



# Phosphine-free Sonogashira coupling: reactions of aryl halides catalysed by palladium(II) complexes of azetidine-derived polyamines under mild conditions

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## ABSTRACT

Readily synthesised, water-stable pyridylazetidine-based Pd(II) complexes have been studied as catalysts for the Sonogashira coupling reaction. Under low catalyst loadings, various aryl bromides and chlorides were efficiently coupled with phenylacetylene at only moderately elevated temperatures (50–70 °C) and, in some cases, even at room temperature. Not only was the catalysis efficient under mild conditions but it was also operative in aerated, partly aqueous and phosphine-free media.

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## 1. Introduction

Many metal-catalyzed coupling reactions have been recognized as convenient one-step methods for the construction of carbon–carbon bonds.<sup>1,2</sup> Among them, the palladium-catalyzed  $sp^2$ – $sp$  Sonogashira coupling reaction of terminal alkynes with aryl halides<sup>2</sup> is one of the most valuable methods for the synthesis of arylated alkynes. Conventionally, the reaction is performed by using catalytic amounts of a palladium–phosphine complex and CuI in the presence of a large excess of a secondary or tertiary amine or various simple bases such as alkali-metal carbonates.<sup>2–8</sup> However, many of the Pd–phosphine complexes are sensitive to both air and moisture, and their cost and toxicity limit any large-scale industrial applications. In addition, commonly used amines such as piperidine, diethylamine and triethylamine add to the environmental burden. The best results have been obtained with reactive aryl iodides or aryl bromides, and the conditions are not suitable for less reactive aryl chlorides unless relatively high catalyst loadings of 1–5 mol% are used. Recently, non-phosphine Sonogashira coupling<sup>7</sup> was reported to be effective with Pd bound

to ligands such as *N*-heterocyclic carbenes,<sup>5e,8</sup> some of which form palladacycle species,<sup>9</sup> with the activity retained even in mixed-aqueous solvents.<sup>6c,10</sup> However, these catalysts worked well only for activated and not for deactivated aryl chlorides. Thus, the search for practical coupling catalysts that exhibit high activity and broad applicability continues. In this context, we considered that stable Pd(II) complexes of a new series of pyridylazetidine ligands,<sup>11</sup> some of which have been recently shown to give useful catalysts for the Suzuki–Miyaura reaction in aqueous media,<sup>12</sup> might well be effective in Sonogashira coupling. The present work is a report of our successful investigation of this possibility using the species shown in Figure 1.

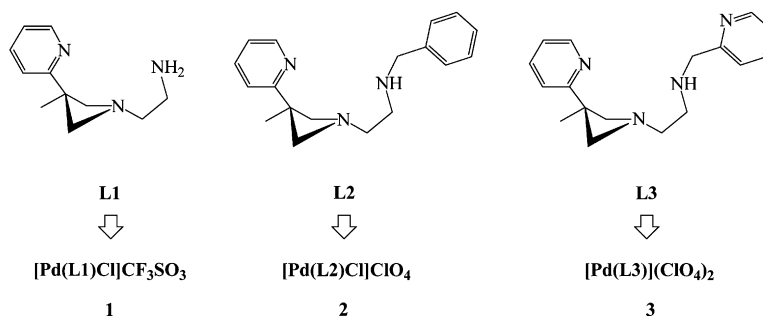
## 2. Experimental

### 2.1. Materials and equipment

All chemicals were purchased from Aldrich and used without further purification. All organic solvents were distilled prior to use. Microanalysis was carried out with a Chemtronics TEA-3000 instrument. GC/GC–MS analyses were performed on an Agilent 6890N GC (He carrier gas, HP-5MS column, 0.25 m coil, 30 m×0.25 μm) coupled to an Agilent 5975 Network Mass Selective Detector (electron impact ionization at 70 eV).

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**Figure 1.** The ligands giving rise to the Pd(II) complexes (composition of the isolated solids indicated) used as catalysts in the present study.

## 2.2. Syntheses

[Pd(L1)Cl]CF<sub>3</sub>SO<sub>3</sub> (**1**), [Pd(L2)Cl]ClO<sub>4</sub> (**2**) and **L3** were prepared as described previously.<sup>12</sup>

## 2.3. {2-(3-Methyl-3-(pyridin-2-yl)azetidin-1-yl)-N-(pyridin-2-yl)methyl}ethanamine}palladium(II) perchlorate, [Pd(L3)](ClO<sub>4</sub>)<sub>2</sub>, **3**

PdCl<sub>2</sub> (0.80 g; 4.5 mmol) was added to a solution of **L3** (1.3 g; 4.6 mmol) in ethanol (80 mL) plus acetone (20 mL). The mixture was heated at reflux under nitrogen for 48 h, during which time most of PdCl<sub>2</sub> dissolved. The remaining insoluble material was filtered off and the yellow filtrate was evaporated to dryness under reduced pressure. Yield: 1.3 g (60%). The yellow powder was redissolved in a mixture of ethanol (20 mL) and acetone (5 mL) containing excess LiClO<sub>4</sub>. Gradual reduction of the solvent volume produced yellow crystals suitable for crystallography. Anal. Calcd for C<sub>17</sub>H<sub>22</sub>Cl<sub>2</sub>N<sub>4</sub>O<sub>8</sub>Pd: C, 34.74; H, 3.77; N, 9.53. Found: C, 34.2; H, 3.7; N, 9.6%.

## 2.4. General procedure for the conduct of Sonogashira coupling

Reactions were carried out in a glass ampoule equipped with a Teflon screw cap. Aryl halide (1.0 mmol), the alkyne (1.1 mmol), Na<sub>2</sub>CO<sub>3</sub> (2.0 mmol), CuI (1.0 mmol) and *n*-dodecane (15–20 mg) as an internal GC standard were dispersed in H<sub>2</sub>O/DMA (2 mL, 1:1 v/v) and then a solution of the catalyst, e.g., **2**, [Pd(L2)Cl]ClO<sub>4</sub>, in H<sub>2</sub>O/DMA (1.0 μmol mL<sup>−1</sup>) was added to the mixture. The resulting mixture was stirred at the appropriate temperature (see Tables 3 and 4). Samples were withdrawn periodically and analyzed by GC/GC-MS. GC yield was determined using *n*-dodecane as an internal standard and based on the amount of aryl halide employed. The reaction mixture was filtered and the filtrate washed with H<sub>2</sub>O and Et<sub>2</sub>O several times. The organic phase in the combined filtrates was separated and dried over MgSO<sub>4</sub>, and the solvent was evaporated under reduced pressure. The product was isolated by column chromatography on silica gel.

## 2.5. Crystallography

X-ray diffraction data for the single crystal were collected at 293(2) K using an ADSC Quantum210 detector at Beamline 4A MXW of the Pohang Light Source. Crystal evaluation and data collection were done using λ=0.76999 Å radiation with a detector-to-crystal distance of 6.0 cm. Preliminary cell constants and an orientation matrix were determined from 36 sets of frames collected at scan intervals of 5° with an exposure time of 1 s per frame. The basic scale file was prepared using the program HKL2000.<sup>13</sup> The reflections were successfully indexed by the automated indexing routine of the DENZO program.<sup>13</sup> The 8750 reflections (see Table 1)

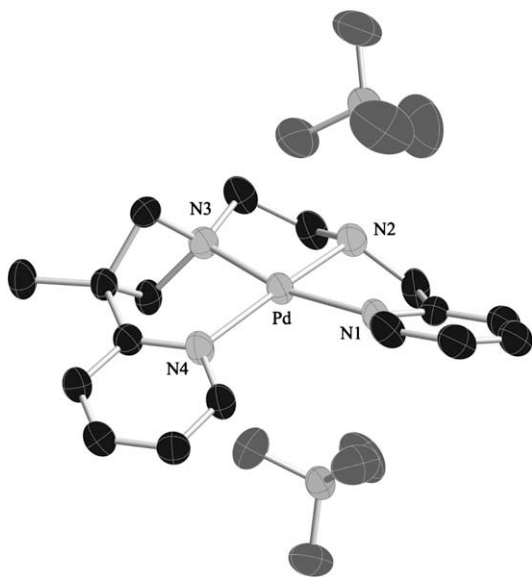
were obtained by collecting 72 sets of frames with 5° scans and an exposure time of 1 s per frame. This highly redundant dataset was corrected for Lorentz and polarization effects; negligible corrections for crystal decay were also applied. The space group *P*-1 was determined by the program XPREP.<sup>14</sup> The structure was solved by direct methods<sup>15</sup> and refined on *F*<sup>2</sup> by full-matrix least-squares procedures.<sup>16</sup> The hydrogen atoms were placed geometrically, with N–H distances in 0.91 Å and C–H distances in 0.97 Å, and these atoms were refined using a riding model. Table 1 contains summary data relating to the crystal structures and their refinements. Full details have been deposited with the Cambridge Crystallographic Data Base under deposition number CCDC 703477. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).

## 3. Results and discussion

Complexes **1**= [Pd(L1)Cl]CF<sub>3</sub>SO<sub>3</sub>, **2**= [Pd(L2)Cl]ClO<sub>4</sub> and **3**= [Pd(L3)](ClO<sub>4</sub>)<sub>2</sub> used as catalysts here were derived from ligands **L1–L3** (Fig. 1) as described previously,<sup>12</sup> except that in the case of **L3** a more extended reaction period and use of a different solvent (see Experimental) led to the isolation of **3** as the diperchlorate, rather than the chloride-perchlorate. This complex was subsequently characterised by a crystal structure determination (Table 1), which showed it to differ from **1** and

**Table 1**  
Crystal and refinement data

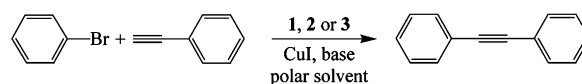
|   |   |
|---|---|
| Chemical formula                                      | C <sub>17</sub> H <sub>22</sub> Cl <sub>2</sub> N <sub>4</sub> O <sub>8</sub> Pd ( <b>3</b> ) |
| <i>M</i> /g mol <sup>−1</sup>                         | 587.69  |
| Crystal system  | Triclinic   |
| Space group   | <i>P</i> -1   |
| <i>a</i> /Å   | 8.4480(17)  |
| <i>b</i> /Å   | 9.7110(19)  |
| <i>c</i> /Å   | 13.702(3)   |
| α/°   | 96.62(3)  |
| β/°   | 103.61(3)   |
| γ/°   | 102.17(3)   |
| <i>V</i> /Å <sup>3</sup>                              | 1051.7(4)   |
| <i>D</i> <sub>c</sub> /g cm <sup>−3</sup>             | 1.856   |
| <i>Z</i>  | 2   |
| Crystal size (mm)                                     | 0.30×0.15×0.05  |
| <i>T</i> (K)  | 100(2)  |
| λ(Mo Kα)/Å  | 0.76999   |
| μ(MoK <sub>α</sub> )/mm <sup>−1</sup>                 | 1.191   |
| 2θ <sub>max</sub> /°                                  | 30.33   |
| <i>hkl</i> range                                      | 0≤ <i>h</i> ≤11, −12≤ <i>k</i> ≤12, −7≤ <i>l</i> ≤17  |
| <i>N</i>  | 4450  |
| <i>N</i> <sub>ind</sub> ( <i>R</i> <sub>merge</sub> ) | 4450 (0.0000)   |
| <i>N</i> <sub>obs</sub> ( <i>I</i> >2σ( <i>I</i> ))   | 3996  |
| <i>N</i> <sub>var</sub>                               | 291   |
| <i>R</i> <sub>1</sub> ( <i>F</i> )                    | 0.0886  |
| <i>wR</i> <sub>2</sub> ( <i>F</i> <sup>2</sup> )      | 0.2797  |
| GoF(all)  | 1.325   |
| Δρ <sub>min</sub> /e Å <sup>−3</sup>                  | −2.090  |
| Δρ <sub>max</sub> /e Å <sup>−3</sup>                  | 2.412   |



**Figure 2.** A view of the stoichiometric unit present in the lattice of complex **3**. Hydrogen atoms omitted for clarity, probability displacement ellipsoids shown at the 50% level.

**Table 3**

Sonogashira coupling of bromobenzene with phenylacetylene<sup>a</sup>



| Experiment no. <sup>a</sup> | Catalyst (mol %)  | Solvent               | Base                            | Temperature (°C) | Time (h) | Yield <sup>c</sup> (%) |
|-----------------------------|-------------------|-----------------------|---------------------------------|------------------|----------|------------------------|
| 1                           | <b>2</b> (0.01)   | DMA/H <sub>2</sub> O  | Na <sub>2</sub> CO <sub>3</sub> | 50               | 2        | 99 (95)                |
| 2                           | <b>2</b> (0.01)   | DMF/H <sub>2</sub> O  | Na <sub>2</sub> CO <sub>3</sub> | 50               | 2        | 97                     |
| 3                           | <b>2</b> (0.01)   | DMSO/H <sub>2</sub> O | Na <sub>2</sub> CO <sub>3</sub> | 50               | 2        | 98                     |
| 4                           | <b>2</b> (0.01)   | NMP/H <sub>2</sub> O  | Na <sub>2</sub> CO <sub>3</sub> | 50               | 2.5      | 97 (93)                |
| 5                           | <b>2</b> (0.01)   | EtOH/H <sub>2</sub> O | Na <sub>2</sub> CO <sub>3</sub> | 50               | 3        | 94                     |
| 6                           | <b>2</b> (0.01)   | MeOH/H <sub>2</sub> O | Na <sub>2</sub> CO <sub>3</sub> | 50               | 3        | 95                     |
| 7                           | <b>2</b> (0.01)   | DMA/H <sub>2</sub> O  | K <sub>3</sub> PO <sub>4</sub>  | 50               | 2        | 94 (91)                |
| 8                           | <b>2</b> (0.01)   | DMA/H <sub>2</sub> O  | K <sub>2</sub> CO <sub>3</sub>  | 50               | 2        | 84                     |
| 9                           | <b>2</b> (0.01)   | DMA/H <sub>2</sub> O  | NaOAc                           | 50               | 2        | 65                     |
| 10                          | <b>2</b> (0.001)  | DMA/H <sub>2</sub> O  | Na <sub>2</sub> CO <sub>3</sub> | 50               | 5        | 91                     |
| 11                          | <b>2</b> (0.0002) | DMA/H <sub>2</sub> O  | Na <sub>2</sub> CO <sub>3</sub> | 50               | 12       | 80 (77)                |
| 12                          | <b>2</b> (0.01)   | DMA/H <sub>2</sub> O  | Na <sub>2</sub> CO <sub>3</sub> | 40               | 5        | 88                     |
| 13                          | <b>2</b> (0.1)    | DMA/H <sub>2</sub> O  | Na <sub>2</sub> CO <sub>3</sub> | 25               | 24       | 73                     |
| 14                          | <b>2</b> (0.01)   | DMA                   | Na <sub>2</sub> CO <sub>3</sub> | 50               | 3        | 11                     |
| 15 <sup>b</sup>             | <b>2</b> (0.01)   | DMA/H <sub>2</sub> O  | Na <sub>2</sub> CO <sub>3</sub> | 50               | 3        | 34                     |
| 16                          | <b>1</b> (0.01)   | DMA/H <sub>2</sub> O  | Na <sub>2</sub> CO <sub>3</sub> | 50               | 2        | 83 (81)                |
| 17                          | <b>1</b> (0.1)    | DMA/H <sub>2</sub> O  | Na <sub>2</sub> CO <sub>3</sub> | 25               | 24       | 51                     |
| 18                          | <b>3</b> (0.01)   | DMA/H <sub>2</sub> O  | Na <sub>2</sub> CO <sub>3</sub> | 50               | 2        | 73 (70)                |
| 19                          | <b>3</b> (0.1)    | DMA/H <sub>2</sub> O  | Na <sub>2</sub> CO <sub>3</sub> | 25               | 24       | 37                     |

<sup>a</sup> All reactions were performed with bromobenzene (1.0 mmol), phenylacetylene (1.1 mmol), base (2.0 mmol), CuI (1.0 mmol), DMA/H<sub>2</sub>O or the other solvent mixtures (2 mL, 1:1 v/v) and the indicated amounts of catalyst **1**, **2** or **3**.

<sup>b</sup> Without CuI.

<sup>c</sup> GC yield was determined using *n*-dodecane as an internal standard. Isolated yield is given in parenthesis.

**2** in that the Pd is present in an approximately square-planar N<sub>4</sub>, rather than N<sub>3</sub>Cl environment (Fig. 2). Coordination of the additional pyridyl unit causes the ligand to adopt a non-planar, helical conformation about the metal ion, as found in various quadridentate, pyridine-donor ligands.<sup>17</sup> However, this distortion has no obvious marked consequences in terms of the Pd–N bond lengths when compared with those in **1** and **2** (Table 2). In the lattice of **3**, perchlorate–O atoms are found in what might be considered axial binding sites on Pd but the Pd···O distances are very long (3.380(8), 3.066(8) Å). In fact, the use of CrystalExplorer<sup>18</sup> to provide *d*<sub>norm</sub> Hirshfeld surfaces indicates that there is no significant interaction and that the proximity of the perchlorate anions to the cation is determined rather by aliphatic CH···O interactions. Such anion–O···HC interactions are also apparent in the lattices of **1** and **2**, where again there are no indications of significant axial interactions with the metal. While the helicity of the complex and of the saturated five-membered chelate ring, as well as the asymmetry of N(2), might be expected to result in diastereoisomerism, in the lattice of **3** only the enantiomeric M(λ)R<sub>N</sub> and P(δ)S<sub>N</sub> species are present. Presumably as a consequence of the coordination of its attached N-donor centre, the 2-pyridylmethyl substituent in **3** occupies an equatorial position of the saturated five-membered ring, in contrast to **2**, where the unbound benzyl group is axially situated.<sup>12</sup> In the solid lattice, there are contacts indicative of CH···π interactions between the substituent pyridine rings, contacts which presumably could also occur as part of the approach of an aromatic substrate to the catalyst.

In our earlier investigation of the Suzuki–Miyaura reaction,<sup>12</sup> amino moieties of complexes **1–3** were found to have a significant effect on their catalytic activities. Complex **1** may be regarded as the parent species, whereas complexes **2** and **3** may be regarded as

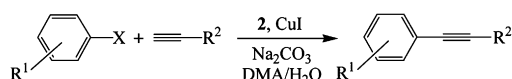
**Table 2**

Environment of the cation in **3**: selected distances (Å) and angles (°). Atom numbering is given in Figure 2. Values in square brackets are the corresponding measures in complexes **1** and **2**, respectively

| Bond distances                        | Bond angles                                |
|---------------------------------------|--|
| Pd–N(1) 2.065(6)                      | N(1)–Pd–N(2) 80.6(2)                       |
| Pd–N(2) 2.017(5) [2.020(3); 2.032(2)] | N(1)–Pd–N(3) 165.2(2)                      |
| Pd–N(3) 2.018(6) [2.020(3); 2.031(2)] | N(1)–Pd–N(4) 104.9(2)                      |
| Pd–N(4) 2.077(5) [2.079(3); 2.061(2)] | N(2)–Pd–N(3) 85.2(2) [84.06(11); 84.52(9)] |
|                                       | N(3)–Pd–N(4) 89.7(2) [90.15(10); 90.07(9)] |

modified ones with a large non-coordinating substituent and a co-ordinating substituent, respectively. The fact that the pyridyl arm in **3** is found to be coordinated to Pd atom raises the important issue of whether a readily replaced ligand (such as Cl in **1** and **2**) is necessary to ensure catalytic activity.

Given that complex **2** had proved to be the most effective catalyst of **1–3** in Suzuki–Miyaura coupling,<sup>12</sup> we began investigation of Sonogashira catalysis with this species, using the coupling of bromobenzene with phenylacetylene in the presence of Na<sub>2</sub>CO<sub>3</sub> and CuI as a model reaction (Table 3). The reaction in DMA/H<sub>2</sub>O (1:1) was initially performed with catalyst loading as low as 0.01 mol %. The reaction proceeded to completion at 50 °C within 2 h (entry 1). Solvent effects on the activity of **2** were examined with different polar solvents. When the reaction was conducted in aqueous DMF, DMSO, NMP, EtOH and MeOH instead of aqueous DMA, similar results were obtained under the same conditions (entries 2–6). It is interesting that the reactions in aqueous ethanol and methanol gave excellent results. Parameters such as the nature of the base, the catalyst loading and the reaction temperature were also surveyed. Na<sub>2</sub>CO<sub>3</sub> as a base gave slightly better results than K<sub>3</sub>PO<sub>4</sub>, K<sub>2</sub>CO<sub>3</sub> and NaOAc (entries 7–9). When the catalyst loading was decreased to 0.001 mol %, high conversion was still achieved (entry 10). Indeed, the reaction remained efficient even when using a much lower catalytic loading of 0.0002 mol %, for which a high TOF of 33,300 h<sup>−1</sup> was obtained (entry 11). Further optimization of the reaction conditions was not attempted. Catalyst **2** still showed outstanding performance at lower temperatures of 25–40 °C (entries 12 and 13), its activity at 25 °C being particularly noteworthy. To apply mild conditions while using Na<sub>2</sub>CO<sub>3</sub> as base appears to require aqueous solvents in order to ensure dissolution of Na<sub>2</sub>CO<sub>3</sub> (entry 14). As expected, the CuI cocatalyst has an important influence on the reaction rate (entry 15). Only very minor changes in the catalyst activity were observed on exposure of the system to air and water during reaction. Under the same conditions as used with **2** at 50 °C, catalysts **1** and **3** gave significantly inferior performance (entries 16 and 18, cf. entry 1). That the ‘parent’ complex **1**, lacking

**Table 4**Sonogashira coupling of aryl halides with terminal alkynes<sup>a</sup>

| Experiment no. | R <sup>1</sup>     | X  | R <sup>2</sup>                           | Catalyst (2) loading (mol %) | Temperature (°C) | Time (h) | Yield <sup>b</sup> (%) |
|----------------|--------------------|----|--|------------------------------|------------------|----------|------------------------|
| 1              | 4-O <sub>2</sub> N | Br | Ph                                       | 0.01                         | 50               | 2        | 99 (95)                |
| 2              | 2-O <sub>2</sub> N | Br | Ph                                       | 0.01                         | 50               | 2        | 97                     |
| 3              | 4-MeO              | Br | Ph                                       | 0.01                         | 50               | 2.5      | 90                     |
| 4              | 2-MeO              | Br | Ph                                       | 0.01                         | 50               | 3        | 93 (89)                |
| 5              | 4-Me               | Br | Ph                                       | 0.01                         | 50               | 2.5      | 91                     |
| 6              | 2-Me               | Br | Ph                                       | 0.01                         | 50               | 3        | 95                     |
| 7              | H                  | Br | CH <sub>2</sub> OH                       | 0.01                         | 50               | 3        | 93                     |
| 8              | H                  | Br | <i>n</i> -C <sub>6</sub> H <sub>13</sub> | 0.01                         | 50               | 4        | 91                     |
| 9              | H                  | Br | Si( <i>i</i> -Pr) <sub>3</sub>           | 0.01                         | 50               | 4        | 94 (90)                |
| 10             | 4-MeO              | Br | CH <sub>2</sub> OH                       | 0.01                         | 50               | 5        | 92                     |
| 11             | 4-MeO              | Br | <i>n</i> -C <sub>6</sub> H <sub>13</sub> | 0.01                         | 50               | 5        | 78                     |
| 12             | 4-MeO              | Br | Si( <i>i</i> -Pr) <sub>3</sub>           | 0.01                         | 50               | 5        | 81                     |
| 13             | H                  | Cl | Ph                                       | 0.01                         | 50               | 24       | 29                     |
| 14             | H                  | Cl | Ph                                       | 0.1                          | 50               | 24       | 45 (41)                |
| 15             | H                  | Cl | Ph                                       | 0.1                          | 70               | 12       | 73                     |
| 16             | H                  | Cl | Ph                                       | 0.5                          | 70               | 8        | 91                     |
| 17             | 4-O <sub>2</sub> N | Cl | Ph                                       | 0.5                          | 70               | 5        | 94                     |
| 18             | 4-MeO              | Cl | Ph                                       | 0.5                          | 70               | 12       | 88                     |
| 19             | 4-Me               | Cl | Ph                                       | 0.5                          | 70               | 12       | 82 (77)                |
| 20             | 2-Me               | Cl | Ph                                       | 0.5                          | 70               | 18       | 71                     |
| 21             | H                  | Cl | CH <sub>2</sub> OH                       | 0.5                          | 70               | 12       | 84 (80)                |
| 22             | H                  | Cl | <i>n</i> -C <sub>6</sub> H <sub>13</sub> | 0.5                          | 70               | 18       | 69                     |
| 23             | H                  | Cl | Si( <i>i</i> -Pr) <sub>3</sub>           | 0.5                          | 70               | 18       | 74                     |
| 24             | 4-MeO              | Cl | Si( <i>i</i> -Pr) <sub>3</sub>           | 0.5                          | 70               | 24       | 51                     |
| 25             | 4-MeO              | Cl | Si( <i>i</i> -Pr) <sub>3</sub>           | 0.5                          | 90               | 24       | 83                     |

<sup>a</sup> All reactions were performed with aryl halides (1.0 mmol), alkynes (1.1 mmol), base (2.0 mmol), CuI (1.0 mmol), DMA/H<sub>2</sub>O (2 mL, 1:1 v/v) and the indicated amounts of catalyst **2**.

<sup>b</sup> GC yield was determined using *n*-dodecane as an internal standard. Isolated yield is given in parenthesis.

a substituent on the terminal amino group, is an inferior catalyst to **2** perhaps reflects the greater ability of a secondary N-donor to enhance electron density on Pd and thus to facilitate intermediate oxidative addition steps or the greater acidity of a secondary NH donor, which could be important in an internal redox reaction of the deprotonated complex to give a Pd(0) intermediate.<sup>2</sup> It is significant that **3** is only a slightly poorer catalyst than **2**, since this indicates that the presence of a readily displaced unidentate ligand such as chloride is not essential to the catalyst activity. The mechanism of the Sonogashira reaction is complicated, though understood in essence,<sup>2</sup> and the present systems extend an area, which has had rather limited study,<sup>2,5–10</sup> this being the use of ligands of denticities higher than two to form the catalyst precursor complex. If it is indeed critical that the bound NH centre is involved in an internal redox reaction to give a Pd(0)–imine complex, then dissociation of one or more donors may occur as a non-rate-determining step in this species.

To extend the scope of our work, we next investigated the coupling of various aryl halides with phenylacetylene. As shown in Table 4, high catalytic activity was observed in the coupling of deactivated aryl bromides such as 4-bromoanisole, 2-bromoanisole, 4-bromotoluene and 2-bromotoluene (entries 3–6) as well as activated 1-bromo-4-nitrobenzene and 1-bromo-2-nitrobenzene (entries 1 and 2). Thus, despite some influence of the substituents, all these aryl bromides were rapidly coupled in the presence of **2**, and a catalyst loading of 0.01 mol % was sufficient to achieve high TOFs, with the reactions being complete at 50 °C in less than 3 h. We extended the scope of the coupling of the aryl bromides to other alkynes such as propargyl alcohol, (triisopropylsilyl)acetylene and 1-octyne (entries 7–12), the reaction rates here being slightly lower under the same conditions as for phenylacetylene.

Encouraged by these results, we investigated the coupling of several aryl chlorides (entries 13–24) expected to be less reactive. The coupling of chlorobenzene at 70 °C in the presence of 0.5 mol % of **2** proceeded rapidly, giving 91% yield in 8 h (entry 16), although at lower temperatures and loadings (entries 13–15) the yields were considerably reduced, even after longer reaction periods. Activated 1-chloro-4-nitrobenzene was coupled almost quantitatively in 5 h at 70 °C with 0.5 mol % catalyst (entry 17). Attempts to couple deactivated aryl chlorides were of limited success and required more extended reaction times for high yields (entries 18–20). Aryl chlorides were found to react with other alkynes such as propargyl alcohol, (triisopropylsilyl)acetylene and 1-octyne at 70 °C (entries 21–23). However, low yields were observed in the case of deactivated aryl chlorides and higher temperatures were required to reach satisfactory conversion (entries 24 and 25).

#### 4. Conclusions

Both tri- and quadri-dentate pyridylazetidine derivatives form Pd(II) complexes, which are efficient catalysts for Sonogashira coupling reactions in aqueous dispersions. Thus, the coupling can be conducted in the absence of phosphine ligands and under conditions requiring minimal precautions. Various aryl bromides undergo coupling with alkynes in the presence of very low amounts of catalyst and the catalyst system is also effective for the reactions of aryl chlorides. The presence of at least one readily replaced unidentate ligand in the Pd(II) complex presumed to be an actual precursor of the true catalytic species appears, on the basis of the present results, to be unnecessary. The addition of CuI to the reaction mixture, although leading to faster rates, does not appear to be essential.

#### References and notes

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