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## Rapid, easy copper-free Sonogashira couplings using aryl iodides and activated aryl bromides

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Abstract—We present here an easy, rapid copper-free methodology for the Sonogashira coupling reaction. It works well for a range of aryl iodides and activated aryl bromides.

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The Sonogashira reaction (palladium and copper cocatalyzed coupling of terminal alkynes with aryl and vinyl halides) is one of the most widely used C-C bond forming reactions.<sup>1,2</sup> It provides an efficient route to aryl alkynes, which are interesting intermediates for the preparation of a variety of target compounds with applications ranging from natural products<sup>3</sup> and pharmaceuticals<sup>4</sup> to molecular organic materials<sup>5</sup> Due to the use of the products, the development of new catalyst systems has received considerable attention. The reaction is generally carried out in organic solvents such as benzene, toluene, THF, DMF and dioxane. It requires a base, which is usually an amine such as triethylamine, diethylamine, diisopropylethylamine. The most widely used catalysts are Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> or  $Pd(PPh_3)_4$  in conjunction with copper(I) iodide. The reaction has been applied to vinyl halides, aryl iodides and bromides and, exceptionally, aryl chlorides.

In the case of aryl iodides and vinyl halides, the Sonogashira reaction can sometimes be carried out under mild conditions, possibly at room temperature, but generally the reaction times are relatively long.<sup>6</sup> The use of higher temperatures and the presence of copper favours side reactions of the terminal acetylenes.<sup>7,8</sup> One way around this problem is to develop a copper-free methodology. There have been a number of recent reports of this, most involving the use of an amine, such as piperidine, triethylamine or pyrrolidine, as a solvent,<sup>9,10</sup> or in large excess.<sup>11,12</sup> These methods can also be adapted to use in conjunction with aqueous solvent mixtures by using an ammonium salt as a phase-transfer agent.<sup>13,14</sup> A copper-free coupling of aryl iodides with terminal alkynes has also been reported using an ionic liquid as a solvent.<sup>15</sup> This enables easy separation of the product from the catalyst-ionic liquid system, which could then be reused. Recently, an amine and copper free methodology for the Sonogashira reaction has been presented.<sup>16</sup> A palladacycle catalyst and an additive, tetrabutylammonium acetate, are employed.

The problems with many of these copper-free methodologies however are that either high palladium catalyst loadings have to be used or else the reaction has to be performed under anaerobic conditions using palladium complexes or ligands that are expensive or hard to make. We wanted to develop an easy, quick copper-free methodology for the Sonogashira reaction that uses readily available palladium complexes and can be run in air and without having to pre-dry reagents and without the need for any solvent.

As a starting point for the development of the methodology we chose to study the coupling of phenylacetylene with 4-iodoanisole. Our optimisation data are shown in Table 1. We found that using 4 mol% Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> as the catalyst and 3.0 equiv. of piperidine as a base it was possible to obtain a quantitative yield of product within 10 min by dipping the reaction mixture into an oil bath pre-heated to 70°C (Table 1, entry 1). We then varied the base and catalyst loading. Triethylamine and pyrrolidine gave good product yields (Table 1, entries 2 and 3). No product was obtained using mineral bases with or without the use of water

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and a phase-transfer catalyst (Table 1, entries 4 and 5). We found that when using piperidine the catalyst loading can be lowered to 2 mol% without any significant decrease in product yield in the 10 min reaction time but this could be lowered further to 1 mol% if the time was extended to 15 min and to 0.5 mol% of the time was extended to 20 min (Table 1, entries 6–8). As an extension of our studies, we tried using phosphine-free sources of palladium as catalysts in conjunction with our copper-free conditions but had no success with palladium acetate or palladium on charcoal. We also tried using palladium on charcoal in the presence of triphenylphosphine, a catalyst system known to work in the presence of copper.<sup>17</sup> but found that it does not work in the absence of copper.

Having optimized the reaction conditions for aryl iodides we turned our attention to aryl bromides. Results are shown in Table 2. From a screen of the reaction between phenylacetylene and 4-bromoacetophenone, 4-bromotoluene and 4-bromoanisole with 4 mol% Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> as the catalyst and 3.0 equiv. of piperidine as the base, it was possible to see that the copper-free conditions worked only for the case of the activated substrate (Table 2, entries 1-3). A 99% yield of the desired product was formed within 10 min using 4-bromoacetophenone. With this in mind, we focused on the coupling of phenylacetylene and 4-bromoacetophenone and investigated the effects of decreasing the catalyst loading. We found that reduction of the catalyst loading to 3 mol% led to a product yield of 82%, increasing the reaction time to 15 min increased the yield to 91% (Table 2, entries 4 and 5). A 96% yield of product was obtained after 20 min using 2 mol% catalyst and a yield of 73% obtained after 30 min using 1 mol% (Table 2, entries 6 and 7). Using 0.5 mol% catalyst gave only a 46% yield after 1 h (Table 2, entry 8).

 Table 1. Screening of conditions for the Sonogashira coupling of 4-iodoanisole with phenylacetylene<sup>a</sup>

$HeO + Ph = \frac{Pd(PPh_2)_2Cl_2}{Ph} Ph = OMe$								
Entry	Base	Catalyst loading (mol%)	Time (min)	Yield (%) <sup>b</sup>				
1	Piperidine	4	10	>99				
2	NEt <sub>3</sub>	4	10	>99				
3	Pyrrolidine	4	10	>99				
4	Na <sub>2</sub> CO <sub>3</sub>	4	10	0				
5	Na <sub>2</sub> CO <sub>3</sub> <sup>c</sup>	4	10	0				
6	Piperidine	2	10	>99				
7	Piperidine	1	15	>99				
8	Piperidine	0.5	20	>99				

<sup>a</sup> Reactions were run using 1 mmol 4-iodoanisole, 1 mmol phenylacetylene and 3 mmol base. The reaction mixture was placed in a pre-heated oil bath at 70°C and held there for the allotted time.
<sup>b</sup> Not isolated.

<sup>c</sup> With 0.2 mL water and 1 mmol tetrabutylammonium bromide.

 Table 2. Screening of conditions for the Sonogashira coupling of bromoarenes with phenylacetylene<sup>a</sup>

R	Br + Ph-==	Pd(PPh <sub>2</sub> ) <sub>2</sub> Cl <sub>2</sub>	► Ph==	≡∕R
Entry	Aryl bromide	Catalyst loading (mol%)	Time (min)	Yield (%) <sup>*</sup>
1	Br	4	10	>99
2	Br	4	10	16
3	Br	4	10	6
4	Br	3	10	86
5	Br	3	15	91
6	Br	2	20	96
7	Br	1	30	73
8	Br	0.5	60	46

a) Reactions were run using 1 mmol aryl halide, 1 mmol phenylacetylene,
3 mmol piperidine. The reaction mixture was placed in a pre-heated oil bath at 70 °C and held there for the allotted time.
b) Not isolated.

We screened a representative range of aryl iodides and activated bromides in the reaction, the results being shown in Table 3. For the aryl iodides we used 2 mol% of catalyst, piperidine as the base and a reaction time of 10 min.<sup>18</sup> We chose aryl iodides from across the spectrum of those bearing electron-donating and electronwithdrawing substituents (Table 3, entries 1-8). For the aryl bromides we focused on activated examples and used the same conditions but increased the catalyst loading to 4 mol% (Table 3, entries 9–12).<sup>19</sup> All the reactions were performed in air and using reagents without any further purification. As there is no copper present, we do not have the problems often encountered of homo-coupling of the alkyne substrate and hence do not need to take any particular precautions in this regard such as, for example, running the reactions under a hydrogen atmosphere.<sup>20</sup>

The results show that the methodology is applicable to a range of aryl iodide and activated aryl bromide substrates with good product yields being obtained. The exception to this is 2-iodotoluene (Table 3, entry 4) where we believe that steric congestion may be a problem although this is somewhat surprising in light of the fact that 2-iodobenzylalcohol couples smoothly (Table 3, entry 8). We also screened representative aryl iodide

Table 3. Screening of conditions for the Sonogashira coupling of 4-iodoanisole with phenylacetylene<sup>a</sup>

X = Br, I, S = substituent, R = Ph, Me<sub>3</sub>Si, C<sub>4</sub>H<sub>9</sub>

Entry	Aryl halide	Alkyne	Yield (%)	Entry	Aryl halide	Alkyne	Yield (%)
1	OMe		91 <sup>b</sup>	12	Br		99°
2	COMe	—	93 <sup>b</sup>	13	OMe	—	79 <sup>d</sup>
3		—	94 <sup>b</sup>	14		—	72 <sup>d</sup>
4		—	0 <sup>b</sup>	15	COMe	—	96 <sup>d</sup>
5		—	96 <sup>b</sup>	16	OMe	Me <sub>3</sub> Si— <del>——</del>	99 <sup>e</sup>
6	ОН	—	92 <sup>b</sup>	17	OMe	с <sub>4</sub> н <sub>9</sub> — <del>—</del>	96 <sup>e</sup>
7	NO <sub>2</sub>	—	99 <sup>b</sup>	18		Me <sub>3</sub> Si— <del>—</del>	99 <sup>e</sup>
8	ОН	—	99 <sup>b</sup>	19	ОН	Me <sub>3</sub> Si— <del>—</del>	40 <sup>e</sup>
9	Br	—=	94 °	20	Br	Me <sub>3</sub> Si— <b>——</b>	75°
10	Br NO2	—	90 °	21	OMe	Me <sub>3</sub> Si— <del>——</del>	28 <sup>d</sup>
11	Br	—	74 °	22	OMe	—	99 <sup>f</sup>

a) Reactions were run using 1 mmol aryl halide, 1 mmol phenylacetylene, 3 mmol piperidine. The reaction mixture was placed in a pre-heated oil bath at 70 °C and held there for the allotted time

b) 2 mol % Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>, reaction time of 10 min

c) 4 mol % Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>, reaction time of 10 min

d) 0.5 mol % Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>, reaction time of 20 min

e) 2 mol % Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> reaction time of 10 min

f) Run on 10 mmol scale. 2 mol % Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> reaction time of 10 min.

substrates using the lower catalyst loading of 0.5 mmol and a reaction time of 20 min to show that this is applicable to the range of aryl iodides from those bearing electron-donating substituents through to those containing electron-withdrawing ones (Table 3, entries 13-15). We then wanted to expand the methodology for use with aliphatic alkynes so screened as examples trimethylsilylacetylene and 1-hexyne. With these we found that the higher catalyst loading is required in order for the reaction to reach completion within a short time (Table 3, entries 16-21).

To show that the reaction can be scaled up without compromising the yield, the reaction of 4-bromotoluene

with phenylacetylene was repeated on a 10 mmol scale with a product yield of 99% being obtained (Table 3, entry 22).<sup>21</sup>

The closest similar methodology to ours (and indeed the one on which ours builds) is that of Linstrumelle and co-workers.<sup>10</sup> In their paper they present the copper-free coupling of iodobenzene, bromobenzene and two vinyl halides with a number of alkynes. They use a high palladium loading (5 mol% Pd(PPh<sub>3</sub>)<sub>4</sub>) and the reactions are run under anaerobic conditions. They also use the base as a solvent and reaction times for the arene substrates vary from 2 to 25 h. We repeated their methodology but using 4-iodoacetophenone and phenylacetylene as substrates. We obtained a 79% yield of product after 18 h. Our methodology is certainly easier, faster and requires less catalyst. Although the substrate scope of aryl bromides is not as wide as that of Bohm and Herrmann<sup>11</sup> or Najera and co-workers,<sup>16</sup> comparison shows that for aryl iodide substrates our method is certainly faster and easier.

In conclusion, we have developed a methodology for easy and rapid copper-free Sonogashira couplings. The methodology has the advantage of short reaction times, ease of reaction and the use of a readily available palladium complex. The quantity of amine used is much less than previously reported for copper-free protocols. Attempts to develop the methodology further and increase its scope are currently underway in our laboratory.

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- 18. Procedure for coupling aryl iodides to alkynes: In a 10 mL glass tube was placed aryl iodide (1.0 mmol), alkyne (1.0 mmol), piperidine (0.3 mL, 3 mmol), PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (14 mg, 0.02 mmol) and a magnetic stir bar. The vessel was sealed with a septum and placed in an oil bath pre-heated to 70°C and held there for 10 min. After this time, the reaction vessel was opened and the contents poured into a separating funnel and the tube washed with water and then with ether, these washings being added to the separating funnel. Further water and diethyl ether (20 mL of each) were added and the organic material extracted and then washed with acid (15% v/v HCl) until the washings were neutral. The organic layer was again washed with water (40 mL) before being dried over MgSO<sub>4</sub> and the ether removed under vacuum leaving the crude product. Products were characterized by comparison of <sup>1</sup>H and <sup>13</sup>C NMR spectra with those of authentic samples or in the literature and yields determined by NMR with reference to a known quantity of an internal standard.
- 19. Procedure for coupling aryl bromides to alkynes: In a 10 mL glass tube was placed aryl bromide (1.0 mmol), alkyne (1.0 mmol), piperidine (0.3 mL, 3 mmol), PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (28 mg, 0.04 mmol) and a magnetic stir bar. The reaction was run and worked up in an identical manner as for the aryl iodides.
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- 21. Procedure for the 10 mmol scale coupling of 4-iodoanisole to phenylacetylene: In a 150 mL capacity Schlenk tube was placed aryl iodide (10 mmol), phenylacetylene (1.1 mL, 10 mmol), piperidine (3 mL, 30 mmol), PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (140 mg, 0.2 mmol) and a magnetic stir bar. The vessel was sealed with a septum and placed into an oil bath pre-heated to 70°C and held there for 10 min. The reaction was worked up in an identical manner as for the reactions on a 1 mmol scale.