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Use of a silicon carbide multi-well plate in conjunction with microwave heating for rapid ligand synthesis, formation of palladium complexes, and catalyst screening in a Suzuki coupling

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ABSTRACT

The preparation of a library of bis-imidazolium salts and corresponding palladium complexes is reported. These complexes are screened as catalysts in the Suzuki reaction between 4-bromoanisole and phenylboronic acid. Each step is performed in parallel using a 24-position silicon carbide plate and microwave heating. The plate allows for use of standard glass vials as reaction vessels. The ease and speed of operation show the potential for microwave heating in conjunction with the silicon carbide plate as a tool for catalyst screening.

Within the chemistry community, the success of combinatorial and parallel approaches to the synthesis of organic compounds has initiated a real burst of interest in using these techniques in other areas.[1–3] One such application is in the area of catalysis.[4,5] Traditionally, chemists developing new catalysts would decide on which experiments to perform based solely on their prior knowledge and experience. However, not all catalyst space can be covered in a timely manner using this approach. By combining the chemist's insight with parallel screening capability, it is possible to evaluate a large number of catalyst candidates in a faster and more comprehensive manner.[6] Ideally, the preparation of ligands, metallation, and catalyst screening steps all could be performed in a parallel manner (Fig. 1).

Microwave heating has proven to be a useful tool for rapid compound synthesis and has found application in catalysis.[7] By bringing together the concepts of parallel catalyst preparation and screening together with the use of microwave heating, there is potential for rapid development of new catalysts for a range of applications. Ideally, parallel synthesis would be performed using well plates that can be interfaced with peripheral robotic instrumentation for loading, unloading, and cataloging.[8] However, there have some significant problems with the use of standard polypropylene, Teflon, or high-temperature polyethylene well plates in a microwave unit. The most important issue to be overcome is uneven heating across the plate. Wells located on the periphery were at a significantly lower temperature than those located inside due to radiative heat loss as well as lower microwave coupling. Recently, two plates made of silicon carbide have been used for parallel organic synthesis in a microwave unit with success.[9,10] Silicon carbide is an inert, highly microwave absorbing material and has previously been used as a heating insert for reaction mixtures containing non-absorbing reagents or solvents.[11] The use of a silicon carbide plate allows for equal heating of the wells. The 48-position plate proves to be useful for rapid library preparation but each well has a working volume of only 0.1–0.3 mL. The 24-position plate can be used in conjunction with standard glass vials capable of holding 0.3–3 mL of reaction mixture (Fig. 2). In our laboratory, we have performed a study on the heating characteristics of both silicon carbide plates by using organic reactions as probes in addition to using the plates for the preparation of three libraries of compounds.

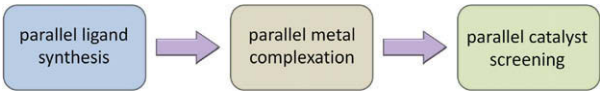

Figure 1. Workflow possible using parallel approach to catalyst design.

We have recently used the 24-position plate in a parallel catalysis project, preparing a range of N-heterocyclic carbene (NHC) ligands, forming palladium complexes from them and screening these in a Suzuki reaction. We report our preliminary results here.[12]

Since Herrmann first reported that palladium complexes bearing NHC ligands efficiently catalyzed the Heck reaction,[13] NHCs have seen great use in a range of metal-catalyzed reactions.[14,15] Indeed, they are now often seen as attractive alternatives to tertiary phosphines. An inherent advantage of NHCs is that their modular design allows for easy derivatization, varying factors such as steric bulk and electronic properties.[16] As a result they are excellent candidates for applications in parallel catalyst design and screening. Palladium complexes bearing NHC ligands can be prepared from

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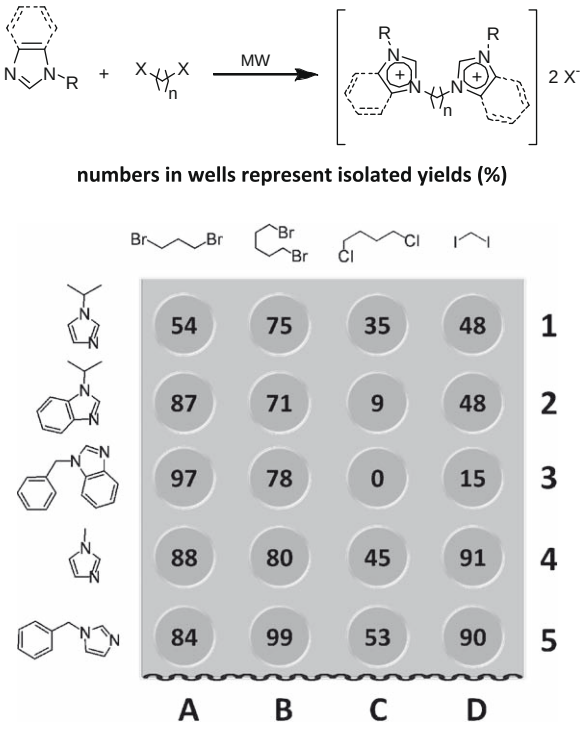
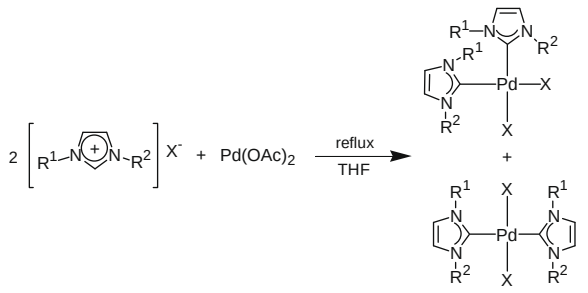


Figure 2. Preparing a library of 20 bis-imidazolium salts in the 24-position plate.



Scheme 1. Preparation of *cis* and *trans* Pd-NHC complexes.

simple palladium salts and imidazolium salts (Scheme 1). We decided to focus our attention on the preparation of bidentate NHC ligands since these form defined complexes with controlled coordination about the palladium center. Previous work in our group using monodentate NHC complexes has shown that while cis-disubstituted square planar complexes formed by reaction of palladium acetate with imidazolium salts are catalytically active in Heck coupling reactions, the trans-isomers are significantly less so.[17] When using bis-imidazolium salts as precursors, given that the tether between the heterocyclic moieties is not long, only the cis-isomer would be expected.

Microwave heating has been used for the preparation of imidazolium salts (ionic liquids) rapidly and with ease.[18] We prepared a library of twenty bis-imidazolium salts using the 24-position silicon carbide block, choosing four dihaloalkanes and five imidazole-based starting materials.[19,20] We loaded glass vials with the reagents (2 mmol dihaloalkane and 4 mmol imidazole) together with 1 mL ethyl acetate as a solvent. We then sealed all the vials with PEEK screw caps equipped with PTFE seals. They were then placed into the silicon carbide plate. The microwave unit is capable of holding four of the plates in a rotor. We performed all our reactions in one plate but for even distribution we placed an empty plate in the vacant diagonally opposite position. The plates were heated over a 5-min period to an external temperature of 140 °C as monitored using an IR sensor located at the bottom of the microwave unit. This corresponds to a temperature of ~156 °C inside the wells. The plates were held at this temperature for 10 min before allowing to cool to 50 °C, this takes approximately 15 min. We then isolated the bis-imidazolium salts formed. Isolated yields are shown schematically in Figure 2. Many of the salts are solids at room temperature and thus could be isolated with relative ease. Others are viscous liquids and were purified by silica gel chromatography. Of the twenty reactions performed, we isolated nineteen bis-imidazolium salts; one reaction yielding no product (C3).

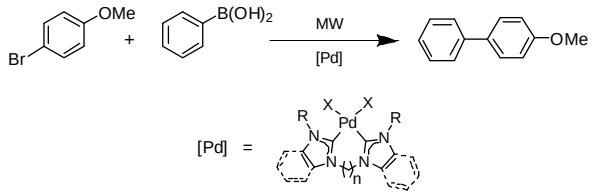
With the bis-imidazolium salts in hand we turned our attention to preparing palladium complexes and screening them in the Suzuki coupling of 4-bromoanisole with phenylboronic acid.[21,22] Our objective was to prepare the palladium complexes by heating the salts and palladium acetate in the plate and then, after allowing the vials to cool, adding an aliquot of aryl halide, boronic acid, and a base to each vial before then re-heating to effect the Suzuki coupling.

We sequentially placed 0.01 mmol of a bis-imidazolium salt together with 0.01 mmol palladium acetate and 1 mL THF into vials. We also loaded a vial with just 0.01 mmol palladium acetate and 1 mL THF to serve as a control (A6) for the Suzuki coupling protocol, that is, with no added bis-imidazolium salt as a ligand. The vials were sealed and replaced in the plate and then heated to a target external temperature of 110 °C (internal temperature of ~125 °C) over the period of 5 min. The plate was allowed to cool before adding to each vial 2 mmol potassium carbonate and 1 mL THF solution containing 1 mmol bromoanisole and 1.1 mmol phenylboronic acid. We also prepared a second control vial (B6) containing 0.01 mmol $Pd(OAc)_2$, 2 mmol K_2CO_3, and 2 mL THF solution containing 1 mmol bromoanisole and 1.1 mmol phenylboronic acid. All the vials were re-sealed, placed back in the plate, and re-heated to a target external temperature of 110 °C (internal temperature of ~125 °C) over the period of 5 min and held at that temperature for 5 min. Upon cooling we assayed the contents of each vial, determining the conversion to biaryl. The results are shown in Figure 3.

We knew from previous studies that the reaction would not be complete within the short heating time used. By stopping the reaction before completion, we can better assess the activity of each palladium complex. If the reaction is run significantly longer, many of the assays could show similar final conversion, thus not allowing us to differentiate between the complexes screened.

The highest yield of biaryl was obtained using the palladium complex originating from the bis-imidazolium salt formed from 1,4-dichlorobutane and *N*-isopropylbenzimidazole (C2). Of note is that the yields in the Suzuki coupling using catalysts bearing ligands derived from diiodomethane (D1–D5) were uniformly lowest of all the dihaloalkanes used. This could be due to the steric constraints of the bis-imidazolium salt and poor reactivity with the palladium acetate precursor, such that little of the NHC complex was formed to catalyze the Suzuki coupling. This is consistent with the observation that the control reaction in A6 also shows a poor yield. In this case, no bis-imidazolium salt was added to the reaction mixture in the metallation step. The second control reaction (B6) gave a higher yield indicating that heating (then cooling) palladium acetate in THF, as is the case with the control in A6, has a deleterious effect on its catalytic activity in the Suzuki coupling.

In summary, we have prepared a library of bis-imidazolium salts. These were then reacted with palladium acetate to form metal-NHC complexes which were then screened as catalysts in the Suzuki reaction between 4-bromoanisole and phenylboronic acid. Each of these sequential steps was performed in parallel using a 24-position silicon carbide plate and microwave heating. The plate



numbers in wells represent product conversions (%) determined by ^{1}H NMR spectroscopy

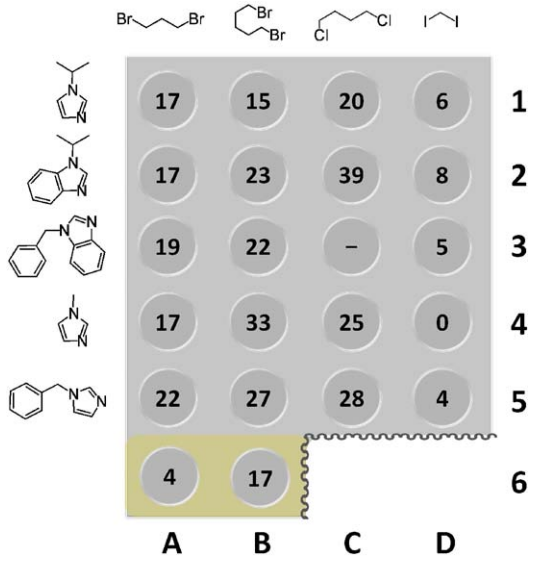


Figure 3. Screening a library of catalysts in a Suzuki coupling protocol. [For ease of reference between Figures 2 and 3, we show the components making up the bisimidazolium salt but report the yield from the Suzuki coupling reaction].

allows for use of standard glass vials as reaction vessels. The ease and speed of operation show the potential for microwave heating in conjunction with the silicon carbide plate as a tool for catalyst screening. Work is now underway in our laboratory to use this as a tool for optimizing a range of metal-catalyzed C–C and C–N bond-forming reactions using a parallel approach.

Acknowledgments

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20. A solution of *N*-alkyl(benz)imidazole (4 mmol) and dihaloalkane (2 mmol) in ethyl acetate (1 mL) was placed in a Wheaton® 15 × 46 mm screw cap vial equipped with a small Teflon-coated magnetic stirbar. The vial was sealed, capped, and placed into a well of the 24-position silicon carbide plate. Once all the vials had been loaded, the filled plate was placed onto the rotor together with an empty plate on the diagonally opposite position, the protective top cover locked in place and then the entire rotor assembly placed into the microwave unit. The plates were heated to an external temperature of 135 °C as measured by the IR sensor (~150 °C internal temperature) over a 10-min period ramping up to a microwave power of 800 W. The plate was then held at this temperature for an additional 10 min. Upon cooling, many of the products crystallized. They were filtered and washed with petroleum ether. Those that did not crystallize or that crystallized as a mixture were purified via a silica gel plug using ethyl acetate to elute the starting materials followed by 1:1 dichloromethane:methanol (v:v) mixture to elute the product.
21. *Formation of the palladium complexes*: Palladium acetate (2.2 mg, 0.01 mmol) was combined with bis-imidazolium salt (0.01 mmol) in THF (1 mL) in a Wheaton® 15 × 46 mm screw cap vial equipped with a small Teflon-coated magnetic stirbar. The vial was sealed, capped, and placed into a well of the 24-position silicon carbide plate. Once all the vials had been loaded, the filled plate was placed onto the rotor together with an empty plate on the diagonally opposite position, the protective top cover locked in place and then the entire rotor assembly placed into the microwave unit. The plates were then heated with a 5-min ramp to 1000 W and a programmed maximum external IR temperature of 110 °C (~125 °C internal), then cooled.
22. *Suzuki coupling protocol*: A THF solution (1 mL) of 4-bromoanisole (1.0 M) and phenyl boronic acid (1.1 M) and potassium carbonate (276 mg, 2.0 mmol) were combined with the mixtures resulting from the preparation of the palladium complexes. The vials were re-sealed and capped, replaced in the silicon carbide plate and loaded onto the rotor. The plates were then heated with a 5-min ramp to 1000 W followed by a 5-min hold with a programmed maximum external IR temperature of 110 °C, then cooled. Crude conversion was determined by ^{1}H NMR.