol) and azide (1.1 equiv). The mixture was dissolved in THF (0.1 M), and the phenyl acetylene (1.5 equiv) was subsequently added. The mixture was stirred at rt for the period indicated followed by heating for 20 h. [b]Yields were determined via ^{1}H NMR spectroscopy of the crude mixture using 1,3,5-trimethoxybenzene as the internal standard. [c]Isolated yield. [d]The reaction was stopped after 4 h. Iodotriazole **4a** was observed in 80% NMR yield.

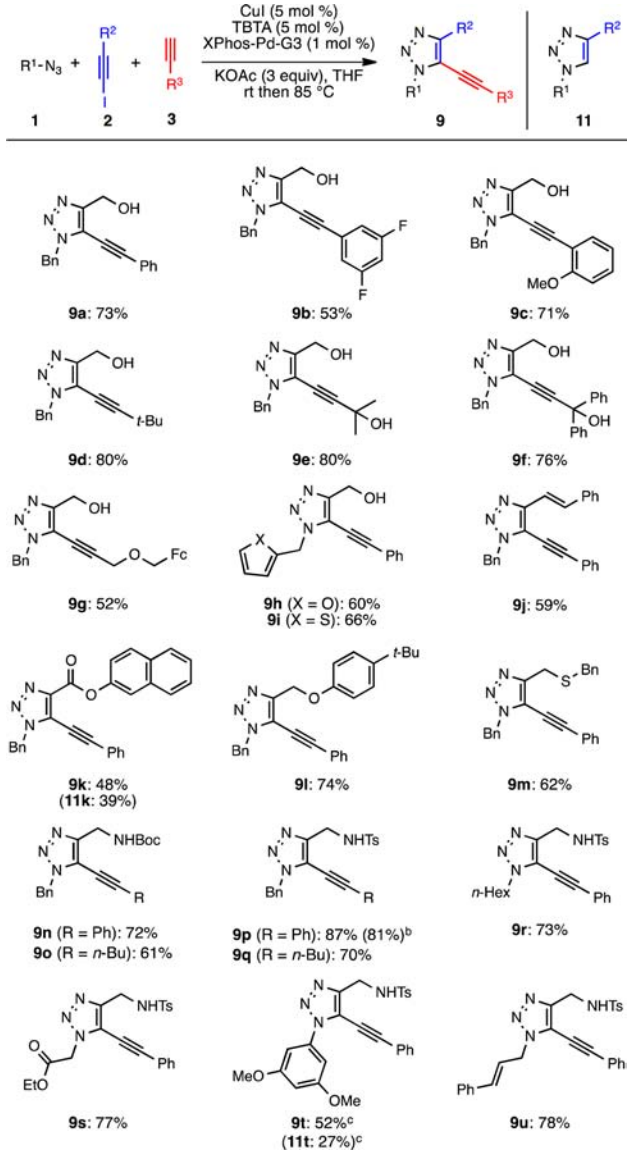
chemoselective CuAAC coupled with the latent Pd activation provided strong temporal control of the multicomponent reaction sequence where all of the closely related reactants and reagents could be placed in one reaction compartment from the outset.

We turned our attention toward demonstrating the scope of the $(MC)^2R$ (Scheme 3). Good yields were obtained with various acetylenes, affording triazoles with R^3 bearing electron-rich and -poor aryl and alkyl groups (**9a**–**9g**). Various iodoalkynes could be employed, providing triazoles with C4 substitution (R^2) including styrenyl (**9j**), phenoxy (**9l**), sulfide (**9m**), and amino groups (**9n**–**9u**).[19,20] In addition, a number of azides bearing heteroaromatic and alkyl groups were also tolerated (**9h**, **9i**, **9r**, **9s**, **9u**). The reaction could also be performed on 2 mmol scale, affording **9p** in 81% yield. During the studies, we found that both R^1 and R^2 influence the ratio of the desired three-component product **9** vs a deiodinated product **11**. For example, we observed a large amount of deiodinated triazole **11** when R^1 is an aryl group (**9t**), or when R^2 is a carboxylate group (**9k**).[21]

The highly efficient diversity-generating CuAAC/Sonogashira process provided an opportunity for further functionalization. For example, we developed a method for the cyclization of products bearing the *N*-tosylamino or benzylsulfide group (Scheme 4). Subjecting **9p** or **9q** to Cs_2CO_3 in dioxane at 120 °C followed by treatment with KO*t*-Bu at room temperature allowed us to access triazolopyridines **12** in a one-pot manner. The iodocyclization of triazole **9m** gave exclusively iodo-substituted 6-*endo-dig* cyclized product **13**. The structure of **13** was confirmed by X-ray crystal structure analysis.

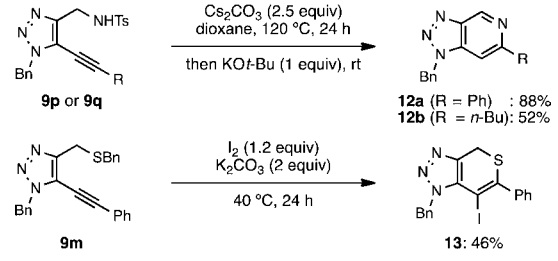
In summary, we have demonstrated the advantage of a multicatalyst approach by coupling chemoselectivity with latent catalysis activation in achieving control in a sequence of catalytic reactions, where all reagents including closely related substrates coexist in the same vessel. This multicomponent multicatalytic reaction provided direct access to fully substituted 1,2,3-triazoles with selectivity, a broad scope, and good to high yields.

Scheme 3. Triazole Scope of the $(MC)^2R$[a]



[a]See Supporting Information for reaction details. Iodoalkyne **2** (0.2 mmol), azide **1** (1.1 equiv), and terminal alkyne **3** (1.5–3.0 equiv) were dissolved in THF. CuI, TBTA, and XPhos-Pd-G3 were added. The mixture was stirred at rt until **2** was consumed followed by heating at 85 °C for 15–24 h. The reported yields were isolated yields after column chromatography. [b]Reaction performed on 2 mmol scale. [c]Reaction performed with 4 Å molecular sieves as a additive. Fc = ferrocenyl.

Scheme 4. Derivatization of Triazoles[a]



[a]The yields were isolated yields after column chromatography.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00975.

Detailed experimental procedures and full compound characterization data (PDF)

X-ray crystal structure of **13** (CIF)

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Notes

The authors declare no competing financial interest.

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(14) See Supporting Information Table S1 for further discussion.

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(16) Using CuI (10 mol %), Pd(OAc) (5 mol %), $P(2\text{-furyl})_3$ (10 mol %), and Et_3N (3 equiv) in THF at 80 °C, we could also obtain the Sonogashira cross-coupling product **9a** in 97% yield.

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(18) When the solution of iodoalkyne was heated at 85 °C in the presence of XPhos-Pd-G3, CuI, and TBTA for 4 h, all of the iodoalkyne was consumed, giving complex mixtures.

(19) The reaction could be performed on 0.25 mmol scale in technical grade THF under air, affording **9p** in 74% yield.

(20) We also demonstrated a traditional one-pot sequential reaction for the synthesis of **9p**. A consecutive addition of phenylacetylene, XPhos-Pd-G3 and KOAc to the same vessel after the initial CuAAC reaction afforded **9p** in 86% yield.

(21) The deiodinated triazoles may be mainly formed in the Sonogashira reaction. When the pure iodotriazole, a precursor of **9t**, was subjected to the optimized reaction conditions, we could also obtain **9t** and **11t** in 51% and 35% yield, respectively.

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