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# ppm Pd-catalyzed, Cu-free Sonogashira couplings in water using commercially available catalyst precursors†

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A new catalyst that derives from commercially available precursors for copper-free, Pd-catalyzed Sonogashira reactions at the sustainable ppm level of precious metal palladium under mild aqueous micellar conditions has been developed. Both the palladium pre-catalyst and ligand are commercially available, bench stable, and highly cost-effective. The catalyst is applicable to both aryl- and heteroaryl-bromides as educts. A wide range of functional groups are tolerated and the aqueous reaction medium can be recycled. An application to a key intermediate associated with an active pharmaceutical ingredient (ponatinib) is discussed.

## Introduction

Development of a Pd-catalyzed process that leads to coupling between a terminal alkyne and an aromatic/heteroaromatic ring by Sonogashira and co-workers back in 1975 (ref. 1) focused on providing an alternative to the corresponding reaction mediated solely by copper, the Castro–Stevens coupling. Today, Sonogashira couplings no longer require use of both catalytic Pd and Cu; rather, catalytic Pd alone is quite sufficient when appropriately complexed by a ligand more modern than the  $\text{Ph}_3\text{P}$  originally employed. Among the array of highly valued Pd-catalyzed coupling reactions, Sonogashira couplings remain unique due to the involvement of an sp carbon center, and are widely utilized in the pharmaceutical industry<sup>2</sup> and in natural products total synthesis,<sup>3</sup> as well as in the construction of organic materials.<sup>4</sup> Nonetheless, improvements continue, looking to enhance functional group tolerance and yields, avoidance of occasional harsh reaction conditions and problematic workups, as well as avoidance of more expensive and sensitive coupling partners (e.g., iodides).<sup>2c,5</sup> Also looming big is the up front cost of Pd catalysts and associated expensive ligands, typically used in the 1–5 mol% range, while at the back end, required removal of residual metal embedded within the desired products is to be expected and must be removed especially when working towards an API.<sup>6</sup> Moreover, from the environmental perspective, most Sonogashira couplings are run in organic solvents, without recycling of either the medium or

precious metal catalyst.<sup>7</sup> Use of these traditional reaction parameters dramatically increase levels of both the organic and aqueous waste to be expected, and fail to acknowledge the endangered status of platinoids.<sup>8</sup>

Previously, we disclosed a sustainable technology for ppm level Pd-catalyzed Sonogashira cross-couplings based on the new ligand HandaPhos, enabled by aqueous micellar catalysis.<sup>9</sup> This approach reduces usage of Pd to a sustainable 1000 ppm (0.1 mol%) loading, without participation by copper. At issue, however, is the preparation of HandaPhos,<sup>10</sup> following the sequence first outlined by Boehringer-Ingelheim,<sup>11</sup> requiring 10 steps. Herein we describe an alternative technology that maintains the ppm level of palladium catalysis under aqueous micellar conditions, but which benefits from readily available precursors that are items of commerce and hence, makes this approach more accessible and far more economically attractive.

## Results and discussion

Based on our earlier work describing room temperature Sonogashira reactions in aqueous nanoreactors derived from the designer surfactant PTS,<sup>12</sup> we re-examined the BRIDP family of ligands developed by Takasago.<sup>13</sup> Screening initially at 1300 ppm (0.13 mol%) of various sources of Pd in 2<sup>nd</sup> generation micellar media (TPGS-750-M/ $\text{H}_2\text{O}$ ) indicated that, yet again, cBRIDP (Scheme 1) imparts the greatest reactivity (also see ESI†).

The source of Pd was also crucial for Sonogashira couplings at the ppm level of this metal. Hence, increasing the lipophilicity of the allylic ligand on Pd (by going from allyl to crotyl to cinnamyl), presumably increasing the binding constant of this catalyst to the inner micellar core,<sup>14</sup> afforded the most effective and active catalyst system. The increased bulkiness at the 1-position may also play an activating role by minimizing formation of less reactive Pd(I) dimeric species, as noted

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**Scheme 1** Structures of cBRIDP ligand, pre-catalyst  $[\text{Pd}(\text{cinnamyl})\text{Cl}]_2$  and *in situ*-derived catalyst **1** used in this model reaction.

previously by Hazari<sup>15</sup> and Colacot.<sup>16</sup> The most effective combination ultimately led to use of a 3 : 1 ratio of ligand to palladium. K<sub>3</sub>PO<sub>4</sub>·H<sub>2</sub>O was found to be the best base for liquid starting materials. However, when the bromide or terminal alkyne is a solid, the resulting viscosity of the medium caused by the (solid) base was found to inhibit stirring. In this case the base could be readily changed to Et<sub>3</sub>N. From these reaction parameters, a variety of substrate combinations using 0.05 mol% of dimeric  $[\text{PdCl}(\text{cinnamyl})]_2$  (*i.e.*, 1000 ppm) was screened (Table 1(A)). At these low levels of handling, the catalyst was added to the reaction vial in the form of a pre-mixed THF stock solution, after which the small amounts of THF were easily removed under vacuum. For substrates that appeared to be more challenging (*e.g.*, slower or incomplete reactions), 1500 ppm (0.15 mol%) of the same palladium pre-catalyst was found to be very effective (Table 1(B)).

Judging from the results shown in Table 1, this new catalytic system displays high functional group compatibility. Heteroaryl bromides leading to 2-, 3-, and 4-substituted pyridines (**3**, **4**, **8**, **11**, **19**), quinoline (**6**), furan (**5**), benzothiophene (**10**), thiophene (**15**), and indole (**16**) were all converted to their corresponding coupling products in good-to-excellent yields. Similarly, sensitive functional groups are tolerant, as in products containing chloro (**9**, **11**, **12**, **14**), enyne (**3**), fluoro (**3**, **5**, **8**, **9**), trifluoromethyl (**12**, **20**), ketone (**4**), aldehyde (**5**, **14**, **15**), thioether (**2**), amide (**7**), acetal (**9**, **17**, **18**), hydroxyl (**6**), ester (**17**, **19**) and carbamate (**16**) residues. Product **13** could be readily generated in gram quantities (*i.e.*, on a 5 mmol scale). Notably, this gram-scale reaction could be carried out with solid palladium pre-catalyst and ligand; *i.e.*, without pre-dissolution in THF.

The products of these reactions<sup>17</sup> produce alkynes attached to aromatic or heteroaromatic rings, which represent electron-withdrawing groups that may provide additional activation useful for secondary processes. For example, as illustrated in Scheme 2 below, a 2-step, 1-pot sequence, initiated by a Sonogashira cross-coupling, is then followed (without isolation or added base) by a selective S<sub>N</sub>Ar reaction to install a diamine-containing residue common to many biologically active compounds.<sup>18</sup> Both reactions take place in virtually quantitative yields to afford internal alkyne **23**.

At typical loadings of Pd in the 1–5 mol% range, residual amounts of Pd in the hundreds of ppm range are to be

**Table 1** Representative Sonogashira couplings in water catalyzed by (A) 1000 or (B) 1500 ppm Pd<sup>a,b</sup>

$(\text{Het})\text{Ar}-\text{Br} + \equiv \text{R} \xrightarrow[\text{K}_3\text{PO}_4 \cdot \text{H}_2\text{O} (2.0 \text{ equiv})]{[\text{cinnamyl}]\text{PdCl}_2 (500-750 \text{ ppm})}$   
 $\text{cBRIDP (3000-4500 ppm)}$   
 $2 \text{ wt } \% \text{ TPGS-750-M/H}_2\text{O, } 45^\circ\text{C}$

**A**

**2**  
 (5 h, 96%)

**3**  
 (16 h, 87%)

**4**  
 (3 h, 88%)

**5**  
 (18 h, 82%)

**6**  
 (12 h, 74%)<sup>c</sup>

**7**  
 (22 h, 98%)<sup>c,e</sup>

**8**  
 (3 h, 97%)<sup>c</sup>

**9**  
 (43 h, 70%)<sup>c,e</sup>

**10**  
 (43 h, 96%)<sup>e</sup>

**11**  
 (5 h, 88%)

**12**  
 (13 h, 86%)<sup>c,d</sup>

**13**  
 (8 h, 95%)<sup>c</sup>  
 (8 h, 87% / 1.27 g)<sup>c</sup>

**B**

**14**  
 (50 h, 83%)

**15**  
 (44 h, 81%)

**16**  
 (48 h, 93%)<sup>c</sup>

**17**  
 (44 h, 88%)

**18**  
 (51 h, 62%)

**19**  
 (42 h, 98%)<sup>c</sup>

**20**  
 (45 h, 83%)

**21**  
 (50 h, 98%)

**22**  
 (45 h, 88%)

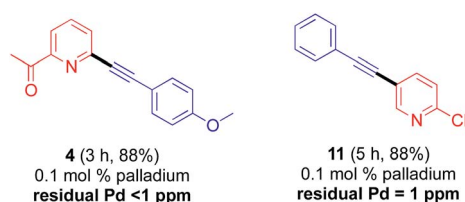
<sup>a</sup> Conditions: bromide (0.5 mmol),  $[(\text{cinnamyl})\text{PdCl}]_2$  (0.05 mol%), cBRIDP (0.30 mol%), terminal alkyne (0.60 mmol), K<sub>3</sub>PO<sub>4</sub>·H<sub>2</sub>O (2.0 equiv.), TPGS-750-M/H<sub>2</sub>O (2 wt%, 1 mL), 45 °C, Ar. <sup>b</sup> Isolated yield. <sup>c</sup> Et<sub>3</sub>N (2.0 equiv.) as base. <sup>d</sup> Reaction run at 35 °C, 1.1 equiv. of terminal alkyne used. <sup>e</sup> 1.5 equiv. of terminal alkyne used.

expected, requiring removal especially when associated with an API. Process chemists have developed systematic methods<sup>6,19</sup> so as to meet FDA regulations for palladium allowance.<sup>20</sup> ICP-MS tests indicated that products from these ppm level Pd-catalyzed Sonogashira couplings contain less than 1 ppm when run at a loading of 1000 ppm palladium (Scheme 3), amounts which are well below acceptable levels.



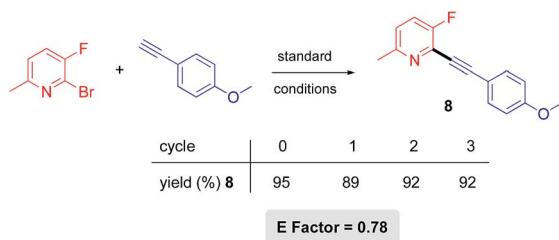


Scheme 2 2-Step, 1-pot process using an initial 1000 ppm Pd-catalyzed Sonogashira coupling in water.

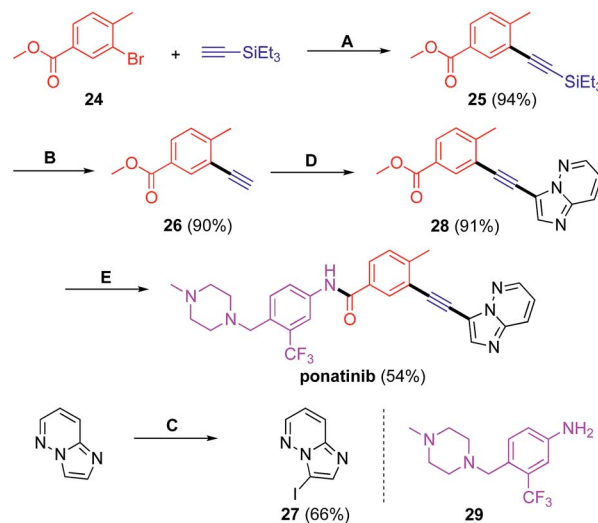


Scheme 3 ICP-MS analyses of residual palladium in products 4 and 11.

Other features associated with this ppm Pd chemistry in water include the facile recycling of the aqueous TPGS-750-M solution being used, and the low *E* factor suggestive of the limited amounts of waste being created. Rather than using an “in flask” extraction process that requires only small amounts of an organic solvent, as done in our previous study,<sup>21</sup> an even lower *E* factor can be achieved by simply filtering the solid product that precipitates out from the reaction. The aqueous filtrate containing the surfactant, engineered to remain in the water, can be collected and used for subsequent couplings. In these cases, the crude product was washed with small amounts of DI water and air-dried. Hence, the only organic solvent required for this reaction is THF, used to prepare the stock solution of catalyst. The resulting *E* factor based on this reaction, as a measure of “greenness”,<sup>22</sup> is only 0.78 (see ESI†). As indicated previously with respect to the gram-scale reaction, preparation of a stock solution is actually not necessary for this reaction, in which case the *E* factor goes to zero. The aqueous



Scheme 4 Recycling study and *E* factor determination.



Scheme 5 Synthesis of ponatinib. Conditions: step: (A) **24** (1.0 equiv.), (triethylsilyl)acetylene (2.0 equiv.), [(cinnamyl)PdCl]<sub>2</sub> (0.075 mol%), cBRIDP (0.45 mol%), Et<sub>3</sub>N (2.0 equiv.), 0.5 M in 2 wt% TPGS-750-M/H<sub>2</sub>O, 45 °C, Ar, 45 h; step: (B) **25** (1.0 equiv.), K<sub>2</sub>CO<sub>3</sub> (20 mol%), 0.5 M in 1 : 1 MeOH/THF, 45 °C, 5 h; step: (C): imidazo[1,2-*b*]pyridazine (1.0 equiv.), *N*-iodosuccinimide (1.2 equiv.), 0.53 M in DMF, 80 °C, Ar, overnight; step: (D): **27** (1.0 equiv.), **26** (1.2 equiv.), [(cinnamyl)PdCl]<sub>2</sub> (0.075 mol%), cBRIDP (0.45 mol%), Et<sub>3</sub>N (2.0 equiv.), 0.5 M in 2 wt% TPGS-750-M/H<sub>2</sub>O, 45 °C, Ar, 47 h. Step (E): **28** (1.0 equiv.), 4-(4-methyl-piperazinomethyl)-3-(trifluoromethyl)aniline (1.0 equiv.), KO-*t*-Bu (2.0 equiv.), 0.17 M in THF, rt, Ar, 12 h.

solution containing the surfactant was then recycled three times with the addition of 1000 ppm palladium plus ligand for each (see ESI†), giving rise to consistently high isolated yields (Scheme 4).

As an illustration of the potential for this coupling chemistry, a key intermediate **28** in the synthesis of the FDA approved tyrosine-kinase inhibitor ponatinib (Iclusig®).<sup>23</sup> is shown in Scheme 5, involving two Sonogashira couplings. The starting material, bromide **24**, was first coupled with TES-acetylene under standard reaction conditions using 750 ppm of the same catalyst derived from [PdCl(cinnamyl)]<sub>2</sub> and cBRIDP. The TES group was then removed using a catalytic amount of potassium carbonate in a mixture of THF and methanol.<sup>24</sup> The second Sonogashira coupling between the substituted phenyl-acetylene **26** and 3-iodoimidazo[1,2-*b*]pyridazine **27**, readily prepared from imidazo[1,2-*b*]pyridazine upon treatment with NIS, proceeded smoothly under standard reaction conditions to afford intermediate **28** in excellent overall yield (77%). The targeted API was then realized by simple exposure of **28** to the aniline partner **29** in dry THF containing KO-*t*-Bu, following the procedure in the Takeda patent.<sup>25</sup>

## Conclusions

In summary, a sustainable, Cu-free, ppm level Pd-catalyzed Sonogashira reaction has been developed that represents the new ‘state-of-the-art’ in such valued cross-couplings, especially from the green chemistry perspective. It relies upon a combination of commercially available palladium pre-catalyst and



ligand, leading to an *in situ*-formed highly active catalyst that is effective with aryl/heteroaryl halides at the 0.10–0.15 mol% level of endangered palladium at 45 °C in water as the reaction medium. Products can be isolated in many cases by simple filtration, thus entirely avoiding organic solvents throughout the process. In addition to documenting the potential for scale up, an application to a timely active pharmaceutical ingredient showcases this environmentally responsible and sustainable technology.

## Conflicts of interest

There are no conflicts to declare.

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