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Aqueous Sonogashira Coupling of Aryl Halides with 1-Alkynes Under Mild Conditions: Use of Surfactants in Cross-Coupling Reactions

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Abstract

Aqueous Sonogashira coupling between lipophilic terminal alkynes and aryl bromides or iodides was moderate to high yielding at 40 ^{o}C using readily available and inexpensive surfactants (2.0 w/v% in water) such as SDS and CTAB. The catalyst precursor was 2 mol% $Pd(PPh_3)_2Cl_2$, and included a 5 mol% Cu(I) co-catalyst for aryl iodide substrates. Aryl-bromide reagents were found to be inhibited by iodide and Cu(I). Studies under Cu(I)-free conditions reveal two competing pathways. A deprotonation pathway gives rise to the traditional Sonogashira product (**3**), while a carbopalladation pathway produces enyne, **5**. The surfactant solution (SDS or CTAB) can be recycled up to three times for coupling between 1-octyne and 1-iodonapthalene in the presence of CuI before yields decrease.

Introduction

The biological and environmental hazards and resulting costly processing and disposal of traditional organic solvents have stimulated demands for more benign reaction media.[1a-e] As a result, substantial effort has been directed towards developing new catalysis technology in non-traditional media such as 'solvent-free' conditions,[2] ionic liquids,[3a-i] supercritical fluids,[3e,4a-g] fluorous solvents,[3e,5a-c] and water.[6a-l] Industrial criteria for these technologies to be adopted as a reliable green approach include adherence to the 'twelve principles of green chemistry', a low value for the 'E-factor', and economically competitive production costs.[7a-c] Under these constraints, water stands out as a particularly attractive alternative, due to its abundance, low expense, and nontoxic properties.

The versatility and utility of cross-coupling reactions in synthetic chemistry are well documented.[8a-d] Traditional coupling conditions employ a variety of organic solvents with physical characteristics that match the needs of the desired reaction. Limiting the reaction medium to water introduces solubility and reactivity complications for catalysts and organic reagents. For some reactions, such as the Diels-Alder cycloaddition, aqueous solubility is a minimal concern because rates and yields are enhanced by hydrophobic effects encountered by the nonpolar reagents in water.[6j,l] However, most

metal-mediated cross-coupling reactions require additional methods to solubilize reagents and improve reactivity in water. Common approaches include the use of biphasic water-organic solvent systems; water-miscible organic co-solvents; phase transfer catalysts; and substrates or ligands with polar moieties (e.g. sulfonates, quaternary amines, hydroxyls, and sugars). However, these methods still depend on organic solvents and can reduce substrate scope. Alternatively, a simple strategy is the use of surfactants to create micelles with an organic interior or pocket that can entrain organic substrates in water. Even though the core of a micelle is largely hydrophobic, the interior can have regions of varying polarity, allowing incorporation of reagents that are both polar and nonpolar.[9a-c]

Studies on the scope of surfactant influence on aqueous metal-mediated reactions have been limited, largely due to the common belief that surfactants are relatively interchangeable.[6h,9b,10a-m] Within the last decade, the development of versatile, three-component designer surfactants derived from vitamin E (Figure 1) has been pioneered by Lipshutz.[10g,k;11a-d] These "green" surfactants have proven to be very useful for Pd-catalyzed cross couplings and Ru-catalyzed metathesis, providing a noticeable decrease in reaction temperature and time.

To explore the influence of surfactants on Pd-catalyzed cross couplings, we turned our attention to a systematic study of the Sonogashira reaction[12a-d] using commercially available surfactants. However, only a few examples of aqueous Sonogashira reactions are reported, with even fewer that incorporate surfactants.[10b,d,h,i,l;11b, 13] Herein, we explore the influence of inexpensive, commercially available surfactants on the Sonogashira cross-coupling reaction and provide additional insight on the catalytic cycle, influence of Cu(I) salts, and the recyclability of the surfactant solution.

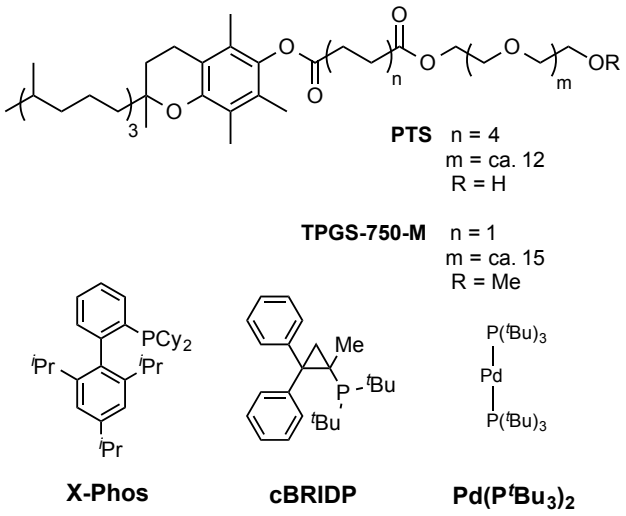


Figure 1. Representative surfactants, ligands and palladium catalyst employed in Lipshutz's work.[11b,c]

Results and Discussion

In this study, we employed four common, inexpensive surfactants (Figure 2), sodium cholate (critical micelle concentration, CMC, 0.388 - 0.603% w/v%), cetyl trimethylammonium bromide (CTAB; CMC 0.32 w/v%), sodium dodecylsulfate (SDS; CMC 0.173 - 0.230 w/v%), and Triton X-100 (CMC 0.0155 w/v%).[9a,14] For convenience and economics, air-stable $Pd(PPh_3)_2Cl_2$ was selected as the catalyst for this modification of the Sonogashira coupling. This catalyst also provided an additional benchmark due to its ubiquitous use in Cu(I) co-catalyzed couplings. Furthermore, complexes such as $PdCl_2$, Na_2PdCl_4, and $Pd(OAc)_2$ in the absence of phosphine ligands were not effective catalysts for coupling under the conditions used herein.

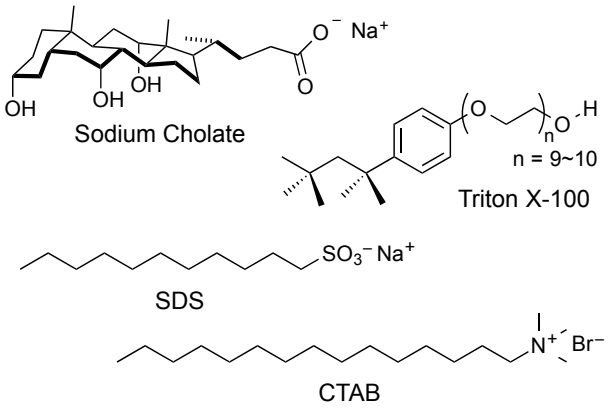
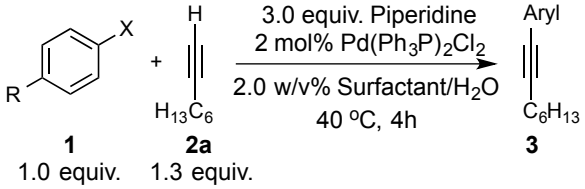


Figure 2. Surfactants used in this work.

Surfactant Screening

Initial screening of surfactants for the coupling of 1-octyne with an electron deficient aryl iodide, 4-iodobenzonitrile, indicated that each surfactant was able to facilitate quantitative coupling when using a concentration of 2.0 w/v%, as long as CuI was present (Table 1). When the aryl halide was switched to the more electron rich 4-iodoanisole, differences between the efficacy of the surfactants emerged. Lower coupling yields in the presence of sodium cholate and Triton X-100 led us to focus on the more effective surfactants, SDS and CTAB, in subsequent studies. Within this initial screening, it was also found that copper iodide strongly hindered the coupling of 4-bromobenzonitrile and octyne with all four surfactants. Moreover, reactions with the electron-rich 4-bromoanisole provided no coupling product within 4 h. Aryl chlorides, such as *p*-nitrophenyl chloride, were generally unreactive and not examined further.

Table 1. Surfactant Screening for the Sonogashira Coupling of Aryl Halides with 1-Octyne.



1 1.0 equiv. **2a** 1.3 equiv. **3**

Entry	R	X	Surfactant	% Yield **3**[a] (CuI)[b]	(No CuI)
1	CN	I	Na Cholate	Quant.	48
2	CN	I	CTAB	97	57
3	CN	I	SDS	Quant.	61
4	CN	I	Triton X-100	Quant.	58
5	OMe	I	Na Cholate	74	30
6	OMe	I	CTAB	92	38
7	OMe	I	SDS	85	30
8	OMe	I	Triton X-100	68	29
9	CN	Br	Na Cholate	24	42
10	CN	Br	CTAB	20	57
11	CN	Br	SDS	16	55
12	CN	Br	Triton X-100	32	44

Reaction conditions: 0.08 mmol aryl halide, 0.1 mmol 1-octyne, 0.24 mmol piperidine, 2.0 mol% $Pd(PPh_3)_2Cl_2$, 0.8 mL surfactant in H_2O, 40 ºC, 4 h; [a]Average ^{1}H NMR yields for duplicate runs (±3). [b] 5 mol% CuI.

Variation of the concentration of the surfactant for both SDS and CTAB indicated that a 2.0 w/v% solution of each surfactant provided optimal yields (Table S1-S2). Product yields were greatly reduced at lower surfactant concentrations, albeit still above the CMC, possibly due to an inadequate quantity of micelles to sufficiently solubilize the organic reagents. CTAB is not soluble at concentrations higher than 2.0 w/v% at room temperature. However, SDS is soluble at room temperature, even at concentrations of 8.0 w/v%, although concentrations this high did not improve coupling activity.

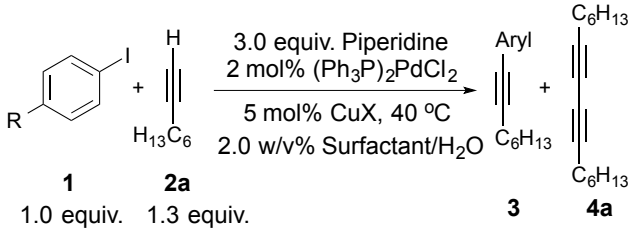
Effect of Base on Sonogashira Coupling

In addition to surfactants, a variety of bases were also screened using SDS and CTAB in the presence and absence of CuI (Table S3). Addition of base aids in proton abstraction during alkynylation of the metal center (either Cu or Pd) and facilitates the elimination of product from the Pd center.[12b,d;15] Overall, water-soluble inorganic bases such as K_2CO_3, NaOAc, and Cs_2CO_3 resulted in low to no coupling product. However, NEt_3, piperidine and pyrrolidine enabled coupling in high yields. Due to improvement of yields and ease of handling, piperidine was selected as the base of choice for this study. Since the properties of the head group (carboxylate, sulfate, amine, etc.) of a surfactant can affect pH, possibly altering the efficacy of the base, the pH of the Sonogashira reaction conditions was monitored (Table S4). A 2.0 w/v% solution of each surfactant had different pH values before addition of the Sonogashira reagents. However, once piperidine was added to the solution, the pH changed to ~11.0 at 40 ^{o}C and remained constant throughout the reaction, regardless of the surfactant.

Functional Group Tolerance of Sonogashira Coupling in the Presence of Surfactant

As shown in Table 2, the optimized aerobic reaction conditions for the Sonogashira coupling of aryl iodides with 1-octyne was general and tolerant of a range of functionalities on the aryl substrate. Both electron deficient and electron rich *p*-substituents afforded high yields of coupled product. When using aryl bromide substrates, moderate yields were also obtained (Table 3, entries 1-8), except for electron rich aryl bromides (entries 9-12). While coupling was achieved with either aryl-iodides or

Table 2. Sonogashira Coupling of Various Aryl-I in the Presence of SDS and CTAB.

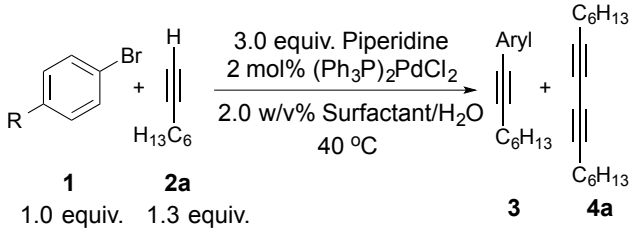


1 1.0 equiv. **2a** 1.3 equiv. **3** **4a**

Entry[a]	R	CuX	Surfactant	% Yield **3**[b,c]	Yield **4a**[d]
1	CN	CuI	CTAB	97 (57)	12
2	CN	CuBr	CTAB	Quant. (57)	12
3	CN	CuI	SDS	Quant. (61)	11
4	CN	CuBr	SDS	Quant. (61)	10
5	CF_3	CuI	CTAB	Quant. (68)	9
6	CF_3	CuBr	CTAB	97 (68)	10
7	CF_3	CuI	SDS	Quant. (60)	10
8	CF_3	CuBr	SDS	90 (60)	9
9	NO_2	CuI	CTAB	91 (75)	14
10	NO_2	CuI	SDS	92 (74)	18
11	Ac	CuI	CTAB	96 (61)	17
12	Ac	CuI	SDS	Quant. (60)	13
13	CO_2Me	CuI	CTAB	89 (50)	18
14	CO_2Me	CuI	SDS	87 (57)	17
15	OMe	CuI	CTAB	97 (50)	16
16	OMe	CuBr	CTAB	93 (50)	17
17	OMe	CuI	SDS	90 (34)	18
18	OMe	CuBr	SDS	94 (34)	18
19	Me	CuI	CTAB	92 (50)	13
20	Me	CuBr	CTAB	88 (50)	13
21	Me	CuI	SDS	81 (39)	16
22	Me	CuBr	SDS	80 (39)	12
23[e]	Napthyl	CuI	CTAB	97 (63)	10
24[e]	Napthyl	CuI	SDS	Quant. (41)	9

Reaction conditions: 0.08 mmol aryl halide, 0.10 mmol 1-octyne, 0.24 mmol piperidine, 2.0 mol% $Pd(PPh_3)_2Cl_2$, 40 ºC, 0.80 mL surfactant (2.0 w/v% in H_2O); [a] Rxns 1-14 ran 4 h, Rxns 15-24 ran 5 h. [b] Average ^1H NMR yields for duplicate runs (±3); [c] Parenthetical value is Cu(I)-free yield; [d] Yield is reported in μmol; [e] Aryl-I is 1-iodonapthalene.

Table 3. Sonogashira Coupling of Various Aryl-Br in the Presence of SDS and CTAB.



1 1.0 equiv. **2a** 1.3 equiv. **3** **4a**

			% Yield **3**[a]		Yield **4a**[b]
Entry	R	Surfactant	(No CuBr)	(CuBr)	(μmol)
1	CN	SDS	67	29	14
2	CN	CTAB	63	41	20
3	NO_2	SDS	64	8	9
4	NO_2	CTAB	74	20	17
5	CHO	SDS	67	8	12
6	CHO	CTAB	63	9	8
7[c]	Napthyl	SDS	68	4	10
8[c]	Napthyl	CTAB	67	10	15
9	Me	SDS	23	8	9
10	Me	CTAB	45	10	13
11	OMe	SDS	22	7	6
12	OMe	CTAB	35	9	8

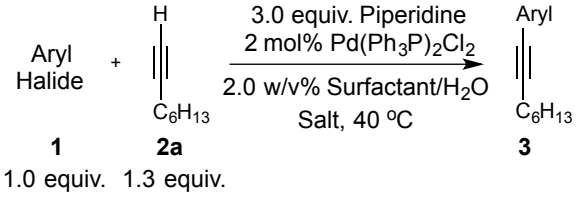
Reaction conditions: 0.08 mmol aryl halide, 0.10 mmol 1-octyne, 0.24 mmol piperidine, 2.0 mol% $Pd(PPh_3)_2Cl_2$, 0.80 mL surfactant (2.0 w/v% in H_2O), 40 ºC, 20 h; [a] Average ^1H NMR yields for duplicate runs (±3); [b] Yield of **4a** in μmol for reactions containing CuBr; [c] Aryl-Br is 1-bromonapthalene.

bromides, the reaction conditions were distinctly different for these two types of halide reagents. Both CuI and CuBr increased product yield in the coupling of aryl-iodide compounds with 1-octyne, but strongly inhibited coupling of aryl-bromides, despite the choice of surfactant or base (Tables 1, 2, S3). This inhibitory effect of Cu(I) with less active aryl-halides was noted earlier, resulting in development of alternative copper-free Sonogashira conditions.[10d,11b,16a-f] Inhibition has been reported to be a result of Cu(I)-catalyzed homocoupling (Glaser coupling) of terminal alkynes, which requires oxygen to proceed.[17,18] In all of our reactions, under aerobic conditions, a secondary diyne product was present, resulting from the homocoupling of the alkyne (*vide infra*).

Cu(I) Salt and Iodide Inhibition on Sonogashira Coupling of Aryl Bromide Reagents

Further exploration showed that CuI was more inhibiting than CuBr in aryl bromide reactions (Table 4). Moreover, the coupling of 1-iodonapthalene and 4-bromobenzonitrile was assessed in the presence of various potassium halide salts. These studies demonstrate that the 4-bromobenzonitrile reactions were strongly inhibited by iodide. Even at a concentration of 0.05 M, KI lowered coupling product yield by 23% and 34% in both SDS and CTAB respectively (Figure 3). The reduction in Sonogashira coupling is most likely due to competitive iodide binding to Pd, possibly hindering the oxidative addition of the aryl bromide.

Table 4. Effect of salt on Sonogashira coupling of aryl halides with 1-octyne.



Entry[a]	Aryl-X	Salt (0.2 M)	% Yield **3**[b] SDS	% Yield **3**[b] CTAB
1	1-iodonapthalene	none	19	45
2	1-iodonapthalene	CuI[c]	86	86
3	1-iodonapthalene	CuBr[c]	88	86
4	1-iodonapthalene	KCl	26	45
5	1-iodonapthalene	KBr	24	43
6	1-iodonapthalene	KI	22	39
7	4-bromobenzonitrile	none	67	63
8	4-bromobenzonitrile	CuI[c]	0	10
9	4-bromobenzonitrile	CuBr[c]	29	41
10	4-bromobenzonitrile	KCl	64	62
11	4-bromobenzonitrile	KBr	62	61
12	4-bromobenzonitrile	KI	47	24

Reaction conditions: 0.08 mmol aryl halide, 0.1 mmol 1-octyne, 0.24 mmol piperidine, 2.0 mol% $Pd(PPh_3)_2Cl_2$, 40 ºC, 0.80 mL surfactant (2.0 w/v% in H_2O; 0.2 M in Salt); [a] Rxn 1-6 ran 4 h, Rxn 7-12 ran 20 h. [b] Average ^1H NMR yields for duplicate runs (±3). [c] 5 mol% CuX was used, SDS and CTAB solutions contained no salt.

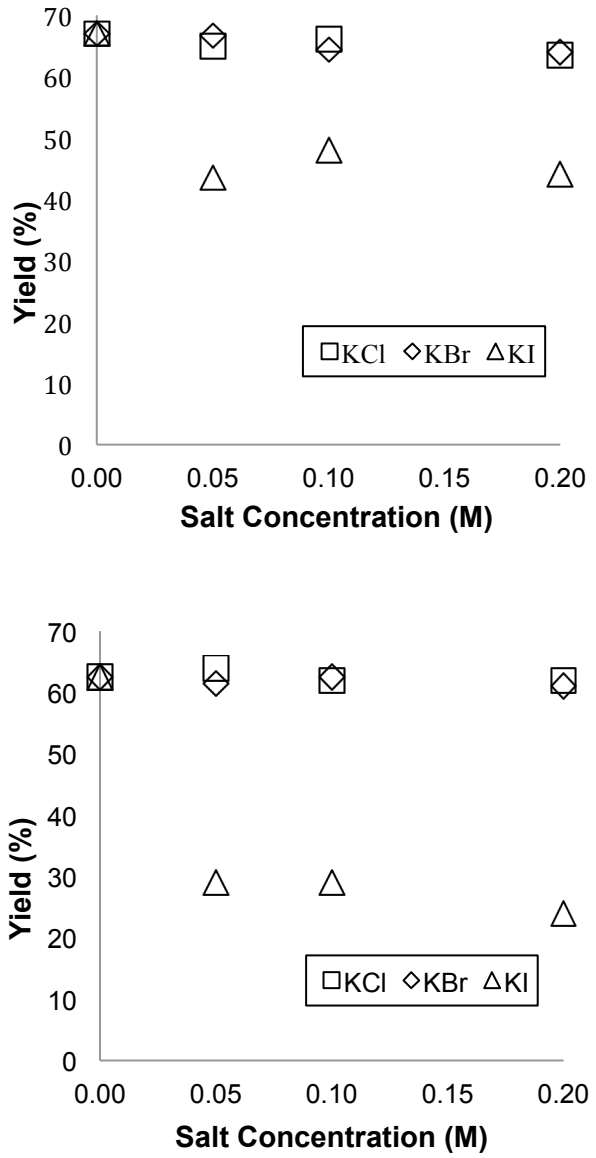


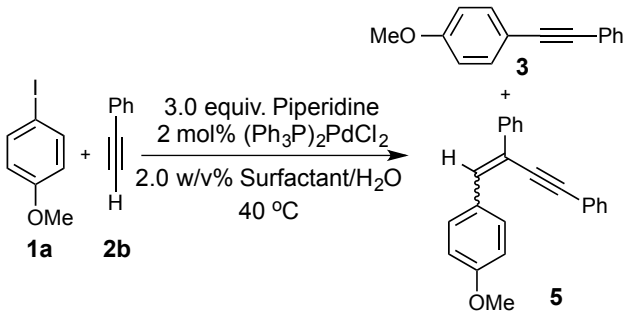
Figure 3. Effect of potassium halide salts on coupling of 4-bromobenzonitrile with 1-octyne. Reaction conditions: 0.08 mmol aryl halide, 0.1 mmol 1-octyne, 0.24 mmol piperidine, 2 mol% $Pd(PPh_3)_2Cl_2$, 0.80 mL, surfactant solution (2.0 w/v% in water), 40 ºC, 20 h; Average ^{1}H NMR yields for duplicate runs (±3). Top: with SDS; Bottom: with CTAB.

Formation of an Enyne Product

Coupling of phenylacetylene with aryl iodide was explored to determine if Cu(I) could be eliminated by using a more reactive alkyne substrate. When coupling excess phenylacetylene to 4-iodoanisole, conversions were high to quantitative using either SDS or CTAB as the surfactant, both with

and without CuI (Table 5). However, in the absence of CuI a significant amount of an enyne side product (**5**) was observed (Table 5). This side product was previously observed by Djakovitch et al. and proposed to originate from the insertion of phenylacetylene **2** into the initial Sonogashira product **3** under thermal or palladium-catalyzed conditions (*vide infra*).[16b] In contrast, the analogous enyne product, that could result from using 1-octyne as the alkyne, was never detected under any of our reaction conditions. When CuI was present, **5** was not detected. Instead, quantitative Sonogashira products were produced and all excess phenylacetylene was converted to 1,4-diphenylbuta-1,3-diyne (**4b**), according to GC analysis.

Table 5. Cu(I)-free Sonogashira Coupling of Aryl-Halides and Phenylacetylene in the Presence of SDS and CTAB.



Entry	Surfactant	Ratio **1a**:**2b**	% Yield **3b**[a,b]	% Yield **5**[a,b]
1	SDS	1:5	58 (Quant.)	39 (0)
2	SDS	1:2	75 (92)	19 (0)
3	SDS	1:1	72 (82)	8 (0)
4	SDS	2:1	50 (71)	8 (0)
5	CTAB	1:5	61 (Quant.)	39 (0)
6	CTAB	1:2	75 (Quant.)	21 (0)
7	CTAB	1:1	65 (84)	10 (0)
8	CTAB	2:1	68 (83)	6 (0)

Reaction conditions: 0.24 mmol piperidine, 2.0 mol% $Pd(PPh_3)_2Cl_2$, 40 ºC, 0.80 mL surfactant (2.0 w/v% in H_2O), 4 h; [a]Average ^1H NMR yields for duplicate runs (±3); [b] Parenthetical value is yield in presence of 5 mol% CuI, homocoupling product yield not determined.

Recycling of Aqueous Surfactant Solution.

The recyclability of the surfactant solution for Sonogashira coupling was assessed for 1-iodonapthalene and 1-octyne (Figure 4). A typical 1.0-mL scale coupling reaction between 1-iodonapthalene and 1-octyne was conducted in a 1.7-mL microcentrifuge tube. After 4 h, 200 µL of EtOAc was added to the tube. The mixture was thoroughly agitated and centrifuged at 10,000 RPM for 2 min to separate the organic reagents from the surfactant solution. This EtOAc wash, centrifugation, and separation was done a total of three times. The aqueous surfactant layer was removed and reused in another coupling reaction between 1-iodonapthalene and 1-octyne. Figure 4 illustrates that over 3 reaction cycles, yields of coupling product remained relatively constant, but decreased with subsequent cycles. Reuse of the CTAB solution caused the surfactant to precipitate over time, contributing to the subsequent lowering of yields.

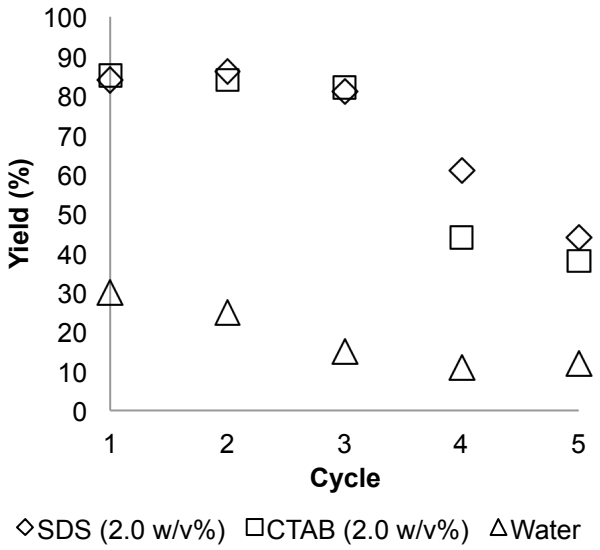


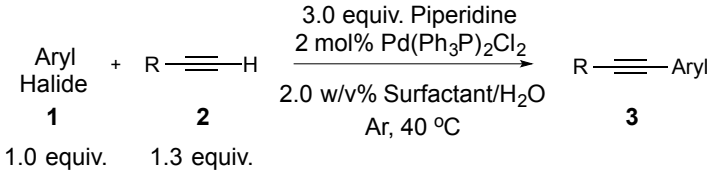
Figure 4. Recycling of aqueous surfactant solution for the Sonogashira coupling between 1-iodonapthalene and 1-octyne. Each cycle was heated at 40 ºC for 4 h.

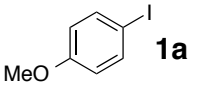
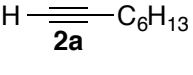
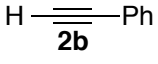
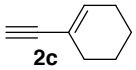
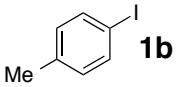
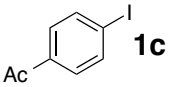
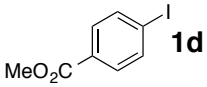
Product Purification

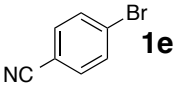
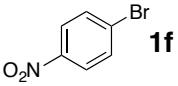
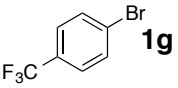
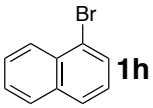
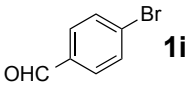
To illustrate the ease of product purification and surfactant removal, both the aryl iodide and bromide reactions were scaled up ten-fold (Table 6). In addition to employing the optimized conditions

developed above, all reagents were added under argon and the aqueous surfactant solution was sparged with argon for 30 min before addition to the reaction vessel. Reducing the atmospheric oxygen lowered or eliminated the formation of the homocoupling product, **4**, in Cu(I) co-catalyzed reactions and gave an increase in isolated yield for aryl-bromide reactions. The alkyne product was easily extracted from the aqueous surfactant solution using hexanes or ethyl acetate. Passing the extracted solution through a plug of silica gel eliminated trace surfactant contamination and residual catalyst. Purification difficulties arose when the homocoupling product was also present. The diyne products (**4a** and **4b**) co-eluted with the Sonogashira product during flash column chromatography, even when using neat hexane as the eluent.

Table 6. Isolated Sonogashira Coupling Yields for Aryl-I and Aryl-Br Substrates.



Entry	Aryl halide	Alkyne	Surfactant	CuI (5 mol%)	Product (% Yield)
1	 **1a**	 **2a**	CTAB	-	45 (**3a**)
2	**1a**	**2a**	CTAB	CuI	92 (**3a**)
3	**1a**	 **2b**	CTAB	-	54 (**3b**)
4	**1a**	**2b**	CTAB	CuI	96 (**3b**)
5	**1a**	 **2c**	CTAB	CuI	93 (**3c**)
6	 **1b**	**2a**	SDS	CuI	91 (**3d**)
7	**1b**	**2b**	SDS	CuI	96 (**3e**)
8	**1b**	**2c**	SDS	CuI	94 (**3f**)
9	 **1c**	**2a**	SDS	-	61 (**3g**)
10	**1c**	**2a**	SDS	CuI	96 (**3g**)
11	**1c**	**2b**	SDS	-	72 (**3h**)
12	**1c**	**2b**	SDS	CuI	97 (**3h**)
13	 **1d**	**2a**	CTAB	CuI	91 (**3i**)

14	**1d**	**2b**	CTAB	CuI	93 (**3j**)
15	 **1e**	**2a**	CTAB	-	77 (**3k**)
16	**1e**	**2b**	CTAB	-	78 (**3l**)
17	 **1f**	**2a**	SDS	-	79 (**3m**)
18	**1f**	**2b**	SDS	-	87 (**3n**)
19	**1f**	**2c**	SDS	-	80 (**3o**)
20	 **1g**	**2a**	SDS	-	74 (**3p**)
21	**1g**	**2b**	SDS	-	79 (**3q**)
22	 **1h**	**2a**	CTAB	-	63 (**3r**)
23	**1h**	**2b**	CTAB	-	76 (**3s**)
24	**1h**	**2c**	CTAB	-	66 (**3t**)
25	 **1i**	**2a**	SDS	-	67 (**3u**)

Condition: 0.8 mmol aryl halide, 1.0 mmol alkyne, 3.0 mmol piperidine, 2 mol% $Pd(PPh_3)_2Cl_2$, 5 mol% CuI if indicated, 8.0 mL surfactant (2.0 w/v% in water), 40 ^oC, under Ar, 5 h for aryl-I and 20 h for aryl-Br reactions.

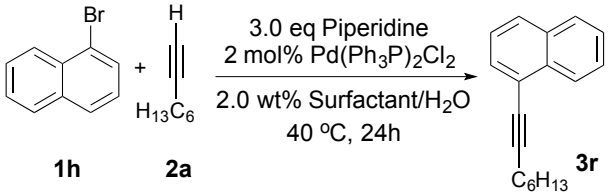
Mechanistic Considerations

Copper(I) co-catalyzed Sonogashira reactions are commonly agreed to have three fundamental steps, 1) oxidative addition of the aryl halide to Pd(0), 2) transmetallation of the acetylide moiety from Cu(I) to the Pd center, and 3) subsequent reductive elimination of alkyne product (Figure 5a).[12d] The key benefit of Cu is facilitating the formation of the Pd-acetylide, which occurs through the formation of a Cu-acetylide intermediate (**G**). However, the Cu-acetylide is also active for homocoupling under aerobic conditions that leads to a diyne product, **4**, a side-reaction that would divert the alkyne substrate from forming the desired Sonogashira product. In our aryl iodide system, this homocoupling process was not detrimental to the formation of the desired product, **3**. Moreover, homocoupling was not the cause of reduced yields in the aryl bromide reactions. In these cases, the formation of diyne, **4a**, was low (< 20 μmol) in all reactions involving aryl bromides. The low yield in aryl bromide reactions was also not

caused by Cu–catalyzed oligomerization of 1-octyne. No oligomers were detected in these reactions and a substantial amount of 1-octyne remained at the end of the reaction.

In seeking to improve the yields of the aryl bromide reactions, we examined the role of the alkyne substrate by varying its amount and rate of addition (Table 7). When 1-octyne was the limiting reagent in reactions with 1-bromonaphthalene, the yield of product **3r** was quantitative, based upon the loading of the alkyne. As the amount of 1-octyne was increased, the yield of **3r** decreased. However, if the alkyne was added in smaller aliquots throughout the duration of the reaction, the yield of **3r** was significantly improved (78%, Table 7, entry 4) as compared to a reaction with the same loading of 1-octyne added entirely at the beginning of the reaction (51%, Table 7, entry 3). This alkyne inhibition is consistent with coordination to Pd^0L_2 (**A**), forming a (η^2-RC≡CR')Pd^0L_2 complex that is less electron rich, further decreasing the extent of oxidative addition of the aryl halide to the Pd center.[19] In support of this alkyne inhibition, 1,4-diphenylbuta-1,3-diyne, **4b**, was added to the coupling of 1-bromonapthalene and 1-octyne. For the reactions with 20 μmol (25 mol%) diyne, the yield of product **3r** was reduced to 51% and 53% for CTAB and SDS respectively (Table 7, entries 6 and 8).

Table 7. Influence of Alkyne and Diyne (**4b**) on Coupling in Cu-Free Aryl-Bromide Reactions.



1h **2a** **3r**

Entry	**1h**:**2a**	**4b** (mol%)	Surfactant	% Yield **3r**[a]
1	1:0.7	-	CTAB	Quant. (67)[b,c]
2	1:1	-	CTAB	56
3	1:1.7	-	CTAB	51
4	1:1.7[d]	-	CTAB	78
5	1:1.3	-	CTAB	67
6	1:1.3	25	CTAB	51
7	1:1.3	-	SDS	68
8	1:1.3	25	SDS	53

Reaction conditions: 0.08 mmol aryl halide, 0.24 mmol piperidine, 2.0 mol% $Pd(PPh_3)_2Cl_2$, 40 ºC, 0.80 mL surfactant (2.0 w/v% in water); [a] Average ^{1}H NMR yields for duplicate runs (±3); [b] % Yield based upon the loading of 1-octyne, 0.05 mmol; [c] Parenthetical value is conversion of 1-bromonapthalene; [d] 0.07 mmol 1-octyne added at t = 0 h and 8 h.

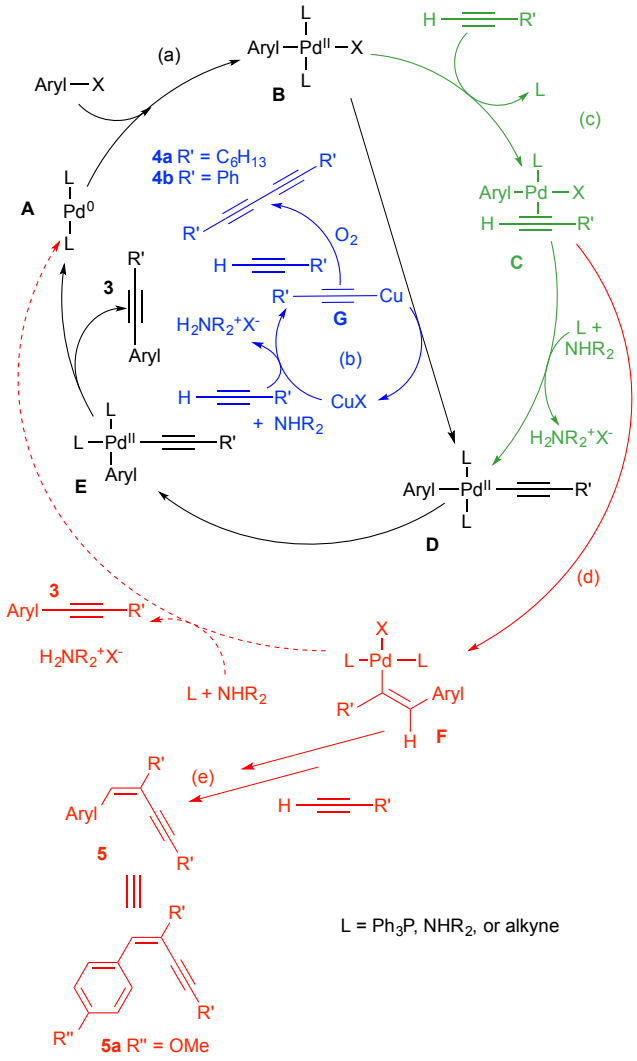


Figure 5. Proposed mechanism of the Sonogashira coupling in the presence of piperidine, with and without a Cu(I) co-catalyst; (a) Traditional Cu(I) co-catalyzed Sonogashira; (b) Catalytic cycle for Cu(I) including formation of diyne, **4**; (c) Cu(I)-free coupling via deprotonation mechanism; (d) Cu(I)-free carbopalladiation cycle forming product **5**.

Two mechanisms have been proposed for the copper-free Sonogashira coupling: a 'deprotonation mechanism' and a 'carbopalladation mechanism' (Figure 5 steps c and d, respectively). Recently, a number of experimental and computational studies indicate that the latter is more feasible than the former. Mårtensson et al. argued against the carbopalladation mechanism because isolated intermediates such as F do produce product **3** and intermediate **A** in the presence or absence of NEt_3.[16a] Additionally, a

computational study for the ambient-temperature coupling of iodobenzene and phenylacetylene catalyzed by $Pd(PPh_3)_2$ produced a calculated energy barrier of 40.4 kcal·mol^{-1} for the pyrrolidine-assisted β-H elimination from intermediate **F** to form product **3**.[20] However, the deprotonation mechanism does not explain the formation of the side product, **5**. We confirmed that under our conditions diphenylacetylene does not form an enyne product with phenylacetylene, indicating that product **5** is not due to alkyne addition to product **3**. More likely, **5** may be formed by the reaction of intermediate **F** with excess alkyne.[16a] Thus, under Cu(I)-free conditions both mechanisms appear to be competing. When alkyne coordinates to Pd to form intermediate **C**, the pathway can undergo base assisted deprotonation to form Pd-acetylide, **D**, or *syn* addition form intermediate **F**. Excess phenylacetylene further favors the formation of product **5** from **F**. When Cu(I) is present, the transmetallation step is so fast that intermediate **C** may not form in high enough concentration, disfavoring the pathway to **5**.

Summary

Our work has shown that inexpensive, commercially available surfactants such as SDS and CTAB are effective in the aqueous-phase Sonogashira coupling for various aryl iodide and bromide substrates with alkynes, providing a substantial improvement of product yields achieved in neat water at the same temperature. Under the surfactant conditions described above, both the deprotonation and carbopalladation mechanisms appear to be active. The deprotonation mechanism forms the desired Sonogashira product, but in the presence of excess phenylacetylene, the enyne product (**5**) derived from a carbopalladation pathway, is observed as a side-product. Copper(I) salts and excess alkyne aryl bromide reactions. Consequently, aryl bromide reactions benefit from slow addition of the alkyne reagent under Cu-free conditions.

Overall, use of a surfactant enhances reactivity in water and thus minimizes the need for organic solvents. However, contaminated water is still a waste material if it cannot be recovered from the organic reagents and reused, detracting from its green benefits. Both SDS and CTAB solutions proved recyclable, maintaining moderate to high yields for coupling of 1-iodonapthalene and 1-octyne. The

efficacy and recyclability of these surfactant solutions as reaction media demonstrates that these conditions are a good foundation for further modifications, including utilizing a more reactive Pd-complex, varying the surfactant structure, and expanding the scope to other catalytic reactions.

Experimental

General Considerations.

Surfactants, aryl-halides, alkynes, bases and copper salts were purchased commercially (≥97% purity) and used without further purification. Bis(triphenylphosphine)dichloropalladium(II) was prepared and characterized according to a literature procedure.[21] Surfactant solutions were prepared using deionized water. All NMR-scale reactions were performed in 1.7 mL microcentrifuge tubes from Corning Incorporated and were shaken with an Eppendorf Thermomixer R for the time and temperature indicated. Preparative scale reactions were performed in 20-mL glass scintillation vials, sealed with a cap containing a Poly-Seal cone liner. ^{1}H NMR spectra were obtained using a Varian MR400 MHz NMR. Mass spectra were collected on a Waters GCT GC-MS.

NMR Scale Procedure for the Sonogashira Reaction.

A suspension of 47 mg (67 μmol) $Pd(PPh_3)_2Cl_2$ was made with 1.0 mL of piperidine in a 20-mL glass vial. If indicated, 168 μmol of CuX (X = I or Br) was also included in this suspension. The suspension was sonicated until homogeneous and clear (30 min), resulting in a bright yellow Pd solution in the absence of Cu(I) and a dark green Pd solution with Cu. A 1.7-mL microcentrifuge tube was charged with 0.08 mmol aryl halide and 0.1 mmol alkyne, and 0.8 mL of aqueous surfactant solution (2.0 w/v%). Finally, 24 μL of the sonicated base/catalyst solution was added. This resulted in 0.24 mmol of piperidine, 1.6 μmol (2 mol%) of $Pd(PPh_3)_2Cl_2$ and 4.0 μmol (5 mol%) CuX per reaction. The tube was sealed, thoroughly mixed, and shaken at 1100 rpm and 40 ^{o}C for the time indicated. After reaction completion, the mixture was cooled to ambient temperature, and 50 μL of a standard solution (400 mg

mesitylene diluted to 10 mL with $CDCl_3$) was added. The samples were extracted with neat $CDCl_3$ (2 x 0.4 mL). To facilitate separation of the organic and water layers, the tubes were centrifuged at 1200 rpm for 2 min after each extraction. The extracts were combined and passed through a plug of Al_2O_3 and $MgSO_4$, into a NMR tube. Yields were determined by ^1H NMR. Each reaction was performed in duplicate.

Preparative Scale Procedure for the Sonogashira Reaction.

The indicated aqueous surfactant solution (2.0 w/v%) was sparged with Ar for 30 min. During this time, a suspension of 47 mg (67 μmol) $Pd(PPh_3)_2Cl_2$ was made in 1.0 mL of piperidine in a 20-mL glass vial. If indicated, 168 μmol of CuX (X = I; 32 mg or Br; 24 mg) was also included in this suspension. The suspension was sonicated until the mixture became homogeneous and clear (30 min), resulting in a bright yellow solution in the absence of Cu(I) and a dark green solution with Cu. Under Ar, a 20-mL glass vial was charged with a stir bar, 0.8 mmol aryl halide, 1.0 mmol alkyne, and 8.0 mL of the sparged aqueous surfactant solution, and 0.24 mL of the sonicated catalyst solution. The vial was briefly purged with Ar (5 min), sealed with a cap and stirred while gently heating at 40 ^oC for the time indicated. After reaction completion, all volatiles were removed under reduced pressure, and the aqueous solution was extracted with EtOAc (3x5 mL). The combined EtOAc extracts were washed with saturated NaCl (3x5 mL), dried with $MgSO_4$, filtered, and all solvent was removed under reduced pressure. The crude product was purified via flash column chromatography using hexane or hexane/EtOAc as the eluent. Product purity was determined via ^1H NMR and GC-MS analysis. Characterization data for all coupling products matched literature values.

1-methoxy-4-(oct-1-yn-1-yl)benzene (**3a**).[22] Clear oil, 161 mg, 92%; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.34 (d, J = 8.8 Hz, 2H), 6.82 (d, J = 8.8 Hz, 2H), 3.81 (s, 3H), 2.39 (t, J = 6.6 Hz, 2H), 1.63-1.54 (m, 2H), 1.50-1.41 (m, 2H), 1.37-1.29 (m, 4H), 0.91 (t, J = 6.0 Hz, 3H); EI-MS: m/z (rel. intensity %)

216.1 (M^+, 52), 201.1 (5), 187.1 (27), 173.1 (48), 158.1 (34), 145.1 (100), 130.0 (17), 121.1 (25), 115.1 (22), 102.0 (23), 91.1 (14).

1-methoxy-4-(phenylethynyl)benzene (**3b**).[22] White solid, 162 mg, 96%; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.54-7.51 (m, 2H), 7.48 (d, *J* = 9.0 Hz, 2H), 7.37-7.30 (m, 3H), 6.89 (d, *J* = 9.0 Hz, 2H), 3.84 (s, 3H); EI-MS: m/z (rel. intensity %) 208.1 (M^+, 100), 193.1 (40), 165.1 (23), 139.1 (8), 115.1 (2), 104.0 (3).

1-(cyclohex-1-en-1-ylethynyl)-4-methoxybenzene (**3c**).[23] Clear oil, 155 mg, 94%; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.36 (d, *J* = 8.8 Hz, 2H), 6.83 (d, *J* = 8.8 Hz, 2H), 6.21-6.18 (m, 1H), 3.81 (m, 3H), 2.26-2.20 (m, 2H), 2.18-2.12 (m, 2H), 1.73-1.56 (m, 4H); EI-MS: m/z (rel. intensity %) 212.2 (M^+, 100), 197.2 (11), 184.2 (23), 169.2 (13), 153.1 (8), 141.1 (12), 132.1 (8), 121.1 (2), 115.1 (10).

1-methyl-4-(oct-1-yn-1-yl)benzene (**3d**).[22] Clear oil, 151 mg, 91%; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.29 (d, *J* = 8.0 Hz, 2H), 7.09 (d, *J* = 8.0 Hz, 2H), 2.41 (t, *J* = 7.0 Hz, 2H), 2.34 (s, 3H), 1.67-1.58 (m, 2H), 1.48-1.44 (m, 2H), 1.36-1.28 (m, 4H), 0.92 (t, *J* = 5.6 Hz, 3H); EI-MS: m/z (rel. intensity %) 200.2 (M^+, 33), 185.2 (3), 171.2 (13), 157.1 (45), 143.1 (33), 129.1 (100), 115.1 (23), 105.1 (21), 91.1 (10).

1-methyl-4-(phenylethynyl)benzene (**3e**).[22] White solid, 149 mg, 96%; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.55-7.52 (m, 2H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.38-7.32 (m, 3H), 7.16 (d, *J* = 8.0 Hz, 2H), 2.38 (s, 3H); EI-MS: m/z (rel. intensity %) 192.2 (M^+, 100), 176.1 (2), 165.1 (10), 152.1 (2), 139.1 (4), 115.1 (2), 96.1 (2).

1-(cyclohex-1-en-1-ylethynyl)-4-methylbenzene (**3f**).[24] Clear oil, 153 mg, 94%; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.32 (d, *J* = 8.0 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 6.23-6.18 (m, 1H), 2.34 (s, 3H), 2.26-

2.20 (m, 2H), 2.18-2.10 (m, 2H), 1.70-1.56 (m, 4H); EI-MS: m/z (rel. intensity %) 196.2 (M^+, 100), 181.1 (52), 165.1 (42), 153.1 (23), 139.1 (13), 128.1 (8), 115.1 (8), 105.1 (7), 89.1 (7).

1-(4-(oct-1-yn-1-yl)phenyl)ethan-1-one (**3g**).[22] Yellow oil, 178 mg, 96%; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.87 (d, *J* = 8.4 Hz, 2H), 7.46 (d, *J* = 8.4 Hz, 2H), 2.60 (s, 3H), 2.44 (t, *J* = 7.2 Hz, 2H), 1.65-1.59 (m, 4H), 1.50-1.44 (m, 2H), 1.38–1.31 (m, 4H), 0.90 (t, *J* = 6.8 Hz, 3H); EI-MS: m/z (rel. intensity %) 228.2 (M^+, 54), 213.1 (100), 199.1 (12), 185.1 (32), 171.1 (12), 157.1 (24), 143.1 (28), 129.1 (60), 114.1 (30).

1-(4-(phenylethynyl)phenyl)ethan-1-one (**3h**).[22] White solid, 174 mg, 97%; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.95 (d, *J* = 8.4 Hz, 2H), 7.62 (d, *J* = 8.4 Hz, 2H), 7.59 – 7.54 (m, 2H), 7.40 – 7.36 (m, 3H), 2.63 (s, 3H); EI-MS: m/z (rel. intensity %) 220.1 (M^+, 65), 205.1 (100), 176.1 (35), 151.1 (15), 126.1 (3), 102.5 (6), 88.0 (8).

methyl 4-(oct-1-yn-1-yl)benzoate (**3i**).[22] White solid, 178 mg, 91%; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.96 (d, *J* = 8.8 Hz, 2H), 7.45 (d, *J* = 8.8 Hz, 2H), 3.92 (s, 3H), 2.43 (t, *J* = 7.0 Hz, 2H), 1.65-1.60 (m, 2H), 1.50 – 1.44 (m, 2H), 1.37 – 1.30 (m, 4H), 0.92 (t, *J* = 6.8 Hz, 3H); EI-MS: m/z (rel. intensity %) 224.2 (M^+, 50), 229.1 (2), 215.1 (43), 201.1 (58), 183.1 (18), 173.1 (35), 149.1 (21), 143.1 (53), 129.1 (100), 115.1 (41), 105.1 (8), 95.1 (12), 91.1 (18).

methyl 4-(phenylethynyl)benzoate (**3j**).[22] White solid, 177 mg, 98%; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.03 (d, *J* = 8.3 Hz, 2H), 7.60 (d, *J* = 8.3 Hz, 2H), 7.57–7.54 (m, 2H), 7.39–7.36 (m 3H), 3.94 (s, 3H); EI-MS: m/z (rel. intensity %) 236.1 (95), 205.1 (100), 191.1 (1), 176.1 (39), 163.1 (1), 151.1 (15), 137.0 (2), 126.1 (3), 111.0 (1), 102.5 (4), 98.0 (2), 88.0 (7).

4-(oct-1-yn-1-yl)benzonitrile (**3k**).[22] Pale yellow oil, 136 mg, 77%; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.57 (d, *J* = 8.0 Hz, 2H), 7.46 (d, *J* = 8.0 Hz, 2H), 2.43 (t, *J* = 7.2 Hz, 2H), 1.66-1.57 (m, 2H), 1.50–1.41 (m, 2H), 1.37–1.29 (m, 4H), 0.91 (t, *J* = 6.6 Hz, 3H); EI-MS: m/z (rel. intensity %) 211.2 (M^+, 28), 196.1 (1), 182.1 (52), 168.1 (100), 154.1 (56), 140.1 (70), 127.1 (28), 116.1 (26), 101.1 (2), 95.1 (11).

4-(phenylethynyl)benzonitrile (**3l**).[22] White solid, 135 mg, 81%; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.70–7.59 (m, 4H), 7.59–7.52 (m, 2H), 7.43–7.36 (m, 3H); EI-MS: m/z (rel. intensity %) 203.1 (M^+, 100), 176.1 (4), 164.1 (1), 151.1 (2), 137.0 (1), 126.0 (1), 111.0 (1), 101.5 (2), 88.0 (2).

1-nitro-4-(oct-1-yn-1-yl)benzene (**3m**).[22] Yellow oil, 143 mg, 79%; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.16 (d, *J* = 8.0 Hz, 2H), 7.52 (d, *J* = 8.0 Hz, 2H), 2.45 (t, *J* = 7.2 Hz, 2H), 1.67–1.58 (m, 2H), 1.51–1.43 (m, 2H), 1.38-1.31 (m, 4H), 0.90 (t, *J* = 6.6 Hz, 3H); EI-MS: m/z (rel. intensity %) 231.1 (M^+, 32), 215.1 (3), 202.1 (78), 188.1 (63), 172.1 (22), 156.1 (53), 142.1 (70), 130.1 (100), 115.1 (63), 102.0 (32), 95.1 (28), 89.0 (18).

1-nitro-4-(phenylethynyl)benzene (**3n**).[22] Yellow solid, 152 mg, 87%; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.30 (d, *J* = 9.2 Hz, 2H), 8.16 (d, *J* = 9.2 Hz, 2H), 7.60–7.55 (m, 2H), 7.47–7.43 (m, 3H); EI-MS: m/z (rel. intensity %) 206.1 (85), 178.1 (100), 152.1 (10), 129.0 (87), 115.0 (2), 101.0 (12), 89.0 (5), 75.0 (15).

1-(cyclohex-1-en-1-ylethynyl)-4-nitrobenzene (**3o**).[25] Yellow Solid, 142 mg, 80%; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.17 (d, *J* = 8.8 Hz, 2H), 7.52 (d, *J* = 8.8 Hz, 2H), 6.32-6.29 (m, 1H), 2.29-2.15 (m, 4H), 1.73-1.61 (m, 4H); EI-MS: m/z (rel. intensity %) 227.1 (M^+, 100), 235.2 (20), 212.1 (11), 199.1 (13), 180.1 (32), 165.1 (60), 152.1 (50), 139.1 (19), 127.1 (9), 115.1 (15), 102.1 (6), 98.0 (2), 89 (8).

1-(oct-1-yn-1-yl)-4-(trifluoromethyl)benzene (**3p**).[26] Pale yellow oil, 146 mg, 74%; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.54 (d, *J* = 8.0 Hz, 2H), 7.48 (d, *J* = 8.0 Hz, 2H), 2.43 (t, *J* = 7.0 Hz, 2H), 1.67–1.58 (m, 2H), 1.45-1.43 (m, 2H), 1.33-1.29 (m, 4H), 0.90 (t, *J* = 6.6 Hz, 3H); EI-MS: m/z (rel. intensity %) 254.3 (M^+, 48), 235.2 (20), 225.2 (78), 211.2 (100), 197.2 (48), 183.1 (84), 170.1 (30), 159.1 (48), 1511 (10), 143.2 (15), 129.1 (52), 115.1 (22), 95.1 (15).

1-(phenylethynyl)-4-(trifluoromethyl)benzene (**3q**).[23] Light yellow solid, 151 mg, 79%; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.67-7.60 (m, 4H), 7.57-7.54 (m, 2H), 7.40-7.36 (m, 3H); EI-MS: m/z (rel. intensity %) 246.0 (M^+, 100), 227.1 (58), 219.1 (3), 207.1 (5), 196.1 (30), 185.0 (1), 176.1 (35), 169.0 (4), 157.1 (1), 151.1 (7), 144.0 (2), 123.0 (12), 113.5 (3), 98.0 (29).

1-(oct-1-yn-1-yl)naphthalene (**3r**).[27] Clear oil, 115 mg, 63%; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.36 (d, *J* = 8.4 Hz, 1H), 7.85 (d, *J* = 8.8 Hz, 2H), 7.79 (d, *J* = 8.4 Hz, 1H), 7.64 (d, *J* = 7.2 Hz, 1H), 7.60-7.48 (m, 2H), 7.45-7.38 (m, 1H), 2.58 (t, *J* = 7.0 Hz, 2H), 1.78-1.67 (m, 2H), 1.61-1.55 (m, 2H), 1.42-1.35 (m, 4H), 0.95 (t, *J* = 7.2 Hz, 3H); EI-MS: m/z (rel. intensity %) 236.2 (M^+, 62), 221.2 (2), 207.1 (23), 193.1 (33), 178.1 (34), 165.1 (100), 152.1 (24), 141.1 (10), 128.1 (3), 115.1 (5).

1-(phenylethynyl)naphthalene (**3s**).[27] White Solid, 133 mg, 76%; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.45 (d, *J* = 8.4 Hz, 1H), 7.88 (t, *J* = 8.4 Hz, 2H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.69-7.36 (m, 8H); EI-MS: m/z (rel. intensity %) 228.1 (M^+, 100), 213.1 (2), 202.1 (32), 187.1 (6), 176.1 (5), 163.1 (3), 150.1 (7), 139.1 (1), 126.0 (3), 113.0 (36), 101.0 (18).

1-(cyclohex-1-en-1-ylethynyl)naphthalene (**3t**).[26] Clear oil, 119 mg, 66%; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.34 (d, *J* = 8.4 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.64 (d, *J* = 7.2 Hz, 1H), 7.58–7.49 (m, 2H), 7.48–7.40 (m, 1H), 6.35 (s, 1H), 2.36 (m, 2H), 2.22 (m, 2H), 1.79–1.64 (m, 4H);

EI-MS: m/z (rel. intensity %) 232.1 (M^+, 100), 217.1 (15), 203.1 (32), 189.1 (12), 176.1 (10), 165.1 (11), 152.1 (15), 141.1 (1), 126.0 (2), 108.0 (3), 101.0 (7), 94.5 (3).

4-(oct-1-yn-1-yl)benzaldehyde (**3u**).[28] Clear oil, 11 mg, 67%; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.99 (s, 1H), 7.80 (d, *J* = 8.3 Hz, 2H), 7.53 (d, *J* = 8.3 Hz, 2H), 2.44 (t, *J* = 6.8 Hz, 2H), 1.68–1.58 (m, 2H), 1.50–1.42 (m, 2H), 1.37–1.30 (m 4H), 0.91 (t, *J* = 7.3 Hz, 3H); EI-MS: m/z (rel. intensity %) 214.2 (M^+, 33), 119.2 (1), 185.1 (23), 171.1 (31), 157.1 (21), 143.1 (63), 129.1 (100), 115.1 (74), 102.1 (5), 95.1 (10), 91.1 (22).

Procedure for Recyclability Study.

A suspension of 47 mg (67 μmol) of $Pd(PPh_3)_2Cl_2$ and 32 mg CuI was made with 1.0 mL of piperidine in a 20-mL glass vial. The suspension was sonicated until the mixture became homogeneous, green, and translucent (30 min). A 1.7-mL microcentrifuge tube was charged with 0.08 mmol 1-iodonapthalene, 0.1 mmol 1-octyne, and 0.8 mL of aqueous surfactant solution (2.0 w/v%). Finally, 24 μL of the sonicated base/catalyst solution was added. This resulted in 0.24 mmol of piperidine, 1.6 μmol (2 mol%) of $Pd(PPh_3)_2Cl_2$ and 4.0 μmol (5 mol%) CuI per reaction. The tube was sealed, thoroughly mixed and shaken at 1100 rpm and 40 ^oC for 4 h. At reaction completion, the mixture was cooled to ambient temperature and extracted with EtOAc (3x200 μL). To assist separation of the organic and water layers, the tubes were centrifuged at 1200 rpm for 2 min after each extraction. The extracts were combined, washed with saturated NaCl (3x0.5 mL), and all volatiles removed under reduced pressure. The crude product was purified via a short column of silica gel using hexanes as the eluent. To the extracted surfactant solution another aliquot of reagents and catalyst/piperidine solution were added. The subsequent solution was treated for the same temperature and time as before. This procedure was repeated 5 times.

Preparative Scale Procedure for the Synthesis of Diyne (**4**).

A suspension of 47 mg (67 μmol) of $Pd(PPh_3)_2Cl_2$ and 32 mg CuI was made with 1.0 mL of piperidine in a 20-mL glass vial. The suspension was sonicated until homogeneous, translucent, and green in color (30 min). A 25-mL round bottom flask was charged with 0.80 mmol of aryl halide, 1.0 mmol of alkyne, and 8.0 mL of aqueous CTAB (2.0 w/v%). Subsequently, 240 μL of the sonicated catalyst solution was added. The reaction was stirred at 40 ^oC for 12 h without exclusion of oxygen. After reaction completion, all volatiles were removed under reduced pressure, and the aqueous solution was extracted with EtOAc (3x5 mL). The combined EtOAc extracts were washed with saturated NaCl (3x5 mL) and all solvent was removed under reduced pressure. The crude product was redissolved in hexane and residual catalyst was removed by passing through a plug of neutral Al_2O_3 and silica gel. Removal of hexane under vacuum afforded pure diyne product, which was confirmed via ^1H NMR and GC-MS analysis. Characterization data for the diyne products matched literature values.

hexadeca-7,9-diyne (**4a**).[29] Clear oil: 77 mg, 69%; 1H NMR (400 MHz, CDCl3): d 2.24 (t, J = 7.0 Hz, 4H), 1.56 - 1.47 (m, 4H), 1.42 - 1.34 (m, 4H), 1.29 (ddd, J = 10.2, 8.7, 2.5 Hz, 8H), 0.89 (t, J = 6.9 Hz, 6H).

1,4-diphenylbuta-1,3-diyne (**4b**).[30] 106 mg, 98%; 1H NMR (400 MHz, CDCl3): 7.56-7.53 (m, 4H), 7.41-7.33 (m, 6H); EI-MS: m/z (rel. intensity %) 202.1 (M^+, 100), 174.0 (4), 163.1 (2), 150.0 (7), 137.0 (1), 126.0 (3), 110.0 (2), 101.0 (8), 88.0 (6).

Preparative Scale Procedure for the Synthesis of Enyne Addition Product. (**5**)

An aqueous CTAB solution (2.0 w/v%) was sparged with Ar for 30 m. While sparging, a suspension of 47 mg $Pd(PPh_3)_2Cl_2$ was made with 1.0 mL of piperidine in a 20-mL glass vial. The suspension was sonicated until homogeneous and clear (30 m), resulting in a bright yellow Pd solution. Under Ar, a 20

mL-glass vial was charged with a stir bar, 195 mg (0.8 mmol) 4-iodoanisole, 0.5 mL (4.5 mmol) phenylacetylene, 8.0 mL of the sparged CTAB solution, and 0.24 mL of the sonicated catalyst solution. The vial was briefly purged with Ar (5 min), sealed with a cap and stirred while heated at 40 ^{o}C for 24 h. At reaction completion, all volatiles were removed under reduced pressure, and the aqueous solution was extracted with EtOAc (3x5 mL). The combined EtOAc extracts were washed with saturated NaCl (3x5 mL) and all solvent was removed under reduced pressure. The crude product was purified via flash column chromatography using hexane. Product purity was determined via NMR and GC-MS analysis.

(*Z*)-(4-(4-methoxyphenyl)but-3-en-1-yne-1,3-diyl)dibenzene (**5**).[16e] Yellow solid, 210 mg, 85%; ^{1}H NMR (400 MHz, $CDCl_3$) NMR (400 MHz, CDCl3): 8.02 (d, *J* = 9.2 Hz, 2H), 7.78 (d, *J* = 8.0 Hz, 2H), 7.59–7.55 (m, 2H), 7.43 – 7.32 (m, 6H), 7.18 (s, 1H), 6.96 (d, *J* = 8.8 Hz, 2H), 3.87 (s, 3H); EI-MS: m/z (rel. intensity %) 310.2 (M^+, 100), 295.2 (31), 279.2 (19), 265.1 (23), 252.1 (18), 239.1 (9), 202.1 (8), 189.1 (14), 165.1 (10).

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Notes and References

† Electronic Supplementary Information (ESI) available: Tables on effects of surfactant concentration and pH on yields; ^{1}H NMR spectra, GC, and MS characterization data for coupling products.

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