# Phase-Vanishing Method with Acetylene Evolution and Its Utilization in Several Organic Syntheses

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Ⓢ *Supporting Information*

ABSTRACT: A novel quadraphasic phase-vanishing system in which acetylene is evolved from calcium carbide and directly applied in situ to the Sonogashira coupling reaction was developed. This method, which provides a safe, convenient, and one-pot means to utilize gaseous reagents without special equipment, was also applied to a Cu-catalyzed azide−alkyne cycloaddition (CuAAC) reaction and a three-component aldehyde−alkyne−amine (A^3) coupling reaction with excellent results.
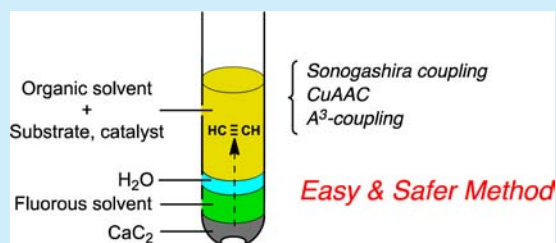
Highly fluorinated compounds are generally immiscible with most organic solvents and water and typically have densities higher than those of organic liquids. Over the past two decades, researchers have utilized these features of fluorous compounds to develop methods for the simplification of postreaction treatments such as quick separation of products and reagents and recovery of reagents and catalysts.[1] Work in our laboratories has been concerned with the design and application of fluorous compounds with the aim of developing novel synthetic methodologies. To this end, we have developed a triphasic phase-vanishing (PV) method, in which the fluorous medium acts as a liquid membrane to steadily transport reagents to a substrate-bearing organic layer.[2]

Since the viability of the PV method was first demonstrated by the bromination of alkenes with molecular bromine,[3] this method has been used to carry out various reactions.[4,5] For example, in a photoirradiative PV method,[4e] hydrogen bromide was efficiently generated in a PV system comprising an alkane, perfluorohexanes, and molecular bromine, and it was subsequently reacted with 1-alkenes to afford terminal bromides in high yields. Recently, we carried out Grignard-type reactions using a quadraphasic PV system comprising a 1:1 mixture of Galden HT135 and HT200 (Figure 1),[6] iodomethane (or
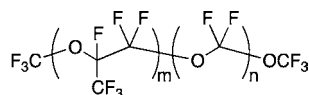

Figure 1. General structure of Galden.

iodoethane), magnesium, ether, and carbonyl compounds. In this method, alkyl magnesium iodide reagents were successfully generated in situ and reacted with carbonyl compounds, affording the desired products in good yields.[7]

In PV methods, the fluorous phase regulates the transport of reagents by passive diffusion. Thus, it is a simple and easy method for controlling heat evolution in exothermic reactions using a common test tube without the need for cooling equipment and dropping funnels. Typical reagents utilized in PV systems are denser than fluorous media ($\rho > 1.7$ g cm^{-3}) and include Br_2, BBr_3, $SnCl_4$, and CH_2I_2. Most of the reagents employed in PV systems are liquids as, with few exceptions,[8] the utilization of gaseous or solid reagents has been unsuccessful. Consequently, we now focus on the study on the use of calcium carbide (CaC_2), which reacts with water to evolve acetylene gas.

Acetylene, the simplest alkyne, is a gaseous reagent and has become widely used as a feedstock in the chemical industry in recent decades. It is known to show versatile reactivity, including dimerization, oligomerization, and polymerization,[9,10] and undergoes not only electrophilic additions to its triple bond with various electrophiles such as molecular bromine or hydrogen bromide but also nucleophilic reactions utilizing the acidic terminal hydrogen.

Acetylene is a dangerous gas. Its ignition point is only 305 °C, and air mixtures containing as little as 2.5 vol % are potentially explosive.[11] Thus, extreme caution is required in its use. Generally speaking, although gaseous reagents are often used in chemical laboratories, handling them is not easy, and much caution is required. Gaseous reagents are usually stored in gas cylinders, and special apparatus such as autoclaves and regulators is usually needed to use them in reactions. In addition, when poisonous gases are employed, extra safety precautions, such as the use of detectors, must be taken.

Herein, we report a novel PV system, where acetylene gas is evolved in situ from CaC_2 and water and reacted with substrates in the organic layer (Scheme 1). Three types of reactions were carried out using this PV method: a Sonogashira coupling, a preparation of a triazole from an azide, and a copper-catalyzed three-component coupling reaction.

We started our investigation of the gas evolution PV method by applying it to the Sonogashira coupling.[12,13] CaC_2 ($\rho = 2.22$ g

Scheme 1. Acetylene Gas Evolution PV System
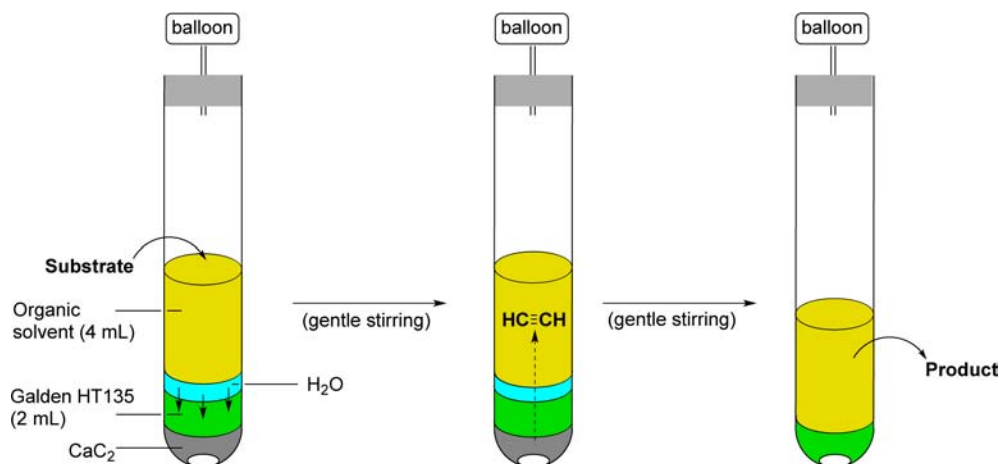
cm^{-3}, 4 equiv) was used as the reagent phase (bottom layer), and THF ($\rho = 0.89$ g cm^{-3}) was employed as the organic phase (top layer). Galden HT135 ($\rho = 1.72$ g cm^{-3}) was used as the fluorous phase, and water (12 equiv) was placed onto it. It should be noted that the order of addition of the components is important in safely carrying out the PV method. Careless addition of water to CaC$_2$ causes intense evolution of acetylene, which is a potentially hazardous situation. The appropriate aryl halide (2 mmol), Pd(PPh$_3$)$_4$ (5 mol %), CuI (5 mol %), and triethylamine (Et$_3$N, 2 equiv) were added to the top layer, and then the air in the test tube was removed by a syringe.[14] The bottom layer was gently stirred at room temperature, taking care not to mix the four layers (Figure 2, left). However, the CaC$_2$ did not react with
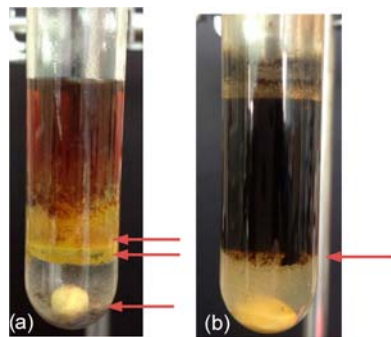

Figure 2. PV Sonogashira coupling of iodobenzene with acetylene. The arrows indicate the interface of the phase. (a) Quadraphasic system: CaC$_2$, Galden HT135, water, THF solution of iodobenzene, Et$_3$N, and catalysts (from the bottom). (b) After completion of the reaction (55 °C, 20 h), the CaC$_2$ layer and aqueous layer disappeared, affording two phases: Galden HT135 and THF phase (from the bottom).

the water, and no acetylene evolution was observed in the test tube, indicating that water does not diffuse into the fluorous phase at room temperature. Consequently, the test tube was heated to 55 °C using an oil bath. Continuous acetylene gas evolution was observed, and after 20 h, the reagent phase (CaC$_2$) and water phase had vanished (Figure 2, right). The organic layer and inorganic salts were then taken, washed with brine, dried over Na$_2$SO$_4$, and concentrated. After column chromatography on silica gel with hexane as an eluent, diphenylacetylene (**2a**) was obtained in 94% yield (Table 1, entry 1).

Using these reaction conditions, we investigated the substrate scope of the PV system with a series of aryl halides (Table 1).

Table 1. Sonogashira Coupling Using the PV Method[a] with Acetylene Evolution

CaC$_2$ (4 equiv)
H$_2$O (12 equiv)
Pd(PPh$_3$)$_4$ (5 mol %)
CuI (5 mol %)
Et$_3$N (2 equiv)
THF (4 mL)
Galden HT135 (2 mL)

entry	1	R	X	2	isolated yield (%)
1	**1a**	H	I	**2a**	94
2	**1b**	OMe	I	**2b**	78
3	**1c**	Me	I	**2c**	95
4	**1c′**	Me	Br	**2c**	<1
5	**1d**	F	I	**2d**	97
6	**1e**	CF$_3$	I	**2e**	96
7	**1e′**	CF$_3$	Br	**2e**	53

[a]Reaction conditions: substrate (2 mmol), Pd(PPh$_3$)$_4$ (5 mol %), CuI (5 mol %), Et$_3$N (4 mmol), CaC$_2$ (8 mmol), THF (4 mL), Galden HT135 (2 mL), H$_2$O (24 mmol), 55 °C, 20 h.

Aryl iodides with electron-donating/withdrawing groups underwent Sonogashira coupling to afford the diphenylacetylene derivatives in good yield (Table 1, entries 3, 5, and 6), while 1-iodo-4-methoxybenzene gave the coupling product in a somewhat lower yield (Table 1, entry 2). However, the yields for aryl bromides were significantly lower than those of aryl iodides (Table 1, entries 4 and 7), and 1-bromo-4-methylbenzene did not undergo the coupling reaction at all (Table 1, entry 4).

We also investigated a copper-catalyzed azide−alkyne cycloaddition (CuAAC)[15,16] using the PV method with acetylene evolution, as shown in Table 2. Employing a similar PV system as that used for the Sonogashira coupling, we replaced the THF in the organic phase with Et$_3$N ($\rho = 0.73$ g cm^{-3}), to which benzyl azide (1 mmol) and CuI (10 mol %) were added. After the air in the test tube was removed, the bottom layer was gently stirred at 55 °C. After 20 h, the reagent phase (CaC$_2$) and water phase disappeared, and following aqueous workup and column chromatography on silica gel with hexane/ethyl acetate (1:1) as an eluent, the desired triazole was obtained from the organic phase in 85% yield (Table 2, entry 1). The yield of the CuAAC reaction using the PV method was almost equal to that of the traditional methodology reported by Liang[16a] and Novák.[16b]

Table 2. CuAAC Using the PV Method[a] with Acetylene Evolution

entry	3	R	4	isolated yield (%)
1	3a	H	4a	85
2	3b	4-Me	4b	58
3	3c	2-Me	4c	57
4	3d	4-Cl	4d	87
5	3e	2-Cl	4e	82
6	3f	4-OMe	4f	82
7	3g	4-CF₃	4g	75
8			4h	83

[a]Reaction conditions: substrate (1 mmol), CuI (10 mol %), CaC$_2$ (4 mmol), H$_2$O (12 mmol), Et$_3$N (4 mL), Galden HT135 (2 mL), 55 °C, 20 h.

Consequently, a scope of substrates was investigated, as summarized in Table 2. Benzyl azides with various substituents on the phenyl ring underwent cyclization with the evolved acetylene to afford the corresponding triazoles in good yields (except xylyl derivatives, entries 2 and 3).

Finally, we performed a three-component aldehyde−alkyne−amine (A^3) coupling reaction using the PV system (Table 3).[17,18]

Table 3. A^3 Coupling Using the PV Method[a] with Acetylene Evolution

entry	5	R	6	isolated yield (%)
1	5a	H	6a	75 (83)[b]
2	5b	4-OMe	6b	42 (72)[b]
3	5c	4-CF₃	6c	< 1
4	5d	4-Me	6d	46 (79)[b]
5	5e	2,5-OMe₂	6e	60 (64)[b]
6	5f		6f	31

[a]Reaction conditions: substrate (1 mmol), pyrrolidine (2 mmol), CuI (20 mol %), CaC$_2$ (4 mmol), H$_2$O (12 mmol), DMF (4 mL), Galden HT135 (2 mL), 55 °C, 20 h. [b]Yields determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as an internal standard are listed in parentheses.[21]

DMF was used as the organic phase, to which benzaldehyde (1 mmol), pyrrolidine (2 equiv), and CuI (20 mol %) were added. After the air in the test tube was removed, the bottom layer was gently stirred at 55 °C, similarly to the previous reactions. After 20 h, the reagent phase (CaC$_2$) and water phase vanished, and the desired product was afforded in an acceptable yield (Table 3, entry 1), indicating that the A^3 coupling in our PV system proceeded with results similar to those seen for the traditional methodology reported by Zhang.[19]

The substrate scope of the PV system was investigated with a series of aryl aldehydes. As shown in Table 3, aryl aldehydes with electron-donating groups afforded the corresponding products in acceptable yields (Table 3, entries 2, 4, and 5), while 4-(trifluoromethyl)benzaldehyde, an aryl aldehyde with an electron-withdrawing group, did not undergo the A^3 reaction at all, resulting in a complex mixture (Table 3, entry 3), and cyclohexanone afforded the coupling product in low yields (Table 3, entry 6). Generally, the yields observed for the A^3 reaction in the PV system were slightly lower[20] than those of Zhang's work. A possible reason for this is that the reaction tube for the PV system is sealed by a rubber septum; therefore, some of the acetylene gas evolved may escape from the test tube before it can be used in the reaction.

In summary, we have presented a new PV method where acetylene gas was generated from CaC$_2$ in a test tube. This method utilized passive diffusion of water into fluorous media as a driving force for the generation of acetylene gas, which was well-controlled, steady, and constant. The evolved acetylene was then successfully applied to the Sonogashira coupling reaction, CuAAC reaction, and A^3 coupling reaction to afford the desired products in yields similar to those obtained by established conditions.[22] Therefore, this method has an advantage for reactions where acetylene gas is required, as it avoids the use of high-pressure apparatus such as regulators and gas cylinders. This method will be of high value not only to synthetic organic chemists but also to other scientists that use acetylene gas. The PV method described here, which employs a simple test tube, may also be expanded to encompass other gaseous reagents. Further applications of this method will be reported in due course.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details and copies of ^{1}H NMR and ^{13}C NMR spectra for all compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b00827.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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(20) No oxidative coupling products of the alkynes were observed.

(21) A significant decrease of isolated yields was caused by the difficulty in the separation of unreacted substrates from the products.

(22) To examine the scalability of the PV system with acetylene gas evolution, Sonogashira coupling with 4.08 g (20 mmol) of iodobenzene was carried out in a larger test tube (30 mm ϕ × 150 mm) to afford diphenylacetylene in 78% yield, indicating that the Sonogashira reaction can be safely performed at the gram scale using the PV method.