6

Liquid- and Liquid–Liquid-phase Reactions – Coupling Reactions

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6.1
Metal-catalyzed Coupling

Metal-catalyzed cross-coupling reactions have been widely studied in organic synthesis, because they represent one of the most powerful tools for carbon–carbon bond formation based on readily available substrates [1]. Attempts to realize cross-coupling reactions using microreactors started with studies using heterogeneous Pd catalysts. In the pioneering efforts by Haswell's group reported in 2000, they used a microreactor having a Pd/SiO$_2$ catalyst bed immobilized on a microchannel for the Suzuki–Miyaura coupling reaction [2]. The Kumada–Corriu reaction catalyzed by polymer-supported nickel in a microflow system was also reported by the same group [3]. Many examples with different catalyst supports have been reported to date [4]. In contrast, applications of microreaction technology in homogeneous catalysis in the solution phase has recently become the focus of many researchers. This section mainly deals with the cross-coupling reactions in a microflow system using homogeneous catalysis.

The typical Sonogashira reaction, which couples aryl or vinyl halides with terminal alkynes in the presence of a Pd catalyst and a Cu co-catalyst, has found many applications in organic synthesis. In 2002, Ryu and coworkers reported that the Sonogashira coupling reaction, using the ionic liquid [bmim]PF$_6$ (1-butyl-3-methylimidazolium hexafluorophosphate), proceeded effectively without a Cu co-catalyst [5]. They examined the Cu-free Sonogashira coupling using a continuous microflow system. When a solution of [bmim]PF$_6$ containing a Pd *N*-heterocyclic carbene complex and a mixture of iodobenzene, phenylacetylene and dibutylamine was mixed using an IMM micromixer having 40 μm interdigitated microchannels at 110 °C with a 10 min residence time, diphenylacetylene, the desired coupling product, was obtained in 93% yield (Scheme 6.1) [5]. After successive biphasic treatment with hexane and water, the Pd-containing ionic liquid solution could be reused, leading to an 83% yield of diphenylacetylene in the second reaction.
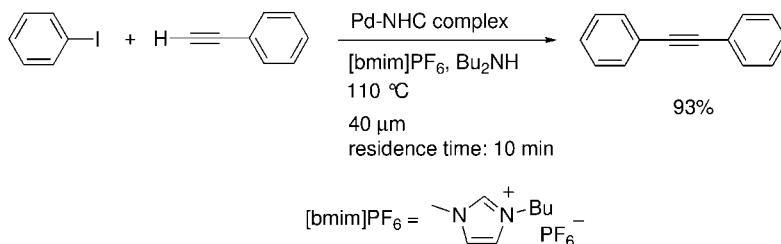
Scheme 6.1 Sonogashira coupling in an ionic liquid.
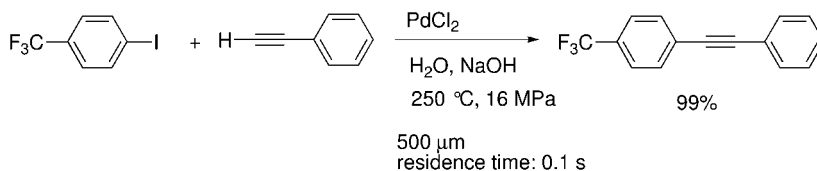
Scheme 6.2 Sonogashira coupling in high-pressure and high-temperature water.

Recently, Kawanami *et al.* showed that high-pressure and high-temperature water is useful for the copper-free Sonogashira coupling reaction using a microflow system (Scheme 6.2) [6]. Under the conditions of 16 MPa and 250 °C, the Sonogashira coupling reaction of aryl iodides with phenyl acetylene proceeded in very short reaction time (0.012–4 s) to give the desired coupling products in high yields.

Taking the Mizoroki–Heck reaction as a model reaction, Ryu and coworkers achieved an effective catalyst recycling system using an ionic liquid as a reaction medium, where integration of all the basic steps, i.e. reaction, separation of the product from the ionic liquid phase and recycling of the ionic liquid containing the Pd catalyst, could be realized in a completely continuous fashion [7]. This 'bench-top' continuous production system was constructed using a continuous microflow reactor, a CPC CYTOS Lab System equipped with a 100 μm microchannel mixer and an originally developed dual microextraction system. After running the system for 11.5 h, during which time 144.8 g (0.71 mol) of iodobenzene was consumed, 115.3 g of *trans*-butyl cinnamate was obtained (80% yield, 10 g h^{-1}) (Figure 6.1). The ionic liquid with the Pd catalyst was recycled about five times during this continuous operation.
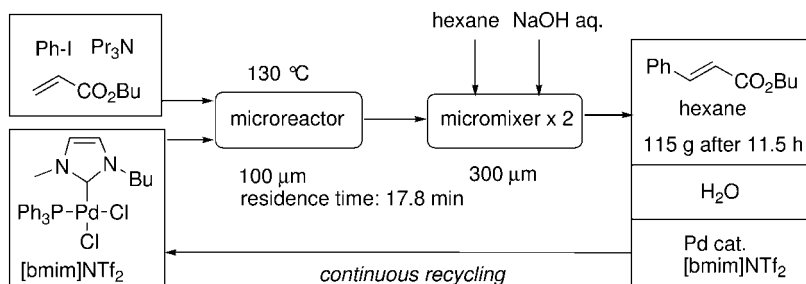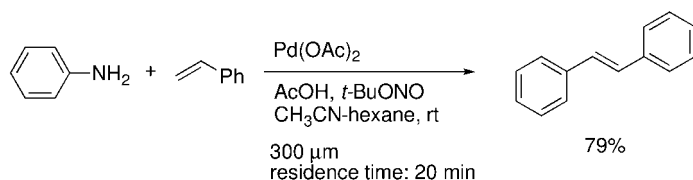

**Figure 6.1** Mizoroki–Heck reaction in an ionic liquid.

**Scheme 6.3** Diazotization/Mizoroki–Heck reaction.

Shwalbe *et al.* reported the continuous flow Mizoroki–Heck reaction using DMF as a solvent [8], in which rapid catalyst screening and optimization of the reaction conditions were performed using a CYTOS-based microreaction system, which they call SEQUOS.

Wirth and coworkers reported on a tandem diazotization/Mizoroki–Heck reaction using a microflow system (Scheme 6.3) [9]. Interestingly, it was demonstrated that the segmented flow, caused by a mixed solvent system comprising acetonitrile and hexane, gave better results than the reaction with monophasic flow using acetonitrile alone. For example, the reaction of aniline with styrene using segmented flow conditions gave a 79% yield of stilbene.

The Suzuki–Miyaura coupling reaction, which can couple organic halides with organoboron compounds in the presence of Pd catalysts, is synthetically important and is a frequent target of microflow reactions. Lee and coworkers reported the Suzuki–Miyaura coupling reaction catalyzed by Pd nanoparticles using a glass capillary microreactor (400 µm i.d.) [10]. Microwave-assisted microflow systems have also been developed. Comer and Organ employed a continuous flow design consisting of a stainless-steel holding/mixing chamber with three inlet ports connected to a simple glass capillary tube (1150 µm i.d.) located in the irradiation chamber [11]. The reaction of *p*-bromobenzaldehyde with phenylboronic acid using Pd(PPh$_3$)$_4$ as the catalyst and KOH as the base gave quantitative yields of the coupling product with a ca. 4 min residence time (Scheme 6.4). Organ and coworkers also reported Suzuki–Miyaura coupling and Mizoroki–Heck reactions catalyzed by a Pd thin film coated on the inner surface of capillaries (1150 µm i.d.) in conjunction with microwave-irradiation [12]. Ley and coworkers reported continuous flow Suzuki–Miyaura coupling reactions using microencapsulated palladium catalyst (Pd EnCat 40) under conventional and microwave heating [13, 14]. In the latter case, it was reported that a single flow reactor could be used to generate multiple products in a sequential fashion or multi-grams of product without regeneration or replacement of the catalyst [14]. Uozumi *et al.* reported a Suzuki–Miyaura coupling reaction using a microreactor equipped with a catalytic membrane of a polymeric palladium complex,
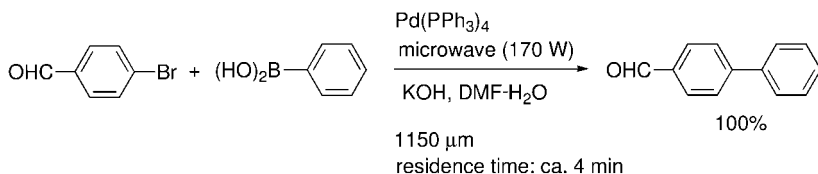
Scheme 6.4 Suzuki–Miyaura coupling using microwave heating.
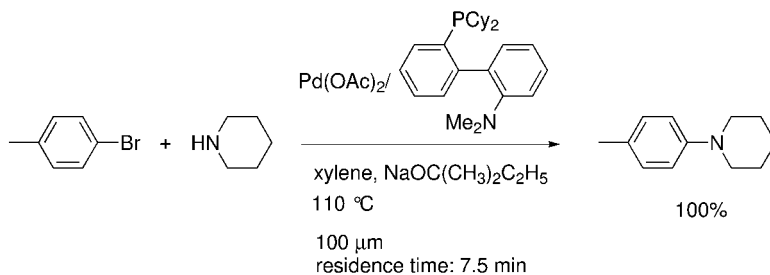
Scheme 6.5 Palladium-catalyzed aromatic amination.

poly(acrylamide)–triarylphosphinepalladium, inside a microchannel (width 100 μm, depth 40 μm) [15].

Palladium-catalyzed aromatic amination of aryl halides, developed independently by Buchwald and Hartwig, is a useful tool for the construction of C–N bonds. Caravieilhes and coworkers examined this aromatic amination using a microreactor [16]. When the reaction of *p*-bromotoluene and piperidine with $Pd(OAc)_2$/ biarylphosphine as a catalyst system and sodium *tert*-pentoxide as a base in xylene was carried out using a CPC CYTOS Lab System, the desired coupling product was obtained in quantitative yield with a 7.5 min residence time (Scheme 6.5).

Weber and coworkers reported catalyst screening of the Stille coupling reaction using a capillary microreactor (75 μm i.d., 6.7 m length) [17]. Optimum palladium catalysts and ligands were screened effectively by the flow regime, where the reaction products were analyzed by on-line gas chromatography.

6.2
Reactions Using Organometallic Reagents

Reactions using organometallic reagents, such as Grignard reagents and organo-lithium reagents, have been widely used for organic synthesis. Both the preparation of such reagents, e.g. Grignard exchange reaction and lithium halogen exchange reaction, and reactions with electrophiles are highly exothermic, hence the reactions using batch reactors have to be carried out at low temperature. However, it often becomes difficult to control the reaction temperature in large-scale synthesis. Recently, reactions using organometallic reagents in a microflow system at elevated temperatures have been examined by several research groups.

Hessel *et al.* reported the synthesis of phenylboronic acid using micromixer/ tubular reactors [18]. A typical industrial process for the synthesis of phenylboronic acid from phenylmagnesium bromide and boronic acid trimethoxy ester requires strict temperature control (-25 to $-55\,°C$) to minimize the formation of side-products. Using a micromixer (width 40 μm, depth 300 μm)/tubular reactor system, they obtained phenylboronic acid in high yield (>80%) even at higher temperatures (22 or 50 °C) (Scheme 6.6). They also achieved pilot-scale production by employing an IMM caterpillar mixer (depth range 1200–1700 μm, width range 1200–2400 μm).
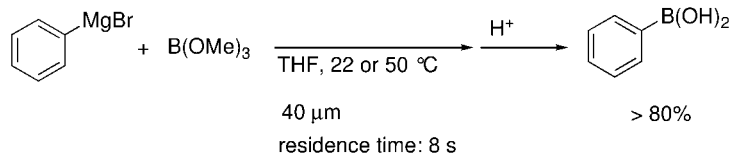
Scheme 6.6 Grignard reaction leading to phenylboronic acid.
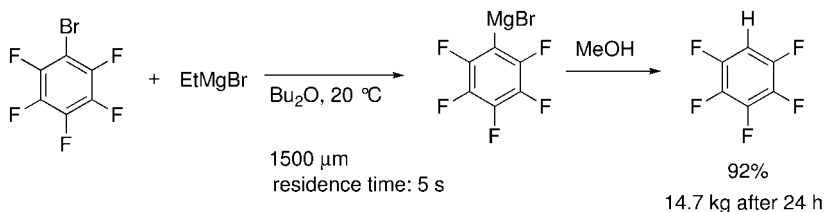
Scheme 6.7 Grignard exchange reaction.

Although the Grignard exchange reaction of ethylmagnesium bromide and bromopentafluorobenzene to give pentafluorophenylmagnesium bromide is highly exothermic, Wakami and Yoshida found that the reaction can be carried out at 20 °C using a microflow system [19]. Several types of micromixers (T-shaped mixer, Yamataka YM-1 mixer, IMM multi-lamination mixer and Toray Hi-mixer) were examined for this study. For the preparation of multi-kilograms of pentafluoroben-zene, they used a system comprising a Toray Hi-mixer having a 1.5 mm channel width with a shell and tube heat exchanger, consisting of 55 microtubes (490 µm i.d., 200 mm length) bundled together and placed in a shell (16.7 mm i.d., 200 mm length), with continuous operation for 24 h (Scheme 6.7).

Zhang *et al.* reported the lithium halogen exchange reaction of *m*-bromoanisole with *n*-BuLi in a microflow system at moderately low temperatures [20]. The lithium–halogen exchange reaction using a CYTOS system at −14 °C with a 17 s residence time and subsequent reaction with cyclohexanone at −40 °C in batch mode gave the tertiary alcohol in 87% yield (Scheme 6.8). Schwalbe *et al.* reported on a two-stage microreaction system based on CYTOS for lithium–halogen exchange reaction of *m*-bromoanisole with *n*-BuLi, followed by formylation with DMF [8]. Sheikh and Schmalz also reported the microflow generation of aryllithium compounds from
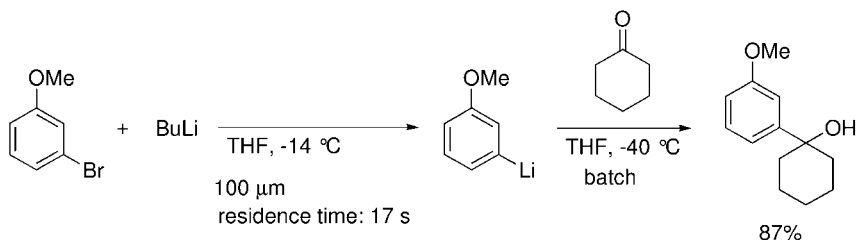
Scheme 6.8 Li–Br exchange reaction followed by reaction with an electrophile.
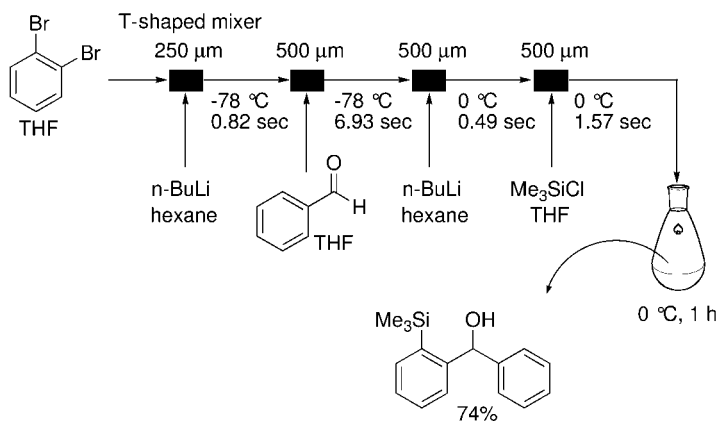
Figure 6.2 Sequential functionalization of two bromine atoms in *o*-dibromobenzene.

aromatic bromides using *n*-BuLi and subsequent quenching with fenchone [21]. Recently, Song and coworkers reported the application of a lithium–halogen exchange reaction in a two-stage continuous microflow system to the synthesis of the materials for an organic light-emitting diode [22].

Yoshida and coworkers reported lithium–halogen exchange of dibromobenzenes with *n*-BuLi [23, 24]. In the case of a conventional batch reactor, Li–Br exchange reaction of *o*-dibromobenzene has to be carried out at −100 °C or below, because highly unstable *o*-bromophenyllithium easily decomposes to form benzyne, which causes undesirable side-reactions. Using a microflow system consisting of two T-shaped micromixer (250, 500 μm) and tubular reactors, they carried out lithiation of *o*-dibromobenzene (−78 °C, 0.8 s residence time) and subsequent reaction with electrophiles (−78 °C) to give functionalized bromobenzenes in good yields [23]. They also demonstrated sequential functionalization of two bromine atoms, where a second Li–Br exchange can be carried out at 0 °C (Figure 6.2). In the case of *m*- and *p*-dibromobenzene, the Li–Br exchange reaction of with *n*-BuLi can be carried out at 20 °C [24].

6.3
Photochemical Coupling

Jensen and coworkers [25] demonstrated the photochemical synthesis of benzopinacol (Scheme 6.9) within a silicon/quartz microreactor (channel dimensions: 500 μm wide × 250 μm deep), which enabled UV light to pass through the quartz layer and irradiate the reaction mixture contained within the microchannel network. Employing on-line UV analysis, they were able to assess the reaction progress rapidly and with ease. Preliminary investigations conducted at flow rates of >10.0 μl min^{-1} showed no benzopinacol formation. Only recovery of the unreacted starting materials benzophenone and 2-propanol was observed. By reducing the flow rate to
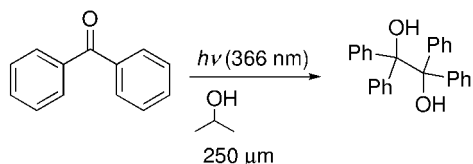
Scheme 6.9 Photochemical synthesis of benzopinacol in a silicon/quartz hybrid reactor.
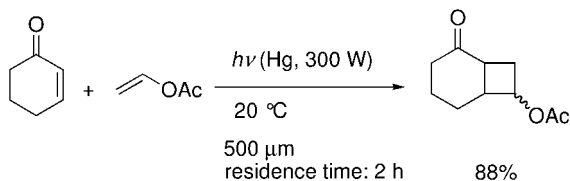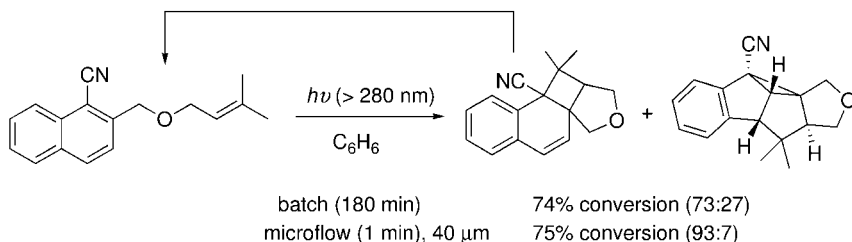

Scheme 6.10 Photochemical [2 + 2] cycloaddition using a glass microreactor.

$4.0 \, \mu l \, min^{-1}$ and hence increasing the amount of light absorbed by the reactants, conversions of up to 60% were achieved.
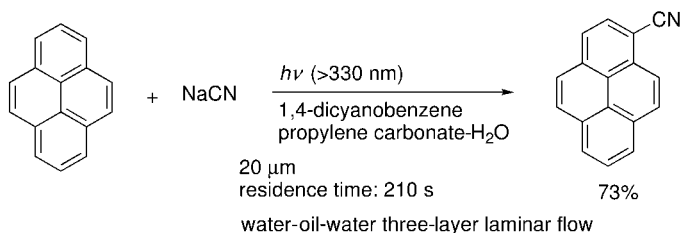
Using a glass microreactor having a 500 μm channel depth, supplied by Mikroglas, Ryu and coworkers modernized the intermolecular [2 + 2]-type cycloaddition of cyclohexenones and alkenes [26]. The device was equipped with a heat-exchanger channel system through which water flowed to maintain isothermal reaction conditions. Using this microreactor, the cycloaddition reaction of 2-cyclohexenone with vinyl acetate gave an 88% yield of cycloaddition product with a 2 h residence time (Scheme 6.10), whereas the same reaction using a Pyrex flask was very sluggish (8% yield after 2 h).

Mizuno and coworkers demonstrated an intramolecular version of [2 + 2] photo-cycloaddition using glass or poly(dimethoxysilane) (PDMS) microreactors (channel dimensions: 100–300 μm wide, 40–50 μm deep) [27]. The reaction using a micro-reactor gave a better regioisomeric ratio than that with a batch reactor, since the possibility of the reverse reaction was reduced by a much shorter residence time, i.e. 1 min, inside the microchannel (Scheme 6.11).

Kitamura and coworkers reported the photocyanation of pyrene using a micro-channel chip (width 100 μm, depth 20 μm, length 350 mm) [28]. Stable organic/

batch (180 min)   74% conversion (73:27)
microflow (1 min), 40 μm   75% conversion (93:7)

Scheme 6.11 Intramolecular [2 + 2] cycloaddition.

Scheme 6.12 Photocyanation of pyrene using a three-layer laminar flow system.

aqueous laminar flow was observed in the microchannel. Whereas a two-layer oil–water system gave only 28% of the desired cyanated product in a 210 s residence time, the yield was improved to 73% by using a water–oil–water three-layer flow system (Scheme 6.12).

6.4
Conclusion

Microreaction technology has already shown a great deal of promise for liquid and liquid-liquid phase reactions, which include transition metal-catalyzed reactions, reactions using organometallic reagents, and photo-induced coupling reactions. In view of the efficient mixing, precise control of reaction temperature and residence time, microreactors would became a promising tool for many organic chemists.

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