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High throughput evaluation of the production of substituted acetylenes by the Sonogashira reaction followed by the Mizoroki–Heck reaction in ionic liquids, in situ, using a novel array reactor

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Abstract—The parallel Sonogashira coupling reaction was carried out under copper-free condition by integrating the advantages of ionic liquids as the reaction media followed by the simultaneous-multiple Mizoroki–Heck reaction in situ by the use of a novel array reactor (SynArray-24). The device provides rapid evaluation of reactions in a short period.

Simultaneous multiple reactions with systematic replacement of reactants, solvents and/or additives such as a base and/or catalysts generate rapid and more efficient evaluation in production of related compounds. Thus, in the last decade, combinatorial and parallel chemical procedures have been employed in concert with high-throughput screening, especially for drug discovery. Recently, an array reactor, designated the SynArray-24 (Fig. 1), was developed for manually operated solution phase chemistry.[1] The present array reactor mimics the simplicity but accommodates the functionality of the classic round-bottom flask.[2]

In recent years room temperature ionic liquids are being considered as potent alternative to volatile organic solvents for numerous catalytic reactions.[3] Facile immobilization of the metal-catalyst, easy work-up and quick separation procedures associated with the ionic liquids make them potential candidates as reaction media for high throughput simultaneous-multiple synthesis.[4] In the present report, we describe utilization of ionic liquid as a reaction medium for the simultaneous-multiple Sonogashira coupling reactions under copper-free conditions.[5]

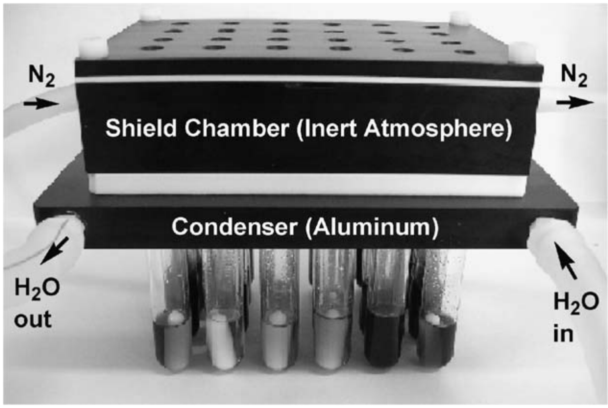

Figure 1. SynArray-24 reactor.

Firstly, we screened for the most suitable ionic liquid for the Sonogashira coupling reaction by the use of the SynArray-24, which allowed rapid and high-throughput

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Keywords: Array reactor; Combinatorial solution synthesis; Sonogashira reaction; Mizoroki–Heck reaction.

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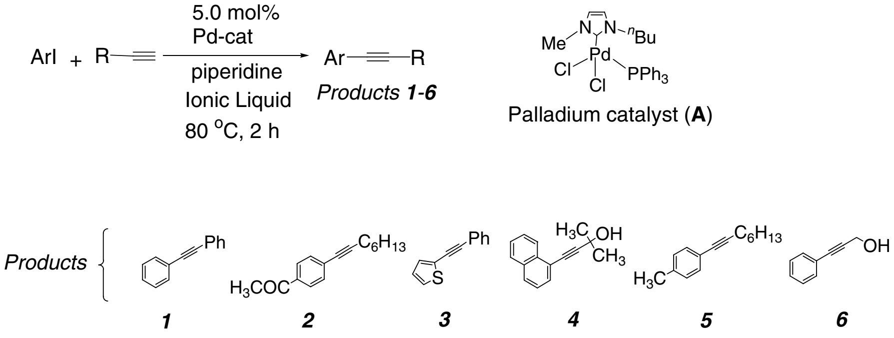
optimization.[1] Twenty-four commercially available culture tubes (13 mm id, 8 mL) are inserted in the holder and fitted with a condenser and a top chamber to allow reflux under inert atmosphere. We carried out a set of six Sonogashira coupling reactions employing a combinations of five different aryl iodides (phenyl iodide, 4-iodoacetophenone, 4-iodotoluene, 1-iodonaphthalene and 2-iodothiophene) and four different terminal alkynes (phenylacetylene, 1-octyne, propargyl alcohol and 2-methyl-3-butyne-2-ol) in four different ionic liquids, that is, 1-butyl-3-methylimidazolium hexafluorophosphate ($[BMIm]PF_6$), 1-butyl-3-methylimidazolium tetrafluoroborate ($[BMIm]BF_4$), 1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide ($[BMIm]NTf_2$) and 1-butyl-1-methylpyrolidinium tetrafluoroborate ($[BMPy]BF_4$) (Scheme 1). We used a palladium–carbene complex **A**[6] as the catalyst, which readily dissolves in ionic liquid. Each of the 24 reaction tubes was charged with 1 mL of ionic liquid (containing 5 mol % Pd–carbene complex **A**), 0.5 mmol aryl iodide, 1.2 equiv terminal acetylene and 3.6 equiv of piperidine and stirred at 80 °C under a nitrogen atmosphere for 2 h.[7] Products were extracted by mixing with suitable organic solvents (3 × 2 mL) and were identified and quantified by ^{1}H NMR.[8] The coupling reactions were quite sluggish in $[BMPy]BF_4$, whereas $[BMIm]PF_6$, $[BMIm]BF_4$ and



	1	2	3	4	5	6
Ionic Liquid-1 $[BMIm]PF_6$	94%[a]	92%	90%	85%	75%	59%
Ionic Liquid-2 $[BMIm]BF_4$	89%	89%	85%	75%	69%	38%
Ionic Liquid-3 $[BMIm]NTf_2$	82%	84%	83%	35%	70%	14%
Ionic Liquid-4 $[BMPy]BF_4$	66%	48%	65%	55%	43%	14%

[a] ^{1}H NMR yields

Scheme 1. Simultaneous-multiple screening of ionic liquid in SynArray-24 reactor.

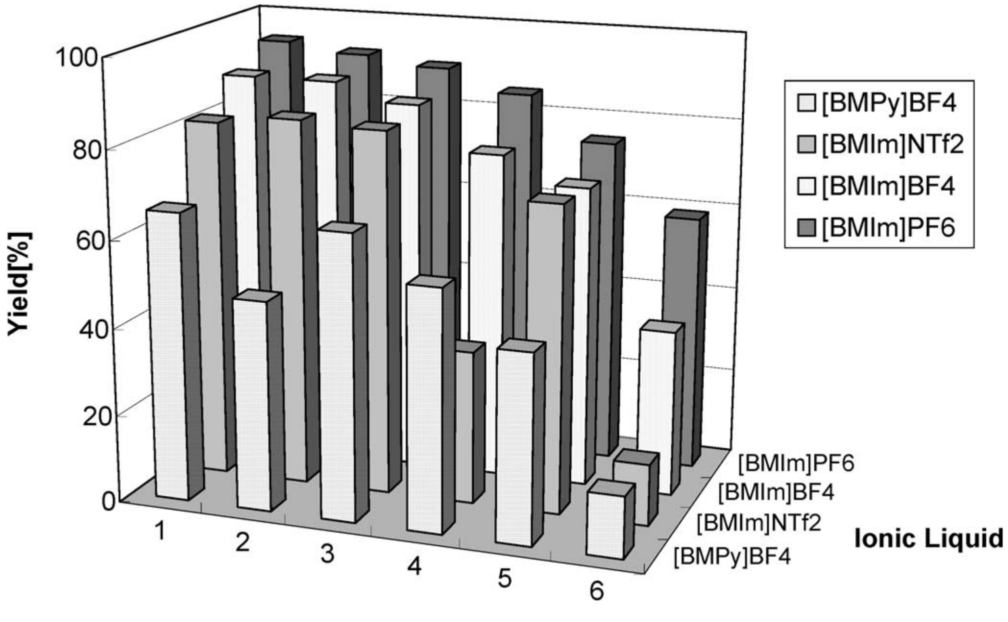


Figure 2. Comparison of efficiency of various ionic liquids used in Sonogashira coupling reactions.

[BMIm]NTf_2, showed comparable efficiency towards the synthesis of **1**, **2**, **3** and **5**. However, [BMIm]PF_6 showed better efficiency when 2-methyl-3-butyne-2-ol and propargyl alcohol were used as the acetylenic coupling partners giving **4** and **6**, respectively. Thus, among the four ionic liquids screened, an overall superior performance of [BMIm]PF_6 could be easily recognized (Fig. 2).

After determining of the most suitable ionic liquid, we employed the array reactor for further parallel syntheses of several 1,2-disubstituted acetylenic compounds. The Sonogashira coupling reactions proceeded well when a variety of aryl iodides, for example, electron-neutral (iodobenzene), electron-deficient (4′-iodoacetophenone) and heterocyclic (2-iodothiophene), were coupled with a variety of both aromatic and aliphatic terminal alkynes, for example (phenylacetylene, 1-octyne, 2-methyl-3-butyne-2-ol and 1-ethynylcyclohexene) (Scheme 2). Nine 1,2-disubstituted acetylenic compounds (**7**–**15**) were obtained in good to excellent yields. The Pd/ionic liquid phase left in each of the tubes was reused in the next reactions in situ.[9]

In the case of catalytic reactions performed in ionic liquids, recycling of the catalyst typically means carrying out a particular reaction with a given set of substrates (e.g., A + B → C) repeatedly, while the catalyst remains substantially active (Fig. 3a). Thus, two more concepts could be added to the well practiced protocol. For example, carrying out (i) a particular reaction (e.g., Sonogashira reaction) taking new substrates in each run (Fig. 3b) and (ii) a different type of reaction with a different set of substrates/reactants in each run (Fig. 3c). The later two concepts would generate more diverse compound libraries from a one-pot recycling operation. In this study, we tested the third concept by carrying out simultaneous-multiple Mizoroki–Heck reactions (Scheme 2) in the recycled mixture of catalyst-ionic liquid. Reactions of aryl iodides with butyl acrylate completed in 1 h, whereas for styrene, a longer reaction time (6 h) was required. The products (**16**–**21**) were obtained in good to excellent yields and, gratifyingly, contained no contamination from the preceding Sonogashira reactions (judged from GC and ^1H NMR analysis of the corresponding reaction mixtures).

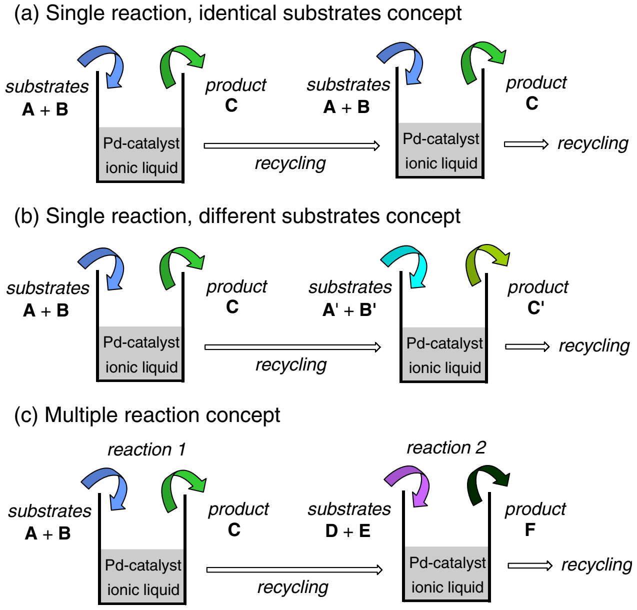
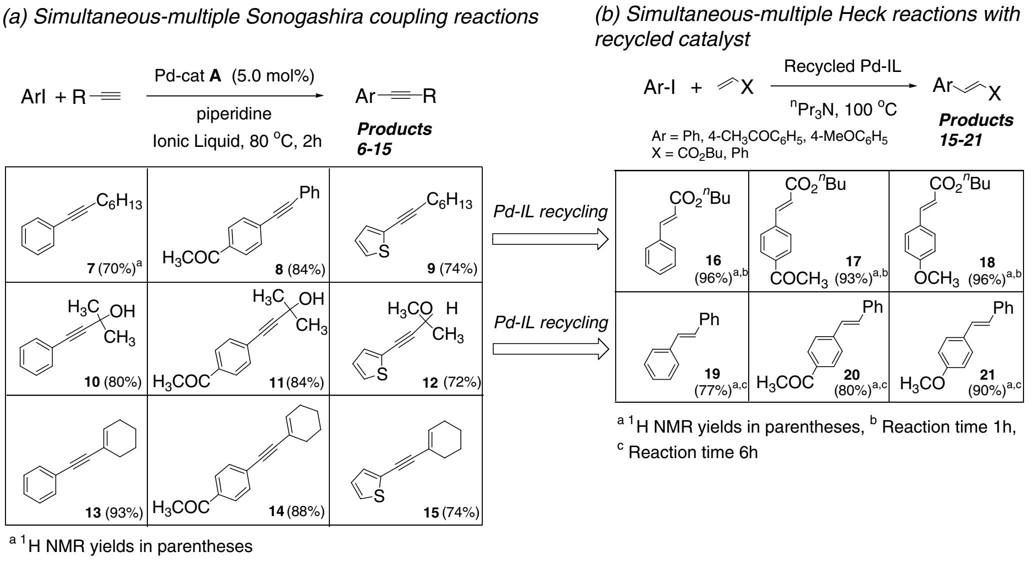


Figure 3. Three types of concepts of catalyst recycling in ionic liquids.

In summary, we have successfully employed the novel array reactor for carrying out palladium-catalyzed reactions in ionic liquid in a parallel fashion. The combination of the array reactor as the reaction device and ionic liquids as the reaction media allowed high throughput and convenient experimental set-up and subsequent workup process. This array reactor has potential applications in many solution phase combinatorial/simultaneous-multiple syntheses. Moreover, the recycling of both costly catalysts and ionic liquids contributes not



Scheme 2. Simultaneous-multiple Sonogashira coupling reactions and Mizoroki–Heck reactions.

only to reaction economics and saving energy but also to environmental protection.

Acknowledgements

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7. The tubes were immersed into a PEG (polyethylene glycol) bath for heating the reaction mixtures.
8. For [BMIm]PF_6 and [BMIm]BF_4 and [BMPy]BF_4, diethyl ether was used for extracting the products, whereas for [BMIm]NTf_2 hexane was used. The yields were calculated based on the aryl iodide used and determined by adding a known quantity of a standard (1,4-dimethoxybenzene).
9. After extracting the products, reaction vessels were removed out of the reactor. The ionic liquid phase was washed with degassed water (2 × 2 mL) to remove the ammonium salt and then dried in vacuo (at 65 °C) for 2 h, then set back into the reactor.