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Capillary-Based, Serial-Loading, Parallel Microreactor for Catalyst Screening

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Soluble metal−ligand complexes are useful as catalysts for many organic reactions. The large number of metals and ligands available suggests a combinatorial approach to catalyst discovery. Carrying out reactions in very small (microliter) volumes in capillaries has many advantages in this regard, including material conservation, isolation from the atmosphere, and ease of transport of species by using pressure-induced flow. We have developed a capillary reactor in which separate zones of catalyst and reactants are combined and react. Zones are loaded serially into the capillary reactor from an autosampler, they react *in parallel* in the capillary reactor (at elevated temperature) and are ejected serially and under computer control for analysis by online GC. Offline analysis following sample collection is also possible. The Stille cross-coupling reaction has been the focus of our recent activity. Known palladium-based precatalysts and phosphine or arsine ligands were screened to validate the approach taken here. The results largely agree with results obtained by traditional organic synthesis, validating the method. The throughput of the nonoptimized system is over two 5-h reactions/h. For example, 40 5-h reactions examining the effect of catalyst loading were performed in 2 9-h runs requiring a total of 2 h of operator time.

In recent years, miniaturized total analytical systems (μTAS) have been an area of great activity.[1−9] Though many μTAS systems involve separations, there are also many that do not. The latter μTASs consist of reagents, microchannels, and an online or offline detection system. Electrokinetic or hydrodynamic pumping generally motivates solution flow. Electroosmotic flow offers a very convenient pumping mechanism for fluidic manipulation, with minimal hydrodynamic dispersion.[5,8,10−13] In the electrokinetically driven system, electrodes are placed in the appropriate reservoirs to which specific voltage sequences can be delivered under automated computer control. Hydrodynamic pumping also exploits conventional or microscale pumps to maneuver solutions around the channel network.[2,14−17] Among the many materials, glass and silica are the most popular materials to construct the microreactors.

While most applications in this area have been directed toward analysis, some have been directed toward synthesis. Several excellent reviews written from different perspectives exist.[18−28] Researchers have investigated fundamental studies on mass transport and fluid flow[10,11,29,30] as well as particular synthetic applications,[13,15,31−34] including the controlled generation of reactive intermediates.[35,36] In a novel application, Comer and Organ have

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mated a microreactor with microwave heating to give a 4-min exposure of the reaction mixture to the radiation.[37] In another novel application, thermochromic liquid crystals reported on temperature in real time.[38] Because of the low capacity of chip devices, most reactions studied are relatively rapid. Nanoparticle syntheses, which are difficult to control, are successfully carried out in microreactors.[39−43]

Microreactors have been applied to catalyst discovery.[44,45] Polymerization catalysts have been investigated[46,47] as have catalysts for gas/liquid systems,[48,49] Kumada coupling,[15] Baeyer−Villager oxidation,[50] enamine formation,[31] and expoxidation.[51]

In these microfluidic systems investigating organic reactions, one reaction is underway at any time. Reagents and catalysts are brought together and reactions occur in a continuous flow before being detected. Parallel reactors are beginning to be developed (see reviews cited above and ref 52).

We present here a powerful tool for high-throughput screening of slow reactions accelerated by homogeneous catalysts. Up to 20 reaction zones containing different catalysts can exist *simultaneously* in the simple fused-silica capillary reactor. The zones are defined by natural hydrodynamic dispersion. The instrument is a hybrid between the simple combine-reagents-and-detect approach common to most simple microfluidic platforms and the far more instrumentally complex approach involving multiple parallel flow streams. In the current instrument, reaction zones are loaded serially, react in parallel, and are analyzed (or collected) serially.

In this work, we focus on the construction and evaluation of this novel instrument. We have investigated catalysts for the Stille reaction, which is one of the most important reactions leading to the formation of new carbon−carbon bonds.[53−55] The reaction is carried out in the presence of 1−2 mol % palladium catalyst. A variety of palladium(II) or palladium(0) complexes with neutral ligands were tested in the screening system we constructed. The reaction products were analyzed by on-line gas chromatography achieving quantitative information about catalyst activity. $PdCl_2(CH_3CN)_2$ (2 mol %) + $AsPh_3$ (6 mol %) is the best catalyst for the Stille reaction in the group that we tested.

EXPERIMENTAL SECTION

Chemicals and Materials. HPLC grade CH_3OH, THF, $Bu_3SnCH{=}CH_2$, phenyl iodide (PhI), dodecane, and styrene were purchased from Sigma (St.Louis, MO). Neutral red was from J.T. Baker Chemical Co. (Phillipsburg, NJ). All the ligands including $AsPh_3$, PPh_3, $(2\text{-furyl})_3P$, $(4\text{-}FC_6H_4)_3P$, and $(4\text{-}ClC_6H_4)_3P$ were also purchased from Sigma. Pd_2dba_3 (dba = dibenzylidine acetone), $Pd[(C_6H_5)_3P]_4$, $Pd[(C_6H_5)_3P]_4$, $PdCl_2[(C_6H_5)_3P]_2$, and $Pd(OAC)_2$ were purchased from Strem Chemicals (Newburyport, MA). $PdCl_2(CH_3CN)_2$ was prepared according to ref 56. Nitrogen, argon, and compressed air were obtained from Valley National Gases Inc. (Washington, PA)

Instrumentation. Syringe pumps were purchased from Harvard Apparatus Inc. (Holliston, MA). The Waters M-45 pump was from Waters Corp. (Milford, MA). The HP 1050 autosampler were purchased from Agilent (Palo Alto, CA). VICI six-port injector (Model E60) and VICI 10-port valve (model EPCA-CE) were purchased from Valco Instruments Co, Inc. (Houston, TX). The Focus GC was purchased from Thermo-Electron. It has a single column (RTX-5, 7 m × 0.32 mm (0.25-μm thick phase)) and detector (FID). A USB 2000 optical fiber UV−visible absorbance detector was purchased from Ocean Optics. Inc. (Dunedin, FL). A pump (M6) for injection into the GC was purchased from Intelligent Motion systems, Inc. The heater for the organic reactions was constructed locally. The temperature controller for the heater was from Minco Products Inc. (Minneapolis, MN). The fused-silica capillary with 75-μm i.d., 360-μm o.d. that was used as the microreactor was purchased from Polymicro Technologies, L.L.C (Phoenix, AZ).

GC Analysis. The initial temperature of the oven was 85 °C and held for 0.8 min. The temperature was increased from 85 to 200 °C at 100 °C/min. Two minutes was allowed for cooling. Typically, flowsplitting was used to inject 10% of the 1.0-μL loop contents.

Construction of the Screening System for Catalyst Libraries. The designed screening setup is shown in Scheme 1. The

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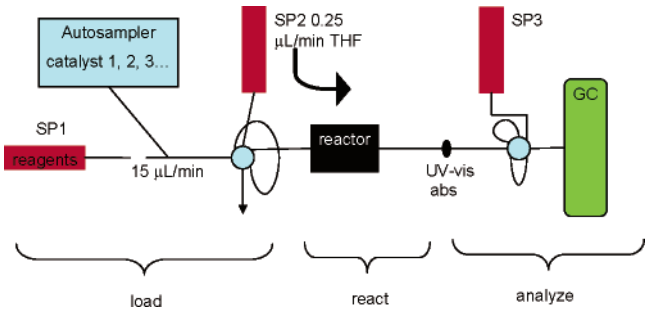
Scheme 1. Schematic Diagram of the Screening System[a]



[a] The loading section consists of a syringe pump (SP1) for the reagents and another for the driving flow (SP2). Catalysts are combined with reagents at equal flow rates in the loop of a six-port injector by an autosampler. Under computer control, when the autosampler has completed its cycle, the loop's contents are pushed into the reactor. The reactor is heated. The detection section consists of a UV−visible absorbance detector for finding the reaction zones. Under computer control, the zones are alternately pushed into one loop in the 2-loop, 10-port microinjector by SP2 and then injected into the capillary GC by SP3. The injection by SP3 initiates the GC program for quantative analysis of the product of the reaction.

system includes three sections: loading, reaction, and GC analysis. Fused-silica capillary joined by homemade low-volume connectors[57−60] comprise the fluidic part of the microreactor. Each of the three sections carries out that function as follows. The "load" section creates a small zone of solvent containing catalysts and reagents and moves the zone into the reactor. Several zones are moved serially into the reactor. The reaction occurs at controlled temperature in the reactor. After reacting in parallel in the capillary reactor (at elevated temperature) for a specific time, the samples are ejected serially and analyzed by online GC under the control of a computer. Each of these three stages is described in more detail below.

Injection. Samples of catalysts loaded into sampling vials are placed onto an autosampler tray. The autosampler samples 20 μL from the vial and pumps the sample zone out. This sample zone passes through the loop of a microinjector. A loop volume of either 1 μL or 750 nL is used. The flow rate of the autosampler pump is 15 μL/min. The reagents are pumped with a syringe pump 1 (SP1) and are combined with the catalyst at an equal flow rate. Thus, the loop contains both catalyst and reagents. The loop contents are injected under computer control into the reactor. The contents of the loop are pushed with THF from a syringe pump (SP2) operating at typically 250 nL/min. Combining the catalyst and reagents before the loop creates distinct zones containing reagents and catalysts with pure solvent from SP2 between them.

Reaction. The reactor consists of a 75-μm-i.d., 6.7-m-long piece of fused-silica tubing. When all the zones are loaded, the temperature is increased to the reaction temperature and the flow from SP2 is stopped for a defined time.

Detection. Detection can be done with the Ocean Optics absorbance detector, by offline GC/MS on collected fractions, or by online GC. Where applicable, we prefer the latter approach. The online injection process is triggered by the absorbance detector. A 10-port valve enables the loading of one loop while the contents of the other loop are chromatographed. The contents of the loop are pushed into the GC with a low-pressure, refillable syringe pump (M6).

To check the screening system, confirm how many zones we can put in the capillary microreactor, and define optimum experimental conditions, the system created zones of a dye, 1.0 mM neutral red in methanol. CH_3OH was pumped by SP2 in this case. The wavelength of the optical fiber absorbance detector was fixed at 530 nm. Flow rates of SP1 and SP2 were optimized to maximize reproducibility and minimize band spreading. Parameters taken into consideration in the timing sequence are the volumes of the microinjector's loop (1 μL) and the capillary microreactor (i.d. 75 μm, length, 6.7 m, the volume of the microreactor is ~30 μL), the microinjector loop loading time, and the microinjector injection time. To use the same flow rate for SP2 in both the loading phase and the detection phase, the GC run time and the loading/injection times were made the same (~5 min).

Screening Experiment. The Stille reaction was carried out in anhydrous THF at 50 °C. Pd_2dba_3, $Pd[(C_6H_5)_3P]_4$, $Pd[(C_6H_5)_3P]_4$, $PdCl_2[(C_6H_5)_3P]_2$, $Pd(OAC)_2$, and $PdCl_2(CH_3CN)_2$ were chosen as the precatalysts and $AsPh_3$, PPh_3, $(2\text{-furyl})_3P$, $(4\text{-}FC_6H_4)_3P$, and $(4\text{-}ClC_6H_4)_3P$ were selected as the ligands. Various mole equivalents of palladium-based precatalysts and ligands were mixed in 6 mL of THF to form the catalyst for the Stille reaction. A 100-μL aliquot of each catalyst solution was placed in a 2-mL glass autosampler vial. The catalyst vials were set on the tray of the autosampler. Reagents PhI (75 μL) and $Bu_3SnCH{=}CH_2$ (250 μL) were mixed in 3 mL containing 24 μL of dodecane as the GC internal standard. The reactants were loaded in a syringe and driven by SP1. SP2 was turned off, and the flow was stopped after all the samples were loaded into the capillary microreactor. The heater was turned on, and the Stille reaction was carried out in the microreactor for varying times at 50 °C. After reaction, SP2 was turned on and the reaction zones were analyzed as described above.

Calibration Curve and the Yields of the Stille Reaction. A calibration curve was prepared from standard solutions of styrene before every run. A stock solution containing 77 μL of styrene, 24 μL of docecane, and 3.224 mL of THF was diluted in THF to obtain standards. Reaction yields are based on styrene to dodecane peak area ratios.

RESULTS AND DISCUSSION

Reactor Components. *Injection.* We have employed a standard HPLC autoinjector for sample management. This apparatus, although specified to have the capability to inject microliter volumes, normally performs those injections into a system in which a 50- or 100-μL injection would be acceptable. Further, low carryover is an important specification. Thus, the contents of the autosampler syringe in normal operating conditions are essentially flushed into an HPLC. The shape of the concentration−time profile of a solute emanating from the autosampler can be determined by using only the autosampler and the absorbance detector with the solute neutral red. The concentration−time profile of the autosampler operating normally does not have a plateau, even when injecting 60 μL of neutral red solution. Without a plateau, it

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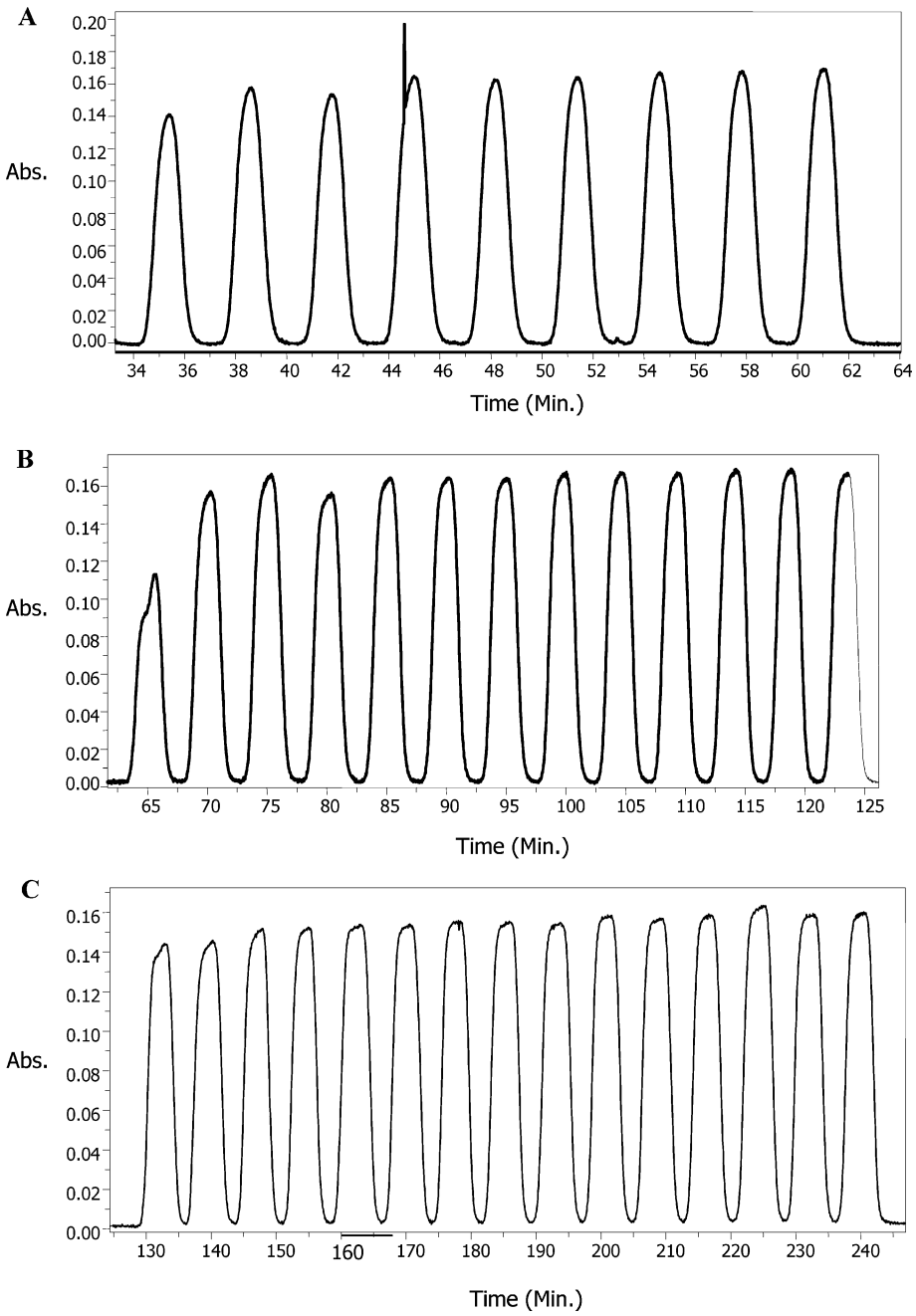

Figure 1. Absorbance response of 1 mM neutral red at 530 nm. Loop volume is 1.0 μL. (A) SP1, 15μL/min; SP2, 1.0 μL/min. (B) SP1, 15μL/min; SP2, 0.5 μL/min. (C) SP1, 15μL/min; SP2, 0.25 μL/min.

is difficult to get reproducible quantities into the loop injector. Consequently, we altered the functioning of the autosampler. After the autosampler syringe aspirates the sample, the sample is not flushed out by the autosampler pump, but by the syringe itself—the plunger of the syringe goes down, ejecting the sample. This can be achieved by changing the autosampler working program. With this modification, a 20-μL sample is enough to create a significant plateau in the concentration−time profile. With suitable timing, a loop microinjector can be reproducibly loaded.

Reactor. The reactor is simply a fused-silica capillary under temperature control. The reactor length and inside diameter have not been optimized. Briefly, smaller diameters allow higher fluid velocities without appreciable band spreading.[61] Longer reactors can contain more zones. Countervailing effects of these changes are the increased pressure required to move liquid through the system (for longer and smaller diameter reactors) and the increased time required to load the larger number of samples (for longer reactors).

Detection. Online detection is preferred over offline. Both have been used. In early investigations, we collected reaction zones for offline GC/MS in order to positively identify the product, styrene. Makeup flow is required for collection in vials. None of these preliminary data are reported here. For online detection, we automated the injection of reaction zones into the capillary GC column. To accomplish this, a 10-port injector with dual injection loops and a refillable syringe pump are required.

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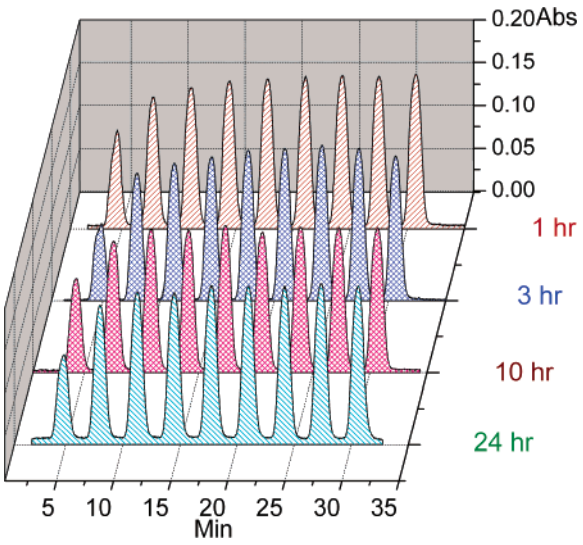
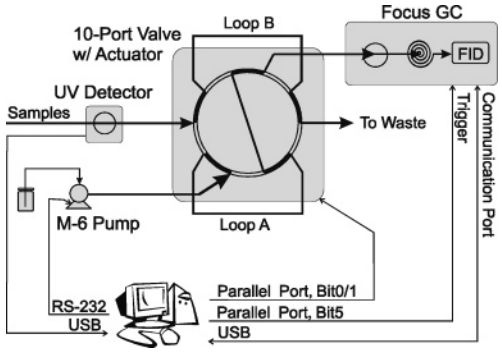


Figure 2. Absorbance responses of 1 mM neutral red in the capillary microreactor for various residence times.

Scheme 2. Scheme of the GC Analyzer[a]



[a] Ten-port valve is used here as a double-loop injector. The injector's output is connected to GC's injection zone by a short capillary. A computer, equipped with locally developed software, monitors the signal from the UV detector. If there is a new zone passing by, the computer will send a command to switch the injector and then start M-6 pump to pump the sample into the GC for a predefined time period, followed by a trigger signal to start the GC. In the meantime, the next reaction zone is filling the other loop.

Parameter Adjustment. *SP1 (Refer to Scheme 1).* The reactants are pumped into the system from SP1. The flow rate should be high because band spreading in this section of the system is not a problem, but the time taken to load the reactor should be a minimum. This flow rate is equal to the flow rate from the autosampler. On the other hand, the pressure cannot be too high. The optimal flow rate of the autosampler and SP1 is 15 μL/min.

SP2 and Injector Timing. The time between reaction zones controls the overlap of the zones in the reactor. Two times, both controllable, dictate the time between zones. One is the time required by the autosampler to pull sample into the syringe and eject it. This is essentially the time required to load the loop. The other is the time needed to empty the loop. SP2 controls the time required to push the loop's contents into the reactor. It also controls the velocity of the zones in the reactor, and thus the band-spreading and the time needed to fill and empty the reactor. Figure 1 shows the UV responses at 530 nm from injections of neutral red. For each flow rate, the sum of the two times was set empirically to ensure good separation. Because the volume of the capillary microreactor is ~30 μL, the time required for the first zone to flow from the injector to the detector is about 30, 60, and 120 min at 1.0, 0.5 and 0.25 μL/min, respectively. The time required to see the last zone is about twice that. Figure 1 shows that 15 (12, 9) samples can coexist in the microreactor at 0.25 μL/min (0.5, 1.0 μL/min). Apparently, the higher flow rate permits more zones per time (9/1.0 = 9 zones/h at 1.0 μL/min compared to 15/4 = 3.5 at 0.25 μL/min). However, in practice, there is a lengthy reaction time. For the Stille reaction, it is typically 5 h or longer. When this time is added to the time for eluting the last peak, the number of zones per hour is actually a maximum at 0.5 μL/min. In considering that 5 h would be the shortest time typically used, 0.25 μL/min was used as the flow rate for SP2.

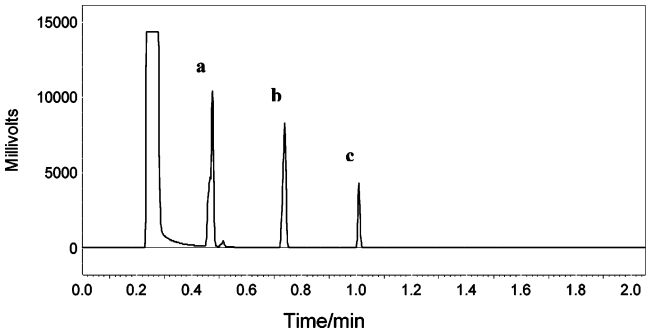


Figure 3. Chromatogram of standard solution (a) styrene, (b) iodobenzene, and (c) dodecane (internal standard). Column: RTX-5, 7 m × 0.32 mm (0.25-μm thick phase). Initial: temperature, 85 °C; for 0.8 min, column temperature increased at 100 °C/min to 200 °C and held for 0.00 min.

In Figure 1, the first peak in each trace has a lower absorbance than the others. This appears not to be an inherent aspect of the instrument, as we never see such an effect when we carry out organic reactions. We suppose that there is some adsorptive loss of the dye at the beginning of each experiment. While this does not detract from the usefulness of the dye for simple optimization, it is a warning that adsorption could potentially be an issue in studies of chemical reactions.

Reaction Time. The zone broadening is primarily from hydrodynamic dispersion. If pure molecular diffusion were important, we would see the band spreading increase with reaction time. We kept zones in the capillary for 1, 3, 10, and 24 h, and then the UV signals were recorded by the optical fiber UV detector. Figure 2 shows that the four UV signals are almost identical. So, the residence time in the reactor can be dictated by the chemistry, and diffusional broadening for up to 24 h is not important.

GC Analyzer. Scheme 2 shows the GC analyzer, which includes the absorbance detector, M-6 pump, 10-port valve, and GC. When the reactions in the microreactor are finished, the samples are pushed out of the microreactor by SP2. The absorbance detector monitors the capillary, finding zones using user-defined absorbances. We define the start of a zone as $A = 0.8$ (absorbance ascending) and the end as $A = 0.2$ (absorbance descending). Zone detection alerts the injector to switch positions so that the just-detected zone is captured. The pump connected to the 10-port valve (SP3) is, at the same time, instructed to inject the contents of the previously filled 1-μL loop into the GC. Finally, also at the same time, the GC is triggered to start its temperature program.

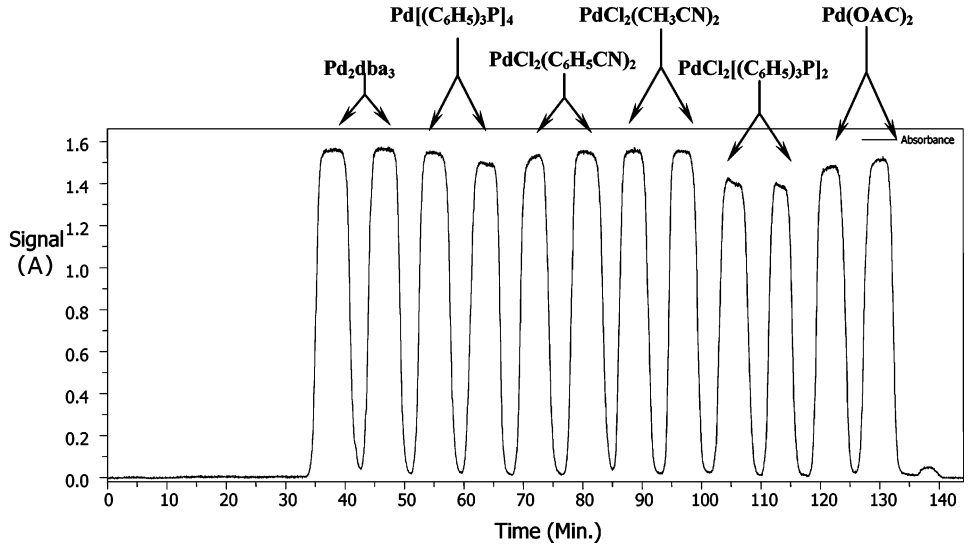


Figure 4. Absorbance response of the products of Stille reactions. Catalyst: Pd compound (2%) + 8.2 mg of $AsPh_3$ (4%) + 3 mL of THF. Reactant: 75 μL of PhI + 250 μL of $Bu_3SnCH{=}CH_2$ + 3 mL of THF. Loop volume, 1.0 μL; SP1, 15 μL/min; SP2, 0.25 μL/min; injection time, 4.2 min.

To accomplish this, specific software was written to control the absorbance detector, pump, valve, and GC.

Stille Reaction. The reaction is shown below

$$R{-}X + R'SnR''_3 \xrightarrow{\text{catalyst}} R{-}R' + XSnR''_3$$

$$R, \quad R' = \text{aryl, vinyl, allyl,} \quad X = \text{Br, I} \qquad \text{(reaction 1)}$$

The mechanism of the palladium-catalyzed Stille reaction has been widely investigated. The original mechanism proposed by Stille,[54] in the case of monodentate ligand L, included four steps: oxidative addition, transmetalation, trans/cis isomerization, and reductive elimination involving saturated 16-electron aryl−Pd(II) complexes, all ligated by two phosphine ligands.[62] The catalyst is the key to the reaction.

In the current work, the Stille reaction was performed within the capillary microreactor of the screening system. PhI reacts with $Bu_3SnCH{=}CH_2$ with the help of a catalyst.

$$PhI + Bu_3SnCH{=}CH_2 \xrightarrow{\text{catalyst}} PhCH{=}CH_2 + Bu_3SnI$$

The microreactor uses GC to calculate reaction yield. Figure 3 shows that standards of styrene (0.47 min) and PhI (0.75 min) are well separated. The calibration curve for styrene/dodecane is linear ($r^2 = 0.997$) in the range from 0 to 100% yield.

Screening the Catalyst Libraries of the Stille Reaction. *Precatalysts*. Six Pd precatalysts and 5 ligands were selected for the Stille reaction.[55,63−67] For screening the precatalysts with a known good ligand, the autosampler was loaded with 2 mol % precatalyst and 4 mol % $AsPh_3$ as the ligand.[55] Each catalyst was loaded twice (total 12 reactions). Figure 4 shows the 12 zones as seen by the absorbance detector. We note that several of the zones have a rather high absorbance at or near the stray light limit of the instrument. As we do not use the absorbance quantitatively, this not a problem. In Figure 5, A and B are two chromatograms from the analysis of the Stille reaction by online GC with 2 mol % $PdCl_2(CH_3CN)_2$ and $Pd[(C_6H_5)_3P]_4$, (each with 4 mol % $AsPh_3$). It

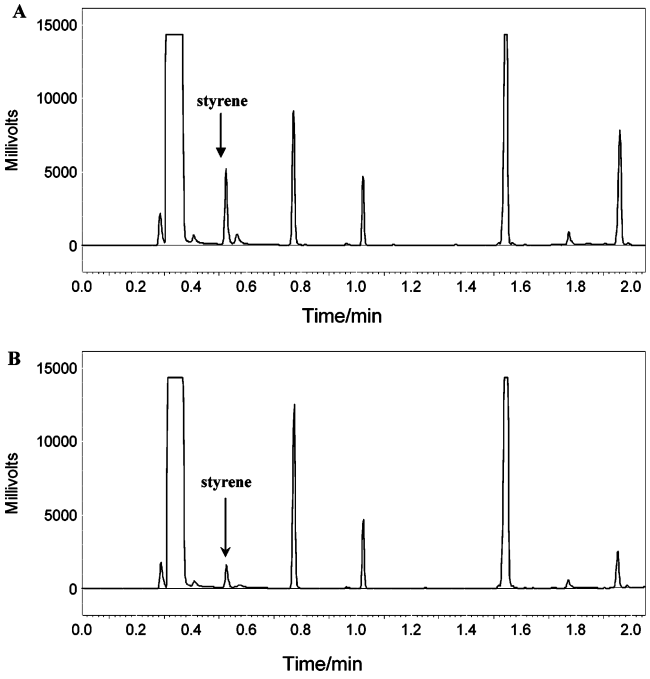


Figure 5. Chromatograms of the products of the Stille reaction by online GC. (A) Catalyst: $PdCl_2(CH_3CN)_2$ (2%) + 8.2 mg of $AsPh_3$ (4%) + 3 mL of THF. Reactant: 75 mL of PhI + 250 mL of $Bu_3SnCH{=}CH_2$ + 3 mL of THF. (B) Catalyst: $PdCl_2[(C_6H_5)_3P]_2$ (2%) + 8.2 mg of $AsPh_3$ (4%)+ 3 mL of THF. Reactant: 75 mL of PhI + 250 mL of $Bu_3SnCH{=}CH_2$ + 3 mL of THF.

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Table 1. Yields of the Stille Reaction with Various Precatalysts[a]

precatalyst (2 mol %)	Pd_2dba_3	$Pd[(C_6H_5)_3P]_4$	$PdCl_2(C_6H_5CN)_2$
yield (%)	49.2 ± 0.9[b]	38.0 ± 0.7	43.8 ± 0.7
precatalyst (2 mol %)	$PdCl_2(CH_3CN)_2$	$PdCl_2[(C_6H_5)_3P]_2$	Pd $(OAC)_2$
yield (%)	50.7 ± 1.1	15.9 ± 0.7	23.0 ± 1.5

[a] Reactants: 75 μL of PhI + 250 μL of $Bu_3SnCH{=}CH_2$ + 24 μL of dodecane + 3 mL of THF. Catalysts: Pd compound (2%) + 8.2 mg of $AsPh_3$ (4%) + 3 mL of THF, 50 °C for 5 h in capillary microreactor. [b] Mean ± SD, $n = 3$.

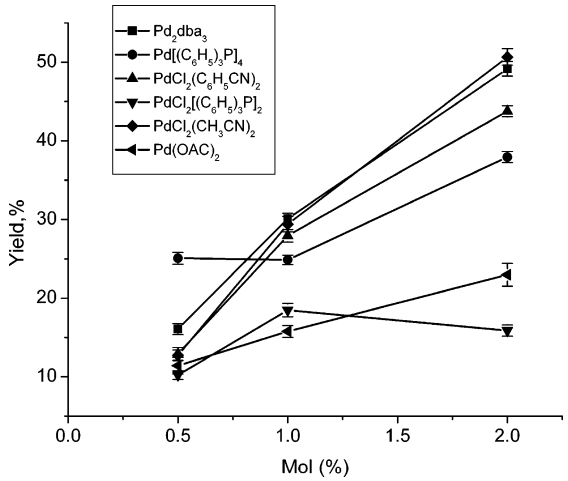

Figure 6. Yields of the Stille reaction with different mole equivalents of precatalysts and 4 mol % $AsPh_3$.

is obvious that the styrene response of Figure 5A is higher than that of Figure 5B. Accordingly, as one of the reactants, the remaining amount of PhI in Figure 5B is higher than that of Figure 5A. This means the $PdCl_2(CH_3CN)_2$ has more catalytic activity than $Pd[(C_6H_5)_3P]_4$. Table 1 shows the yields from the six precatalysts. The reactions with Pd_2dba_3 and $PdCl_2(CH_3CN)_2$/$AsPh_3$ yield ~50% styrene The yield is only 14% with the catalyst $Pd[(C_6H_5)_3P]_4/AsPh_3$. $PdCl_2(CH_3CN)_2$ will be used as the precatalyst in screening ligands (discussed below).

The amount of the catalyst is also important to the reaction yield. Amounts of 0.5, 1, 2, 3, and 4 mol % $PdCl_2(CH_3CN)_2$ and 4 mol % $AsPh_3$ were selected as the catalyst, and all the reactions were performed in the capillary microreactor. Because small particles were deposited from solvent if 3 and 4 mol % $PdCl_2(CH_3CN)_2$ were used for the Stille reaction, only the yields of styrene with 0.5, 1. and 2 mol % $PdCl_2(CH_3CN)_2$ are listed in Figure 6. It shows that generally all the catalytic activities are increased as the concentration of precatalyst increases.

Table 2. Yields of Stille Reaction with Various Ligands[a]

ligands	$AsPh_3$	PPh_3	$(2\text{-furyl})_3P$	$(4\text{-}FC_6H_4)_3P$	$(4\text{-}ClC_6H_4)_3P$
yield (%)	51.7 ± 0.7[b]	28.5 ± 0.5	40.0 ± 0.7	21.1 ± 0.7	15.5 ± 0.4

[a] Reactants: 75 μL of PhI + 250 μL of $Bu_3SnCH{=}CH_2$ + 24 μL of dodecane + 3 mL of THF. Catalysts: $PdCl_2(CH_3CN)_2$ (2 mol %) + ligand (4 mol %) + 3 mL of THF, 50 °C for 5 h. [b] Mean ± SD, $n = 3$.

Experimental Optimization of Throughput. At present, we are trying to make small adjustments in the screening system to increase throughput while maintaining the 6.7-m capillary microreactor and the 5-h reaction time. We have decreased the volume of the loop from 1.0 to 0.75 μL to narrow the reaction zones. Figure 7 is the UV response of 20 reaction zones in the capillary microreactor. The total time for this set of reactions is ~9 h (2-h injection and detection phases plus 5-h reaction time). This represents a throughput of 2.2 5-h reactions/h.

Ligands. Using the same procedures as for the precatalysts except using the higher throughput conditions described above, the ligands, including $AsPh_3$, PPh_3, $(2\text{-furyl})_3P$, $(4\text{-}FC_6H_4)_3P$, and $(4\text{-}ClC_6H_4)_3P$ were screened in the capillary microreactor. Table 2 compares the yields from the five ligands using one precatalyst (2 mol % $PdCl_2(CH_3CN)_2$). $AsPh_3$ and the furyl phosphine show significant catalytic activity. The effect of various mole equivalents

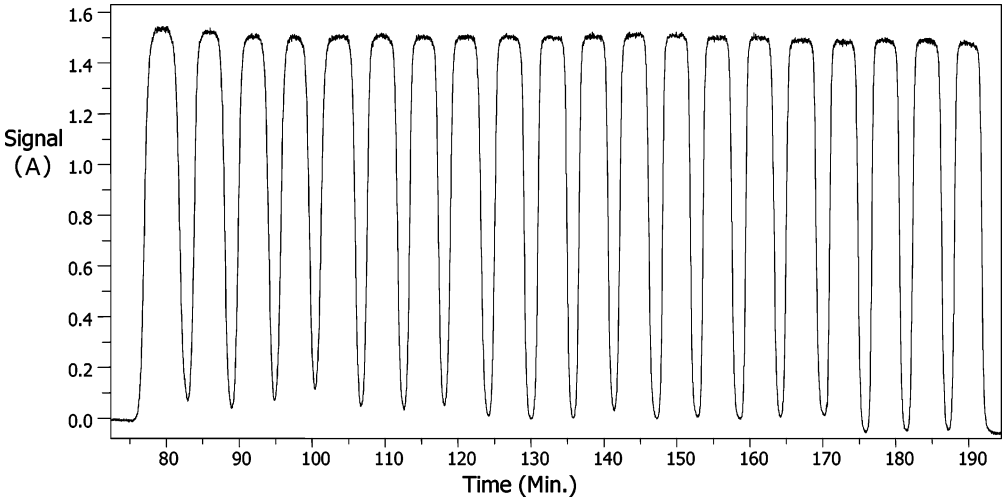

Figure 7. UV response of the products of 20 Stille reactions. Catalyst: Pd compound (2 mol %) + 8.2 mg of $AsPh_3$ (6 mol %) + 3 mL of THF. Reactant: 75 μL of PhI + 250 μL of $Bu_3SnCH{=}CH_2$ + 3 mL of THF. Loop volume, 0.75 μL; SP1, 15 μL/min; SP2, 0.25 μL/min; stop time, 1.0 min; injection time, 3.0 min.

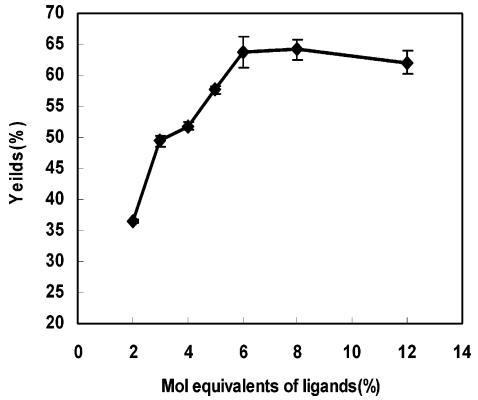

Figure 8. Yields of the Stille reaction with different mole equivalents of $AsPh_3$ and 2 mol % equiv $PdCl_2(CH_3CN)_2$.

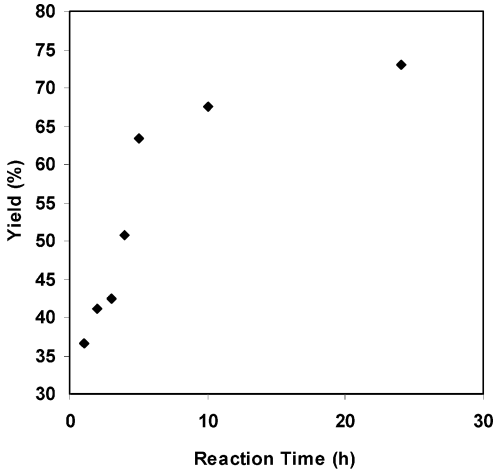

Figure 9. Effect of reaction time to the Stille reaction in the capillary microreactor. Two mole % of $PdCl_2(CH_3CN)_2$ + 6 mol % $AsPh_3$.

of $AsPh_3$ for the Stille reaction is shown in Figure 8. The yield of styrene is only ~35% with 2 mol % $AsPh_3$ and 2 mol % $PdCl_2(CH_3CN)_2$. It increases to ~65% as $AsPh_3$ increases to 6 mol %, and then the yield reaches a plateau up to 12 mol %. So, in this work, the catalyst composed of 2 mol % $PdCl_2(CH_3CN)_2$ and 6 mol % $AsPh_3$ is the most active. This stoichiometry was also obtained by traditional synthesis,[55,66] proving the validity of the screening system. Note that Figure 8 displays statistical error bars from $n = 4$ or 8. This plot consists of 40 determinations of reaction yield. This represents two 9-h runs on the instrument requiring no more than 2 h of operator time in total.

Reaction Time. The reaction time is also an important factor for this obviously slow organic reaction. Various reaction times were used in the microreactor (Figure 9). When the reaction time is in the range of 1−3 h, the yield increases slowly from 36 to 42%. But the yield increases very quickly from 42 to 63% when the reaction time is 5 h. The yield seems to plateau after 5 h. This reaction time is also similar to that found by the traditional method.[53−55,66]

Reproducibility. Ten reactions were carried out at the optimal catalyst and reaction time. The yields are 61.99 ± 0.36% (mean ± SEM, $n = 10$). The reproducibility is remarkable.

CONCLUSION

Microliter volumes of reagents and catalysts can be brought together and reacted in parallel for a specified time. Online GC analyzes the components of the reaction zones. The Stille reaction was studied by the micro total analytical screening system. Six precatalysts and five ligands with different mole equivalents were screened in the capillary microreactor at the same time. $PdCl_2(CH_3CN)_2$(2 mol %) + 8.2 mg of $AsPh_3$(6 mol %) was selected as the optimum catalyst for the Stille reaction. It is a high-throughput and efficient, enviromentally friendly method and can shorten the development time from laboratory to commercial production. This system with capillary microreactor technology promises to yield a wide range for combinatorial synthesis, screening of catalysts, and reaction kinetics.

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