Faster and Greener Chemical Reaction Workup Using Silicone Elastomer-Coated Glass Powders

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ABSTRACT: We have developed a substantially faster and greener technique for routine chemical reaction workups. We use silicone elastomer-coated glass powder ("FastWoRX") as an absorbent to extract organic products from a quenched aqueous reaction mixture. After filtration, FastWoRX powder loaded with organic products can serve as a convenient input for flash chromatographic separations. With this technique, tedious and solvent-consuming liquid–liquid extractions are replaced by a simple filtration. Use of FastWoRX reduces solvent use and the E-factor by up to an order of magnitude compared to traditional liquid–liquid extraction-based workup.

INTRODUCTION

Organic synthesis is of fundamental importance in the discovery of new pharmaceuticals, agrochemicals, and advanced materials. For example, during the discovery phase to develop a drug, the synthesis of a large number of compounds is needed for biological evaluation and optimization. However, the labor-intensive nature of organic synthesis and its hazardous conditions have not changed fundamentally despite other significant advances. Typically, after reaction completion, a workup or cleanup procedure is needed to quench the active intermediate (e.g., acid chloride) and catalyst(s) and remove water-soluble inorganic byproducts (e.g., salts) and polar solvents, which can affect chromatographic separation. Reaction workup is a particularly time- and labor-consuming practice.1

The most common reaction workup procedure is liquid–liquid extraction (LLE) using a separatory funnel. A typical LLE-based procedure has the following steps: the crude reaction mixture is quenched with a suitable aqueous solution (e.g., saturated NH₄Cl solution) to stop the reaction and destroy excess reagent(s)/intermediate(s)/catalyst(s) and to dissolve water-soluble byproducts. Then, the mixture is extracted with organic solvents (e.g., diethyl ether or ethyl acetate) in an iterative fashion and the combined organic layers are washed with an aqueous solution to remove inorganic byproducts. Next, the organic phase is dried using a drying agent such as Na₂SO₄. The drying agent is then filtered and the solvents in the filtrate are removed under vacuum. Finally, the organic residue is further purified by flash chromatography. All of these steps are indeed labor- and time-consuming, especially for the workup of a large number of reactions. Additional disadvantages of LLE include the use of relatively large volumes of solvent, possible emulsion formation that blurs the separation between liquid phases, and a relatively high chance of contact with potentially hazardous chemicals and solvents.

To overcome these drawbacks, we originally developed a substantially faster technique for workup that relied on a porous organic polymer ("Porelite")-supported solvent phase (a "rigid solvent") to extract organic products from an aqueous reaction mixture.2 Porelite was based on a then-new type of porous polymer—a high internal phase emulsion polymer ("polyHIPE") containing extremely large and interconnected pores.3–10 However, large-scale preparation of a polyHIPE-type polymer such as Porelite was later found to be difficult. A large amount of a templating surfactant was used in the preparation of Porelite and the complete removal of the surfactant was not easy. Also, the density of polystyrene foam-like Porelite is very low (ca. 0.15 g/mL),2 which was later found to cause handling and weighing problems, particularly in low ambient humidity conditions that promote static electric charge generation.

RESULTS AND DISCUSSION

It is highly desired to develop a fast reaction workup protocol using an easy-to-handle absorbent which can be prepared using a scalable protocol. Instead of using a porous organic polymer, our next-generation extraction absorbent is based on the encapsulation of an inert inorganic support with a permeable organic elastomer (Figure 1a). The support is inert to most organic compounds. It will typically be an inorganic such as glass powder or beads of suitable size but could be organic if suitable for the application. The inorganic support we chose is glass powder, which is generally chemically inert and readily
available at commercial scale. We chose a commercially available and inexpensive silicone elastomer (silicone rubber) precursor 1 for coating the glass powder (Figure 1a). Precursor 1 has the poly(dimethylsiloxane) backbone with reactive acetoxy sites for cross-linking. Precursor 1 reacts with the surface hydroxy groups on the glass powder and cross-links by reacting with the moisture in the air, releasing the byproduct acetic acid. As a result, the glass powder is coated with a thin layer of silicone elastomer. Of course, other siloxane compounds, including fluorinated ones, could also be used depending on the application. Silicone elastomers are generally hydrophobic, inert, and highly permeable and their high permeability has been applied in membranes for blood oxygenation, gas separation, drug delivery, catalyst immobilization, and solid-phase microextraction. The high flexibility of the silicon–oxygen chain in silicone elastomers provides “openings” and “free volume” that permit the incorporation and diffusion of organic products and solvents (Figure 1a). After coating a thin layer of silicone elastomer on glass powder, the sorbent (we named it FastWoRX, now commercially available from Faster Chemistry LLC) can be used for the next-generation reaction workup (Figure 1b). The concept is simple: the organic product/solvent mixture will have an affinity for the organic silicone polymer layer because of the high permeability and high internal “free volume” of silicone.

It should be noted that FastWoRX is different than solid-phase extraction (SPE), widely used in analytical work, although they both utilize a solid to do an extraction. SPE is based on adsorption—the surface of the support is treated with a compound to give the surface an affinity for a certain class of target compounds present in the aqueous phase. However, using only the surface limits the SPE resin’s capacity to hold organics. The SPE resin best suited for a given target compound is found on a case-by-case basis. In contrast, FastWoRX is based on the broad absorption of organics—the powder absorbs most organics into the bulk volume of its relatively thick polymer coating, removing the capacity limit imposed by surface area. The nonspecific affinity of the hydrophobic polymer coating for organic compounds allows compounds to be absorbed into the polymer while excluding water. This forms a “solid solvent” phase in which the absorbed...
organics are immobile compared to the usual liquid solvent.\textsuperscript{12,25} Therefore, our process is similar to traditional LLE but without one of the liquids. SPE is good for analytical work but due to the high price of the resins and their relatively low capacity, it is impractical for preparative applications such as reaction workup. On the other hand, FastWoRX is relatively inexpensive, organic nonspecific, and has high organic-holding capacity, making it very suitable for preparative applications. Therefore, FastWoRX can practically separate mixtures at a scale ranging from milligrams to kilograms.

The typical workflow of a FastWoRX-based reaction workup is straightforward (Figure 1c). The reaction is conducted in the usual way and quenched with a suitable aqueous solution. Instead of using a relatively large amount of a conventional organic solvent such as ethyl acetate to extract the aqueous reaction mixture, we added FastWoRX powder to the mixture. Then, after evaporating most of the solvent and a simple filtration of the FastWoRX powder from the aqueous mixture, the desired organic products are incorporated in the FastWoRX powder. The desired products can be eluted from the FastWoRX powder by a suitable organic solvent during chromatography. By doing this, tedious and solvent-consuming LLE(s) is avoided. In addition, a common problem with LLE—emulsion formation—is eliminated because there is no need for the separation of two liquid phases. Also, automation and parallelization of FastWoRX-based workups is much easier than automating traditional LLE. Compared to traditional LLE-based workup, our FastWoRX-based workup saves a lot of time and solvent and greatly reduces the chance of contact with potentially hazardous chemicals.

The ideal reaction workup protocol should have a high recovery rate (recovery of organic products from a quenched aqueous mixture). The recovery rate for FastWoRX-based workup will depend on two factors: (1) the complete transfer of the sorbent from the reaction flask to the filtration device and (2) the water solubility of the target products. In our model system (Table 1), a test compound (p-toluenesulfonamide) was dissolved in an organic solvent (ethyl acetate) and pure water or a saturated solution of NaCl was added under stirring to simulate the quenching of a chemical reaction. We investigated the effect of the particle size of the glass powder and the amount of silicone coating on the recovery rate. We found that noncoated glass powder is not effective (Table 1, entry 1), the optimum particle size is about 180 mesh, and the optimum amount of coating is about 5 wt/wt % of the support weight (Table 1, entry 8). When the particles are too small (e.g., 400 mesh), the particles tend to stick to the glass wall of the reaction flask, making complete transfer to a filtration device more difficult (Table 1, entry 9). Because p-toluenesulfonamide has moderate water solubility (0.32 g/100 mL water), the recovery rate from pure water is only 88%. The recovery can be greatly improved (to 97%) by using brine instead of water (Table 1, entry 8).

With our optimized parameters, the FastWoRX particles loaded with organic products are relatively nonsticky toward the glass walls of the reaction vessel and the transfer of the sorbent from the reaction flask to the filtration device is relatively complete by rinsing with a small amount of water or brine. Therefore, the recovery rate is mostly determined by the water solubility of the target products. We studied the recovery rate of diverse organic products with various water solubilities (Table 2). Our protocol is widely applicable and gave excellent recoveries for most test compounds investigated (including hydrocarbon, alcohol, heterocycle, acid, and ester functionalities) (Table 2). The only exception was the extraction of glucose and an amino acid, but this result was not surprising as these compounds are only soluble in water and are not soluble in most organic solvents.

After filtration, FastWoRX powder loaded with organic products can serve as a convenient input for flash chromatographic separations. The quality of the separation achieved with our new workup method (e.g., peak width) is similar to the conventional method of dry loading on silica gel (Figure 2) with a test mixture of 1:1:1 of ferrocene, p-Cl-benzaldehyde, and p-NO\(_2\)-benzaldehyde.

Our new workup also worked very well in diverse synthetic reactions (Figure 3). Compared to the traditional LLE-based reaction workup, our procedure gave comparable or slightly better isolated yields (after chromatographic purifications) with an order of magnitude less solvent use. All reactions in

### Table 1. Study of Sorbent Parameters on Recovery Rate\textsuperscript{a}

| no. | powder size (mesh) | silicone coating (wt/wt %) | difficulty of transfer | recovery from water (%) | recovery from brine (%) |
|-----|-------------------|---------------------------|------------------------|-------------------------|-------------------------|
| 1   | 100               | 0                         | easy                   | <50                     | <50                     |
| 2   | 100               | 1                         | moderate               | <50                     | <50                     |
| 3   | 100               | 3                         | easy                   | 75                      | 91                      |
| 4   | 100               | 4                         | easy                   | 74                      | 92                      |
| 5   | 100               | 5                         | easy                   | 78                      | 91                      |
| 6   | 180               | 1                         | moderate               | 83                      | 92                      |
| 7   | 180               | 3                         | easy                   | 87                      | 95                      |
| 8   | 180               | 5                         | easy                   | 88                      | 97                      |
| 9   | 400               | 5                         | high                   |                         |                         |

\textsuperscript{a}Procedure: the test compound, p-toluenesulfonamide (100 mg), was dissolved in 5 mL of ethyl acetate, then 5 mL of water or 5 mL of saturated NaCl solution was added with stirring (this is a simulation of a reaction mixture after quenching), and then 1.0 g of the sorbent was added. After stirring for 2 min, most of the ethyl acetate was removed with vacuum and the mixture was filtered and washed with water or brine (ca. 5 mL) and finally washed with ethyl acetate to recover the product.

### Table 2. Recovery Rates of Test Compounds\textsuperscript{a}

| compounds       | recovery from water (%) | recovery from brine (%) |
|-----------------|-------------------------|-------------------------|
| p-toluenesulfonamide | 88                      | 96                      |
| ferrocene       | 95                      | 97                      |
| p-toluene sulfonyl hydrazide | 63                      | 92                      |
| indole          | 98                      | 97                      |
| 2-methyl indole | >99                     | >99                     |
| 2-hydroxynaphthalene | >99                    | >99                     |
| 1-naphthylboronic acid | 95                    | >98                     |
| benzyl phenylacetate | >99                    | >99                     |
| glucose         | 0                       | 0                       |
| l-phenylalanine | 0                       | 0                       |

\textsuperscript{a}Procedure: the test compound (100 mg) was dissolved in 5 mL of ethyl acetate, then 5 mL of water or 5 mL of saturated NaCl solution was added with stirring (this is a simulation of a reaction mixture after quenching), and then 1.0 g of the sorbent was added. After stirring for 2 min, most of the ethyl acetate was removed with vacuum and the mixture was filtered and washed with water or brine (ca. 5 mL) and finally washed with ethyl acetate (ca. 20 mL) to recover the product.
benzaldehyde, and wavelengths of 254, 220, and 280 nm, respectively.

In general, the FastWoRX-based reaction workup has many benefits over LLE-based workup including:

(1) Solvent savings—For a typical reaction conducted at 100 mg scale and depending on the chemist’s preferences, 20 to 50 mL of more of solvent is typically needed for traditional LLE-based work-up. FastWoRX-based reaction work-up can be done with only 0–5 mL of solvent (depending on the reaction solvent—if the reaction solvent is not water-miscible, no extra solvent need be added)—a significant reduction (see E-Factors in Figure 3).

(2) Time savings—traditional LLE-based reaction workup requires many steps such as LLE (10+ min per extraction, longer if there is emulsion formation), drying of the organic layers with Na₂SO₄ and filtration of Na₂SO₄ (20+ min), removing excess solvents with a rotavap (10 min), and loading the residue to a loading cartridge (10 min). Therefore, typically, the total time will be more than 50 min (Figure 3). Our FastWoRX-based method only requires the solvent removal and filtration steps so the total time will typically be 15 min or less. Also, our filtration-based method can be set up in parallel using a commercially available filtration station. Therefore, much greater time savings can be realized if doing multiple reactions in parallel. It should be noted that for the LLE-based workups, the time required for drying of the reaction mixture after LLE using a drying agent such as Na₂SO₄ is not included. This normally requires from 0.5 h to a few hours so the actual LLE-based workup times will be much longer. Also, the time for washing glassware (e.g., separatory funnels) and other ancillary tasks is not included in our estimates.

(3) Reduction in potential human contact with hazardous reagents and solvents.

**CONCLUSIONS**

In summary, we have developed a substantially faster, more efficient, and greener technique for workup after chemical reactions. FastWoRX is commercially available now (fasterchemistry.com). Other applications of this new technique are currently being pursued in our laboratory.

**EXPERIMENTAL SECTION**

General. ¹H NMR (400 MHz) and ¹³C NMR (101 MHz) spectra were recorded on a Bruker NMR apparatus. The chemical shifts are reported in δ (ppm) values (¹H and ¹³C NMR relative to CHCl₃, δ 7.26 ppm for ¹H NMR, and δ 77.0 ppm for ¹³C NMR) or alternatively, ¹H NMR chemical shifts were referenced to tetramethylsilane signal (0 ppm). Multiplicities are recorded by s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), h (hexet), m (multiplet), and br (broad). Coupling constants (J) are reported in hertz (Hz). Gas chromatography (GC) analyses were performed using a Shimadzu GC-2010 GC—mass spectrometry instrument equipped with a Shimadzu AOC-20s autosampler. Combiflash RF 200 (Teledyne ISCO) was used for chromatographic separation. Silicone elastomer precursor 1 (structure shown in Figure 1) was purchased from Dow Corning. Glass powder (180 mesh) was purchased from Hangzhou High-Tech Composite Material Company. Other chemicals were purchased from Aldrich, Strem, Acros, and Adamas.

**Preparation of the Silicone-Coated Absorbent (FastWoRX).** Ten grams of silicone rubber precursor 1 was dissolved in 150 mL of ethyl acetate in a 500 mL round-bottom flask under stirring; then, 190 g of glass powder (180 mesh) was added. The mixture was stirred for 10 min and then excess ethyl acetate was removed using a rotavap under vacuum. The obtained powder was placed on a tray and kept in open air for 48 h to cure (caution—the curing process generates acetic acid). The obtained powder (ca. 200 g) was washed with ethyl acetate (ca. 250 mL) and dried in vacuum.

**General Procedure for LLE-Based Reaction Workup.** After the reaction was quenched with a suitable aqueous solution, such as saturated ammonium chloride solution (5 mL), the reaction mixture was extracted with EtOAc (10 mL × 2); the combined organic phases were dried with Na₂SO₄, filtered, and Na₂SO₄ cake was washed with EtOAc (30 mL); the solvent was evaporated under reduced pressure. The residue was purified by an automatic flash chromatography system.

**General Procedure for FastWoRX-Based Reaction Workup.** After the reaction was quenched with a suitable aqueous solution, such as saturated ammonium chloride solution (1 mL), EtOAc (5 mL) and FastWoRX powder...
(1.0 g) were added to the reaction mixture. Then, most of the solvents were evaporated under reduced pressure. Then, the reaction mixture was filtered through a CombiFlash loading cartridge and the reactor was rinsed with 5 mL of brine. The loading cartridge was flushed with vacuum for 5 min and then was connected to an automatic flash chromatography system for purification.

4-Methoxy-1,1′-biphenyl (3). Under argon protection, two parallel dry Schlenk tubes were each charged with phenylboronic acid 2 (122 mg, 1 mmol), Pd(OAc)2 (1.2 mg, 0.01 mmol, 1%), XPhos (4.8 mg, 0.02 mmol, 2%), and K3PO4 (212 mg, 1 mmol). Then, toluene (2 mL) and 4-bromoanisole 1 (93.5 mg, 0.5 mmol) were introduced. The resulting mixture was stirred at 80 °C for 12 h. Both reactions were quenched with saturated ammonium chloride solution. The reaction
mixtures were worked-up and purified according to the general methods. Eluent: (EtOAc/hexanes = 1:50). LLE method (90.0 mg, 98%) and FastWoRX method (91.3 mg, 99%). White solid. 1H NMR (400 MHz, CDCl3): δ 7.46 (t, J = 8.4 Hz, 4H), 7.33 (t, J = 7.6 Hz, 2H), 7.22 (t, J = 7.3 Hz, 1H), 6.90 (d, J = 8.7 Hz, 2H), 3.76 (s, 3H). Its spectroscopic data is consistent with the literature report.29

1-(4-Methoxyphenyl)naphthalene (5). Under argon protection, two parallel dry Schlenk tubes were each charged with 1-naphthylboronic acid (138 mg, 0.54 mmol), Pd(OAc)2 (2 mg, 0.025 mol %), and K2PO4 (170 mg, 0.8 mmol). Then, 1-bromoanisole (100 mg, 0.5 mmol) were introduced. The resulting mixture was stirred at 80 °C for 24 h. Both reactions were quenched with a saturated ammonium chloride solution. The reaction mixtures were worked-up and purified according to the general methods. Eluent: (EtOAc/hexanes = 1:50). LLE method (90.0 mg, 98%) and FastWoRX method (91.3 mg, 99%). White solid. 1H NMR (400 MHz, CDCl3): δ 7.84 (d, J = 8.4 Hz, 2H), 7.47 (d, J = 8.3 Hz, 2H), 7.35 (m, 2H), 4.06 (s, 3H). Its spectroscopic data is consistent with the literature report.30

1-(4-methylphenyl)naphthalene (6). Under argon protection, two parallel dry Schlenk tubes were each charged with 1-naphthylboronic acid (138 mg, 0.54 mmol), Pd(OAc)2 (2 mg, 0.025 mol %), and K2PO4 (170 mg, 0.8 mmol). Then, 4-bromoanisole (100 mg, 0.5 mmol) were introduced. The resulting mixture was stirred at 80 °C for 24 h. Both reactions were quenched with a saturated ammonium chloride solution. The reaction mixtures were worked-up and purified according to the general methods. Eluent: (EtOAc/hexanes = 1:50). LLE method (90.0 mg, 98%) and FastWoRX method (91.3 mg, 99%). White solid. 1H NMR (400 MHz, CDCl3): δ 7.68 (d, J = 7.7 Hz, 1H), 7.52 (d, J = 8.1 Hz, 1H), 7.37 (d, J = 8.3 Hz, 2H), 7.33−7.24 (m, 3H), 7.23−7.11 (m, 2H), 6.66 (d, J = 3.1 Hz, 1H), 2.40 (d, J = 14.0 Hz, 3H). Its spectroscopic data is consistent with the literature report.33

(E)-4,4,5,5-Tetramethyl-2-styryl-1,3,2-dioxaborolane (17). Under argon protection, two parallel dry Schlenk tubes were each charged with bis(pinacolato)diboron (190 mg, 0.75 mmol), nanocopper powder (6.4 mg, 0.1 mmol), and MeONa (5.4 mg, 0.1 mmol). Then, EtOH (2 mL) and phenylacetylene (51 mg, 0.5 mmol) were introduced. The resulting mixture was stirred at room temperature for 12 h. Both reactions were quenched with a saturated ammonium chloride solution. The reaction mixtures were worked-up and purified according to the general methods. Eluent: (EtOAc/hexanes = 1:50). LLE method (63.4 mg, 55%) and FastWoRX method (65.7 mg, 57%). Colorless oil. 1H NMR (400 MHz, CDCl3): δ 7.53 (d, J = 7.1 Hz, 2H), 7.45 (d, J = 18.4 Hz, 1H), 7.34 (dd, J = 13.8, 7.3 Hz, 3H), 6.22 (d, J = 18.4 Hz, 1H), 1.34 (s, 12H). Its spectroscopic data is consistent with the literature report.34

Methyl 4-(Phenylethynyl)benzoate (20). Under argon protection, two parallel dry Schlenk tubes were each charged with methyl 4-iodobenzoate (131 mg, 0.5 mmol), PdCl2(PPh3)2 (7 mg, 2 mol %), and CuI (3.8 mg, 4 mol %). Then, tetrahydrofuran (THF) (2 mL), triethylamine (75.9 mg, 0.75 mmol), and phenylacetylene (56.2 mg, 0.55 mmol) were introduced. The resulting mixture was stirred at 45 °C overnight. Both reactions were quenched with a saturated ammonium chloride solution. The reaction mixtures were worked-up and purified according to the general methods. Eluent: EtOAc/hexanes = 1:20. LLE method (110.8 mg, 94%) and FastWoRX method (114.6 mg, 97%). Yellow solid. 1H NMR (400 MHz, CDCl3): δ 8.02 (d, J = 8.3 Hz, 2H), 7.59 (d, J = 8.3 Hz, 2H), 7.57−7.52 (m, 2H), 7.41−7.33 (m, 3H), 3.92 (s, 3H). Its spectroscopic data is consistent with the literature report.35

4-Phenylbut-3-yn-1-ol (22). Under argon protection, two parallel dry Schlenk tubes were each charged with CuI (2 mg, 2 mol %) and PdCl2(PPh3)2 (7 mg, 2 mol %). Then, triethylamine (2 mL), iodobenzene (102 mg, 0.5 mmol), and but-3-yn-1-ol (42 mg, 0.6 mmol) were introduced. The resulting mixture was stirred at 60 °C for 3 h. Both reactions were quenched with a saturated ammonium chloride solution. The reaction mixtures were worked-up and purified according to the general methods. Eluent: EtOAc/hexanes = 1:20. LLE method (65.4 mg, 90%) and FastWoRX method (67.1 mg, 92%). Yellow oil. 1H NMR (400 MHz, CDCl3): δ 7.48−7.40 (m, 2H), 7.31 (dd, J = 8.7, 5.5 Hz, 3H), 3.84 (t, J = 6.3 Hz, 2H), 2.71 (t, J = 6.3 Hz, 2H), 2.14 (s, 1H). Its spectroscopic data is consistent with the literature report.36

2-(Phenylethynyl)aniline (24). Under argon protection, two parallel dry Schlenk tubes were each charged with CuI (2.4 mg, 2.5 mol %) and PdCl2(PPh3)2 (17.5 mg, 0.5 mol %). Then, triethylamine (2 mL), 2-iodoaniline (125 mg, 0.5 mmol), and phenylacetylene (42 mg, 0.6 mmol) were introduced. The resulting mixture was stirred at 60 °C for 3 h. Both reactions were quenched with a saturated ammonium chloride solution. The reaction mixtures were worked-up and purified according to the general methods. Eluent: EtOAc/hexanes = 1:20. LLE method (93.3 mg, 97%) and FastWoRX method (93.8 mg, 97%). Yellow solid. 1H NMR (400 MHz, CDCl3): δ 7.59−7.47 (m, 2H), 7.42−7.28 (m, 4H), 7.17−7.09 (m, 1H), 6.79−6.67 (m, 2H), 4.27 (s, 2H). Its spectroscopic data is consistent with the literature report.37
2-((Trimethylsilyl)ethynyl)benzaldehyde (27). Under argon protection, two parallel dry Schlenk tubes were each charged with CuI (2.0 mg, 2 mol %) and PdCl2(PPh3)2 (3.5 mg, 1 mol %). Then, triethylamine (2 mL), 2-bromobenzaldehyde (92 mg, 0.5 mmol), and trimethylsilylacetylene (58.8 mg, 0.6 mmol) were introduced. The resulting mixture was stirred at 60 °C for 3 h. Both reactions were quenched with a saturated ammonium chloride solution. The reaction mixtures were worked-up and purified according to the general methods. Eluent: EtOAc/hexanes = 1:10. LLE method (156.7 mg, 90%). Colorless solid. 1H NMR (400 MHz, CDCl3): δ 10.36 (fl, J = 4.6 Hz, 1H), 7.86–7.62 (m, 1H), 7.36 (dd, J = 9.0, 7.7, 1.3 Hz, 2H), 7.24 (dd, J = 7.4, 0.6 Hz, 1H), 0.15–0.04 (m, 9H). Its spectroscopic data is consistent with the literature report.40

1-Benzyl-1H-indole (29). Under argon protection, two parallel dry Schlenk tubes were each charged with indole (58.6 mg, 0.5 mmol) and NaH (22 mg, 0.55 mmol, 60% in mineral oil) in an ice bath. Then, dimethylformamide (DMF) (1 mL) was introduced, the ice bath was removed, and the resulting mixture was stirred at room temperature for 30 min. Then, under an ice bath again, benzyl bromide (94 mg, 0.55 mmol) was slowly introduced. The resulting mixture was stirred overnight at room temperature. Both reactions were quenched with a saturated ammonium chloride solution. The reaction mixtures were worked-up and purified according to the general methods. Eluent: EtOAc/hexanes = 1:10. LLE method (154.2 mg, 89%) and FastWoRX method (87.4 mg, 90%). Brown solid. 1H NMR (400 MHz, CDCl3): δ 7.4, 0.6 Hz, 1H), 0.15 7.27–6.99 (m, 9H), 6.52 (d, J = 3.1 Hz, 1H), 5.19 (s, 2H). Its spectroscopic data is consistent with the literature report.38

2,2-Diphenylethanol-1-ol (36). Under argon protection, two parallel dry Schlenk tubes were each charged with LiAlH4 (33.5 mg, 0.88 mmol) in an ice bath. After addition of THF (2 mL), methyl diphenylacetate (93.5 mg, 0.44 mmol) was introduced dropwise. The resulting mixture was stirred at room temperature overnight. Both reactions were quenched with a saturated ammonium chloride solution. The reaction mixtures were worked-up and purified according to the general methods. Eluent: EtOAc/hexanes = 1:20. LLE method (77.3 mg, 89%) and FastWoRX method (78.4 mg, 90%). White solid. 1H NMR (400 MHz, CDCl3): δ 3.73–7.13 (m, 10H), 4.17–4.10 (m, 1H), 4.06 (d, J = 7.0 Hz, 2H). Its spectroscopic data is consistent with the literature report.42

(3-((3-Methylbut-2-en-1-yl)oxy)prop-1-yn-1-yl)benzene (39). Under argon protection, two parallel dry Schlenk tubes were each charged with NaH (20 mg, 0.5 mmol, 60% in mineral oil) in an ice bath. Then, DMF (1 mL) was added as the solvent and 3-phenyl-2-propyn-1-ol (66.1 mg, 0.5 mmol) was introduced slowly. The resulting mixture was stirred for 30 min and 3,3-dimethylallyl bromide (68.6 mg, 0.46 mmol) was introduced slowly at room temperature. After the addition, the reaction mixture was stirred for 2 h. Both reactions were quenched with a saturated ammonium chloride solution. The reaction mixtures were worked-up and purified according to the general methods. Eluent: EtOAc/hexanes = 1:50. LLE method (58.2 mg, 63%) and FastWoRX method (61.3 mg, 67%). Yellow oil. 1H NMR (400 MHz, CDCl3): δ 7.36 (dd, J = 6.5, 2.9 Hz, 2H), 7.25–7.16 (m, 3H), 5.30 (t, J = 7.0 Hz, 1H), 4.26 (s, 2H), 4.04 (d, J = 7.1 Hz, 2H), 1.66 (d, J = 17.1 Hz, 6H). Its spectroscopic data is consistent with the literature report.43

Diethyl 2-(p-Tolyl)malonate (41). Under argon protection, two parallel dry Schlenk tubes were each charged with Pd(OAc)2 (3.2 mg, 2 mol %), SPhos (9.5 mg, 4 mol %), and K2PO4 (212 mg, 1 mmol). Then, toluene (2 mL), 4-bromotoluene (85.7 mg, 0.5 mmol), and diethyl malonate (96.1 mg, 0.6 mmol) were introduced. The resulting mixture was stirred at 100 °C for 40 h. Both reactions were quenched with a saturated ammonium chloride solution. The reaction mixtures were worked-up and purified according to the general methods. Eluent: EtOAc/hexanes = 1:10. LLE method (60.4 mg, 48%) and FastWoRX method (67.4 mg, 54%). Colorless oil. 1H NMR (400 MHz, CDCl3): δ 7.29 (d, J = 8.1 Hz, 2H), 7.17 (d, J = 8.0 Hz, 2H), 4.57 (s, 1H), 4.32–4.08 (m, 4H), 2.34 (s, 3H), 1.26 (t, J = 7.1 Hz, 6H). Its spectroscopic data is consistent with the literature report.45

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.8b00966.

Detailed experimental procedure and copies of spectra (PDF)

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REFERENCES

(1) Cork, D.; Hird, N. Work-up strategies for high-throughput solution synthesis. Drug Discovery Today 2002, 7, 56–63.
(2) Xu, R.; Hammond, G. B. Rapid Chemical Reaction Workup Based on a Rigid Solvent Extraction. Org. Lett. 2014, 16, 5233–5241.
(3) Desorges, A.; Arpontet, M.; Deleuze, H.; Mondain-Monval, O. Synthesis and functionalisation of polyHIPE beads. React. Funct. Polym. 2002, 53, 183–192.
(4) Moine, L.; Deleuze, H.; Maillard, B. Preparation of high loading PolyHIPE monoliths as scavengers for organic chemistry. Tetrahedron 2003, 44, 7813–7816.
(5) Brown, J. F.; Krajnc, P.; Cameron, N. R. PolyHIPE Supports in Batch and Flow-Through Suzuki Cross-Coupling Reactions. Ind. Eng. Chem. Res. 2005, 44, 8565–8572.
(6) Barbetta, A.; Cameron, N. R. Morphology and Surface Area of Emulsion-Derived (PolyHIPE) Solid Foams Prepared with Oil-Phase Soluble Porogenic Solvents: Three-Component Surfacant System. Macromolecules 2004, 37, 3202–3213.
(7) Barbetta, A.; Cameron, N. R. Morphology and Surface Area of Emulsion-Derived (PolyHIPE) Solid Foams Prepared with Oil-Phase Soluble Porogenic Solvents: Span 80 as Surfactant. Macromolecules 2004, 37, 3188–3201.
(8) Krajnc, P.; Brown, J. F.; Cameron, N. R. Monolithic Scavenger Resins by Amine Functionalizations of Poly(4-vinylbenzyl chloride-co-divinylbenzene) PolyHIPE Materials. Org. Lett. 2002, 4, 2497–2500.
(9) Féraud-Martin, C.; Briot, M.; Deleuze, H.; Desorges, A.; Backov, R. Integrative chemistry toward the first spontaneous generation of gold nanoparticles within macrocellular polyHIPE supports (Au@polyHIPE) and their application to eosiin reduction. React. Funct. Polym. 2007, 67, 1072–1082.
(10) Cameron, N. R.; Barbetta, A. The influence of porogen type on the porosity, surface area and morphology of poly(divinylbenzene) PolyHIPE Foams. J. Mater. Chem. 2000, 10, 2466–2471.
(11) Grassard, D. M. The Silicone Elastomer Handbook: A Guide to Applications Guide and Bibliography: A Resource for Sample Preparation Methods Development, 6th ed.; Waters: Milford, MA, 1995; p 464.
(12) Warrick, E. L.; Pierce, O. R.; Polmanteer, K. E.; Saam, J. C. Silicon Elastomer Developments 1967-1977. Rubber Chem. Technol. 1979, 52, 437–525.
(13) Bonnette, F.; Kato, T.; Destarac, M.; Mignani, G.; Cossio, F. P.; Baceiredo, A. Encapsulated N-heterocyclic carbines in silicones without reactivity modification. Angew. Chem., Int. Ed. 2007, 46, 8632–8635.
(14) Motoyama, Y.; Abe, M.; Kamo, K.; Kosako, Y.; Nagashima, H. Encapsulated molecular catalysts in polysiloxane gels: ruthenium cluster-catalyzed isomerization of alkenes. Chem. Commun. 2008, 5321–5323.
(15) Motoyama, Y.; Kamo, K.; Nagashima, H. Catalysis in Polysiloxane Gels: Platinum-Catalyzed Hydrosilylation of Polymethylhydrosiloxane Leading to Reusable Catalysts for Reduction of Nitroarenes. Org. Lett. 2009, 11, 1345–1348.
(16) Mwangi, M. T.; Schulz, M. D.; Bowden, N. B. Sequential Reactions with Grubbs’ Catalyst and AD-mix-α/β Using PDMS Thimbles. Org. Lett. 2009, 11, 33–36.
(17) Motoyama, Y.; Kamo, K.; Yusa, A.; Nagashima, H. Catalytic atom-transfer radical cyclization by copper/bipyridine species encapsulated in polysiloxane gel. Chem. Commun. 2010, 46, 2256–2258.
(18) Yang, H.; Xu, M.; Guo, L.-X.; Ji, H.-F.; Wang, J.-Y.; Lin, B.-P.; Zhang, X.-Q.; Sun, Y. Organocatalysis in polysiloxane gels: a magnetic-stir-bar encapsulated catalyst system prepared by thiol-ene photo-click immobilization. RSC Adv. 2015, 5, 7304–7310.
(19) Zhang, W.; Hu, Y.; Ge, J.; Jiang, H.-L.; Yu, S.-H. A Facile and General Coating Approach to Moisture/Water-Resistant Metal-Organic Frameworks with Intact Porosity. J. Am. Chem. Soc. 2014, 136, 16978–16981.
(20) Vankelecom, I. F. J.; Tas, D.; Parton, R. F.; Van de Vyver, V.; Jacobs, P. A. Chiral Catalytic Membranes. Angew. Chem., Int. Ed. 1996, 35, 1346–1348.
(21) Mwangi, M. T.; Runge, M. B.; Bowden, N. B. Occlusion of Grubbs’ Catalysts in Active Membranes of Polymethylsiloxane: Catalysis in Water and New Functional Group Selectivities. J. Am. Chem. Soc. 2006, 128, 14434–14435.
(22) Xu, L.; Xu, B. Encapsulation of nano-catalysts in permeable silicone elastomers. Tetrahedron Lett. 2017, 58, 2542–2546.
(23) Balussen, E.; Sandra, P.; David, F.; Janssen, H.-G.; Cramers, C. Study into the Equilibrium Mechanism between Water and Poly(dimethylsiloxane) for Very Apolar Solutes: Adsorption or Sorption? Anal. Chem. 1999, 71, 5213–5216.
(24) Lee, J.; Park, C.; Whitesides, G. M. Solvent Compatibility of Poly(dimethylsiloxane)-Based Microfluidic Devices. Anal. Chem. 2003, 75, 6544–6554.
(25) Watson, J. M.; Payne, P. A. A study of organic compound pervaporation through silicone rubber. J. Membr. Sci. 1990, 49, 171–205.
(26) Wang, P. G. High-Throughput Analysis in the Pharmaceutical Industry; CRC Press: Boca Raton, FL, 2009; p 413.
(27) Simpson, N. J. K. Solid-Phase Extraction: Principles, Techniques, and Applications; Marcel Dekker: New York, 2000; p xi, 514 p.
(28) McDonald, P. D.; Bouvier, E. S. P. Millipore Corporation. Waters Chromatography Division. In Solid Phase Extraction: Applications Guide and Bibliography: A Resource for Sample Preparation Methods Development, 6th ed.; Waters: Milford, MA, 1995; p 646.
(29) Alacid, E.; Nájera, C. First Cross-Coupling Reaction of Potassium Aryltrifluoroborates with Organic Chlorides in Aqueous Media Catalyzed by an Oxime-Derived Palladacycle+; Org. Lett. 2008, 10, 5011–5014.
(30) Chtrchigrovsky, M.; Lin, Y.; Ouchao, K.; Chaumontet, M.; Robitzer, M.; Quignard, F.; Taran, F. Dramatic Effect of the Gelling Catalyst Activation Pathway. J. Org. Chem. 2012, 78, 7536–7541.
(31) Maligres, P. E.; Krska, S. W.; Dormer, P. G. A Soluble and Stable Pd(II), Pd(I), and Pd(0) Complexes of Di(tert-butyl)neopentylphosphine (DTBNpP) in the Arylation of Amines Catalyzed by Chiral Palladium Catalysts. J. Org. Chem. 2012, 77, 5011–5014.
(32) Johansson Seechurn, C. C. C.; Parisel, S. L.; Colacot, T. J. Air-Stable Pd(R-alkyl)Cl(LCl) (L= Q-Phos, P(t-Bu)₃, etc.) Systems for C-C/ C-N Couplings: Insight into the Structure-Activity Relationship and Catalyst Activation Pathway. J. Org. Chem. 2011, 76, 7918–7932.
(33) Maligres, P. E.; Kraska, S. W.; Dormer, P. G. A Soluble Copper(II) Source and Stable Salts of Volatile Ligands for Copper-Catalyzed C-X Couplings. J. Org. Chem. 2012, 77, 7646–7651.
(34) Jang, H.; Zhu, K.; Hoveyda, A. H. Highly Selective Methods for Synthesis of Internal (α-) Vinylboronates through Efficient NHC-Cu-Catalyzed Hydroboration of Terminal Alkynes. Utility in Chemical Synthesis and Mechanistic Basis for Selectivity. J. Am. Chem. Soc. 2011, 133, 7589–7591.
(35) Sletten, E. M.; Bertozzi, C. R. A Bioorthogonal Quadricyclane Ligation. J. Am. Chem. Soc. 2011, 133, 17570–17573.
(36) Pantelev, J.; Huang, R. Y.; Liu, E. K. J.; Lautens, M. Addition of Arylboronic Acids to Arylpropargyl Alcohols en Route to Indenes and Quinolines. Org. Lett. 2011, 13, 5314–5317.
(37) Ding, Q.; Wu, J. A Facile Route to 2,4-Dihydro-1H-benzo[d][1,3]thiazines via Silver-Catalyzed Tandem Addition-Cyclization Reactions. J. Comb. Chem. 2008, 10, 541–545.

(38) Park, J. H.; Bhilare, S. V.; Youn, S. W. NH-Catalyzed Oxidative Cyclization Reactions of 2-Alkynylbenzaldehydes under Aerobic Conditions: Synthesis of O-Heterocycles. Org. Lett. 2011, 13, 2228–2231.

(39) Greulich, T. W.; Daniluc, C. G.; Studer, A. N-Aminopyridinium Salts as Precursors for N-Centered Radicals - Direct Amidation of Arenes and Heteroarenes. Org. Lett. 2015, 17, 254–257.

(40) Semple, G.; Skinner, P. J.; Cherrier, M. C.; Webb, P. J.; Sage, C. R.; Tamura, S. Y.; Chen, R.; Richman, J. G.; Connolly, D. T. 1-Alkylbenzotriazole-S-carboxylic Acids Are Highly Selective agonists of the Human Orphan G-Protein-Coupled Receptor GPR109b. J. Med. Chem. 2006, 49, 1227–1230.

(41) Swamy, N. K.; Yazici, A.; Pyne, S. G. Copper-Mediated Cyclization–Halogenation and Cyclization–Cyanation Reactions of β-Hydroxyalkynes and Alkynylphenols and Anilines. J. Org. Chem. 2010, 75, 3412–3419.

(42) Gómez, C.; Maciá, B.; Lillo, V. J.; Yus, M. [1,2]-Wittig rearrangement from chloromethyl ethers. Tetrahedron 2006, 62, 9832–9839.

(43) Nieto-Oberhuber, C.; Pérez-Galán, P.; Herrero-Gómez, E.; Lauterbach, T.; Rodríguez, C.; López, S.; Bour, C.; Rosellón, A.; Cárdenas, D. J.; Echavarren, A. M. Gold(I)-Catalyzed Intramolecular [4+2] Cycloadditions of Arylalkynes or 1,3-Enynes with Alkenes: Scope and Mechanism. J. Am. Chem. Soc. 2008, 130, 269–279.

(44) Xie, X.; Cai, G.; Ma, D. Cul/l-Proline-Catalyzed Coupling Reactions of Aryl Halides with Activated Methylene Compounds. Org. Lett. 2005, 7, 4693–4695.