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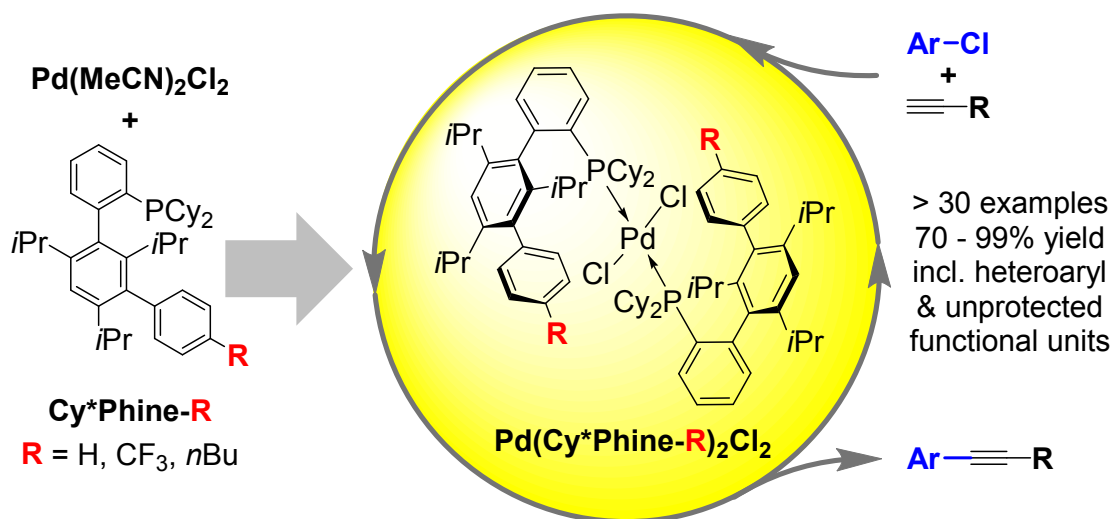
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# Palladium Precatalysts Containing *meta*-Terarylphosphine Ligands for Expedient Copper-Free Sonogashira Cross-Coupling Reactions

Yong Yang,<sup>\*a</sup> Joyce Fen Yan Lim,<sup>b</sup> Xinying Chew,<sup>a</sup> Edward G. Robins,<sup>c</sup> Charles W. Johannes,<sup>a</sup> Yee Hwee Lim<sup>a</sup> and Howard Jong<sup>\*a</sup>

## Abstract

Novel precatalysts with *meta*-terarylphosphine ligands demonstrate excellence in copper-free Sonogashira cross-coupling catalysis. Together with simple and reliable protocols, these systems set a new standard for high performance and practicality.



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ARTICLE TYPE

## Palladium Precatalysts Containing *meta*-Terarylphosphine Ligands for Expedient Copper-Free Sonogashira Cross-Coupling Reactions

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Three novel palladium complexes utilizing different variations of the evolutionary *meta*-terarylphosphine ligand, Cy\*Phine, were developed. These air- and moisture-stable complexes, PdCl<sub>2</sub>L<sub>2</sub> (L = Cy\*Phine, Cy\*Phine-CF<sub>3</sub> and Cy\*Phine-*n*Bu), demonstrated exceptional broad-based performance and operational simplicity in the copper-free Sonogashira cross-coupling of challenging (hetero-)aryl chlorides and terminal alkynes. Modifications to the periphery of the ligand scaffold showed modest improvements in the reaction rate when more electron-donating substituents were incorporated, which hints at potential design upgrades in the future.

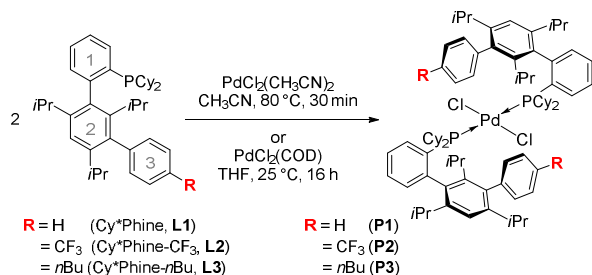
The continuous development of palladium-based catalysts for cross-coupling applications has been recognized by the scientific community as some of the most valuable contributions to synthetic chemistry.<sup>1</sup> Within this space, there are two general methods by which catalysts are introduced to the reaction mixture: 1) made *in situ*, where the ligand and the Pd source are added separately; and 2) *via* preformed Pd complexes, or often referred to as precatalysts, which are complexes that (should) already contain all the components required to promote catalysis. In consideration of which type of catalyst should be employed, recent mechanistic insights offer valuable guidance to facilitate the decision. Well-defined preformed catalysts tend to promote catalysis *via* one prevailing metal species, whereas *in situ* generated catalysts have the propensity to involve various metal-based species that are dynamic in solution – resembling that of a cocktail.<sup>2</sup> Nevertheless, advantages exist for both types. The cocktail format of catalysts prepared *in situ* enable self-tuning and dynamic adjustment to accommodate different substrates. This auto-tuning feature contrasts the single species model for preformed catalysts that benefit from increased stability, predictability and reproducibility. The flexibility of *in situ* systems also facilitates the preparation of stock solutions for combinatorial evaluations *via* screening arrays; however, they lack the robustness of precatalysts, which are typically air and moisture stable in their solid state. Previously, our group reported the development of an *in situ* Pd catalyst system, which incorporates the evolutionary *meta*-terarylphosphine ligand, Cy\*Phine.<sup>3</sup> Herein, we describe the development of Pd precatalysts, PdCl<sub>2</sub>L<sub>2</sub> (L = Cy\*Phine,<sup>3</sup> Cy\*Phine-CF<sub>3</sub><sup>4</sup> and

Cy\*Phine-*n*Bu<sup>4</sup>), that reinforce the performance benefits of the Cy\*Phine architecture, with the added advantage of practicality and operational simplicity. The activity differences between the *in situ* prepared and precatalyst forms of the Cy\*Phine-based Pd systems for copper-free Sonogashira (or Heck alkynylation<sup>5</sup>) cross-coupling reactions are also examined and discussed.

A critical precatalyst design feature that was carefully assessed was the ligand-to-metal (LTM) ratio, which has been shown by numerous groups to have a significant impact on the catalyst's ability to transform difficult aryl chloride substrates.<sup>6-9</sup> In general, the LTM effect seems to be predicated on a multitude of factors including the ligand characteristics, the substrate class and the reaction type. To our knowledge, there are currently no reports of any catalyst system that is capable of effectively performing the Sonogashira reaction (with or without a copper co-catalyst) with aryl chloride substrates using an LTM of less than 2:1. The necessity of the higher LTM ratio for Sonogashira cross-coupling is not completely understood at this time, but it is clearly beneficial for improved catalyst performance in copper-free Sonogashira cross-coupling reactions. A literature survey reveals that six precatalysts are reportedly able to perform the transformation with aryl chlorides.<sup>1k,10</sup> However, only two examples, PdCl<sub>2</sub>(PCy<sub>3</sub>)<sub>2</sub><sup>10e, 10f</sup> and Pd(Amphos)<sub>2</sub>Cl<sub>2</sub> [Amphos = *t*Bu<sub>2</sub>(*p*-NMe<sub>2</sub>C<sub>6</sub>H<sub>4</sub>)P]<sub>2</sub><sup>1k,10g-h</sup> have shown the capacity to couple challenging electron-rich substrates without the need for additional ligand. These state-of-the-art precatalysts both utilize a di-ligated palladium(II) dichloride format to achieve good catalytic performance, are tolerant of air and moisture in their solid state, and operate without copper co-catalysts. A catalyst design that performed in the absence of copper salts was also an important feature as CuI was previously shown by our group,<sup>3</sup> and others,<sup>11</sup> to be detrimental to Sonogashira reactions. Furthermore, the presence of Cu<sup>I</sup> salts have also demonstrated the capacity to instigate ligand transfer from Pd at elevated temperatures causing interference.<sup>12</sup> Thus, we envisaged that a PdCl<sub>2</sub>L<sub>2</sub> setup using Cy\*Phine as the ligand, L, could make an effective precatalyst for Cu-free Sonogashira cross-coupling.

PdCl<sub>2</sub>(Cy\*Phine)<sub>2</sub> (**P1**) was prepared in a facile manner by reacting 2 equivalents of Cy\*Phine with PdCl<sub>2</sub>(CH<sub>3</sub>CN)<sub>2</sub> in CH<sub>3</sub>CN at 80 °C for 30 minutes under an argon atmosphere. A yellow precipitate was formed, which was collected *via* vacuum filtration to obtain the PdCl<sub>2</sub>(Cy\*Phine)<sub>2</sub> precatalyst in high yield (85 %). Optionally, PdCl<sub>2</sub>(COD) can be combined with 2

equivalents of Cy\*Phine in THF at room temperature to produce the equivalent precatalyst after overnight agitation.<sup>13</sup> The synthetic procedure was found to be highly robust and enabled the synthesis of related precatalysts **P2** and **P3** to evaluate the performance impact of modifications to the ligand periphery (Scheme 1). Notably, all of the precatalysts, **P1** – **P3**, were isolated as air- and moisture-stable solids.<sup>14</sup>



**Scheme 1.** Synthesis of preformed palladium complexes PdCl<sub>2</sub>L<sub>2</sub>

(**L** = Cy\*Phine, Cy\*Phine-CF<sub>3</sub>, Cy\*Phine-nBu).

The catalytic performance of precatalyst **P1** was first evaluated against our recently reported Pd-Cy\*Phine *in situ* system (**IS-1**) by performing the identical benchmark reaction studied previously (Table 1).<sup>3</sup> Under these conditions, complete conversions were achieved for both **P1** and **IS-1**, affording the desired product, 1-(*tert*-butyl)-4-(phenylethynyl)benzene (**3a**) and the concomitant byproduct (*E*)-but-1-en-3-yne-1,4-diyldibenzene (**4a**), in 87 and 13 % yield, respectively for **P1** (Table 1, Entry 3). The results showed marginally lower yields and selectivity than that obtained for **IS-1**, which achieved 91 and 9 % for **3a** and **4a**, respectively (Table 1, Entry 1). While the outcome from the head-to-head comparison was satisfactory, a solvent and base screen was conducted to determine if the performance of **P1** responded similarly to **IS-1** in different environments. From the evaluation, the combination of K<sub>3</sub>PO<sub>4</sub> in CH<sub>3</sub>CN was found to be most effective, furnishing a yield ratio of 94:6 for **3a:4a** (Table 1, Entry 6). This result was significantly different from that of **IS-1**, which afforded a substantially lower yield ratio of 47:2 (**3a:4a**) (Table 1, Entry 2). On this basis, it is postulated that the active catalyst for **P1** and **IS-1** may not be equivalent due to the possibility of **IS-1** existing as a cocktail of dynamic Pd species in solution.<sup>2</sup> Nonetheless, the significant response variance in the different reaction environments was not anticipated, or fully understood at this time.<sup>15</sup> The final outcome of the optimization experiments, however, was that the performance of **P1** was found to be comparable to **IS-1** using a different solvent and base combination for substrates **1a** and **2a**.

To gauge the performance level of **P1**, we evaluated it against other commercially available di-ligated palladium precatalysts for the coupling of **1a** and **2a** (Chart 1). Phosphine-based Pd systems including PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, PdCl<sub>2</sub>(PCy<sub>3</sub>)<sub>2</sub> and the state-of-the-art, Pd(Amphos)<sub>2</sub>Cl<sub>2</sub> were selected. The *N*-heterocyclic carbene-based precatalyst, PEPPSI-IPr was also included to offer a broader perspective and completeness. As we were also interested to directly compare the *m*-terarylphosphine architecture against the biarylphosphine congener, we prepared and included a new precatalyst, PdCl<sub>2</sub>(XPhos)<sub>2</sub> (**P4**) to the evaluation. Encouragingly, precatalysts **P1**, **P2** and **P3** were all far superior to the current commercial alternatives for copper-free Sonogashira cross-

coupling. Importantly, **P1** – **P3** were also considerably better than the biarylphosphine-based system **P4** under the standard conditions. **P4** provided 75 % yield of the desired product **3a** along with 19 % of byproduct **4a** in approximately a 4:1 ratio whereas **P1**, **P2** and **P3** provided **3a** in greater than 94 % yield with product selectivity better than 15:1.

**Table 1.** Optimization of Reaction Conditions.<sup>a</sup>

Entry	Precatalyst	Solvent	Base	Yield (%) <sup>b</sup>
1	<b>IS-1</b> <sup>c</sup>	CH <sub>3</sub> CN	Cs <sub>2</sub> CO <sub>3</sub>	91:9
2	<b>IS-1</b> <sup>c</sup>	CH <sub>3</sub> CN	K <sub>3</sub> PO <sub>4</sub>	47:2
3	<b>P1</b>	CH <sub>3</sub> CN	Cs <sub>2</sub> CO <sub>3</sub>	87:13
4	<b>P1</b>	CH <sub>3</sub> CN	K <sub>2</sub> CO <sub>3</sub>	85:10
5	<b>P1</b>	CH <sub>3</sub> CN	Na <sub>2</sub> CO <sub>3</sub>	56:6
6	<b>P1</b>	CH <sub>3</sub> CN	K <sub>3</sub> PO <sub>4</sub>	94:6
7	<b>P1</b>	CH <sub>3</sub> CN	CsF	78:12
8	<b>P1</b>	CH <sub>3</sub> CN	Piperidine	24:19
9	<b>P1</b>	CH <sub>3</sub> CN	Et <sub>3</sub> N	24:22
10	<b>P1</b>	Toluene	K <sub>3</sub> PO <sub>4</sub>	86:12
11	<b>P1</b>	DMSO	K <sub>3</sub> PO <sub>4</sub>	15:8
12	<b>P1</b>	DMF	K <sub>3</sub> PO <sub>4</sub>	48:15
13	<b>P1</b>	1,4-dioxane	K <sub>3</sub> PO <sub>4</sub>	54:7
14	<b>P1</b>	1,2-DCE	K <sub>3</sub> PO <sub>4</sub>	32:13
15	<b>P1</b>	NMP	K <sub>3</sub> PO <sub>4</sub>	30:11
16	<b>P2</b>	CH <sub>3</sub> CN	K <sub>3</sub> PO <sub>4</sub>	94:6
17	<b>P3</b>	CH <sub>3</sub> CN	K <sub>3</sub> PO <sub>4</sub>	95:5

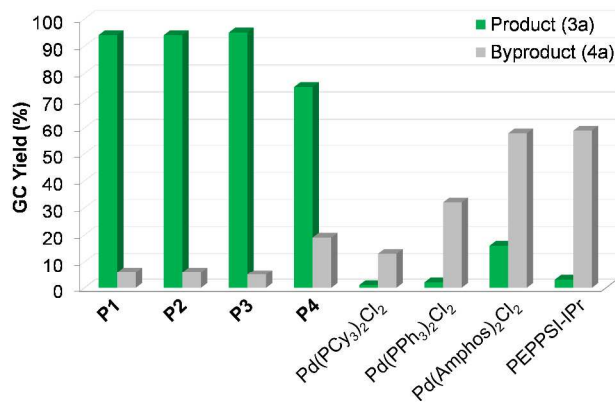
<sup>a</sup> Reaction conditions: 1 mol% Pd precatalyst, 0.5 mmol of 1-*tert*-butyl-4-chlorobenzene (**1a**), 0.6 mmol of phenylacetylene (**2a**), 1 mL of solvent, 1 mmol base, 90 °C, 6 h. <sup>b</sup> GC-FID yield of **3a** and **4a** as a ratio of **3a:4a** based on 0.5 mmol of **1a** using dodecane as an internal standard. <sup>c</sup> **IS-1** = PdCl<sub>2</sub>(CH<sub>3</sub>CN)<sub>2</sub> and 2 equiv of Cy\*Phine added separately to the reaction mixture to form the catalyst *in situ*.

These results provide clear evidence that the *meta*-teraryl-based precatalysts (**P1** – **P3**) offer a significant performance advantage compared to the biaryl-based system. Furthermore, the excellent capability demonstrated by the Cy\*Phine-based systems circumvented drawbacks associated with other precatalysts, such as the requirement of copper co-catalysts (e.g. PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> and PEPPSI-IPr), the need for slow addition strategies (e.g. Pd(Amphos)<sub>2</sub>Cl<sub>2</sub>), or a general substrate scope limitation (e.g. PdCl<sub>2</sub>(PCy<sub>3</sub>)<sub>2</sub>).

To establish the effect of modifications to the periphery of Cy\*Phine, an electron-withdrawing group (**P2**) and an electron-donating group (**P3**) were selected and independently incorporated into the third ring of the *meta*-teraryl scaffold. From

the results of our benchmark reaction using substrates **1a** and **2a**, it was found that the ligand substitutions did not evoke a significant performance impact relative to **P1** as all three precatalysts (**P1** – **P3**) afforded excellent results (94 – 95 % yields) with negligible selectivity differences (Table 1, Entries 6, 16-17).

**Chart 1.** A performance comparison of **P1** – **P4** with commercially available precatalysts in the benchmark reaction using **1a** and **2a**.<sup>a</sup>

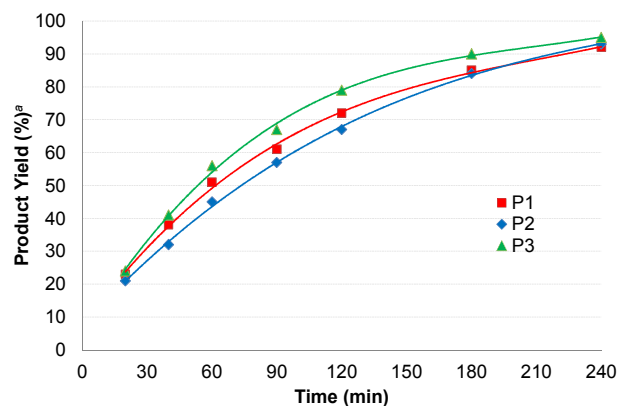


<sup>a</sup> Reaction conditions: 1 mol% Pd precatalyst, 0.5 mmol of 1-*tert*-butyl-4-chlorobenzene (**1a**), 0.6 mmol of phenylacetylene (**2a**), 1 mL of CH<sub>3</sub>CN, 1 mmol K<sub>3</sub>PO<sub>4</sub>, 90 °C, 6 h. GC-FID yield of **3a** and **4a** based on 0.5 mmol of **1a** using dodecane as an internal standard.

However, to gain further insight, a more in-depth comparison was conducted by which the test reactions were monitored over time. The empirical rate comparison between **P1** – **P3** revealed kinetic differences between the precatalyst series (Chart 2) with a general trend that correlated an improved reaction rate with more electron-donating substituents on the third phenyl ring of Cy\*Phine. After 2 h, the product yields showed a rate trend of **P3** > **P1** > **P2** in approximately 5 % increments, which corresponded with the electron-donating properties of the R-substituent of the third ring (R = -*n*Bu > -H > -CF<sub>3</sub>). Similarly, a performance enhancement effect was also reported by the Buchwald group with the incorporation of an electron-donating group (-*n*Bu) to the peripheral ring of their Pd-terarylphosphine system for nucleophilic aryl fluorination reactions.<sup>16</sup>

A substrate scope overview for **P1** is provided in Table 2 with a more comprehensive list found in the Supporting Information. Overall, highly electron-rich, or unprotected, aryl chloride substrates such as pyrimidines, pyrazines, aldehydes, phenols and anilines – which are typically problematic for copper-free Sonogashira reactions – were all efficiently coupled with **P1** using Method I without complications (Table 2, Entries 1-7). Potential catalyst poisons, such as 2-ethynylpyridine and electron-rich alkynes such ethynyl-3,5-dimethoxybenzene could also be cross-coupled smoothly (Table 2, Entries 8-9, 40 respectively). More sensitive substrates, like chloropyridazines, required a lower reaction temperature (60 °C) and a different solvent and base combination (THF/NEt<sub>3</sub>, Method II) to efficiently promote the alkylation reaction (Table 2, Entries 10-12).

**Chart 2.** Kinetic profiles of precatalysts **P1** – **P3** for the benchmark reaction using **1a** and **2a**.



<sup>a</sup> Yields determined by GC-FID using dodecane as an internal standard.

Initially, it was determined that the performance of **P1** and **IS-1** were similar; however, a closer examination across several different substrates revealed subtle differences (Table 2, Entries 13–18). Using only Method I, **P1** was able to achieve results that were comparable with, or greater than, **IS-1** which utilized three different methods for five different substrate pairs (Table 2, Entries 13-17). Despite being able to streamline the protocol for **P1**, a significant difference in performance was observed when propargyl alcohol was coupled with 4-chlorobenzonitrile (Table 2, Entry 18). The employment of **IS-1** with Method D achieved nearly double the yield of **P1** using Method I. The major differential was the LTM ratio of 3:1 utilized by **IS-1** opposed to **P1** that had a preformed LTM of 2:1. This increased LTM ratio was found to be generally effective to improve the performance of **IS-1** in the presence of very challenging substrates, such as propargyl alcohols and propargyl amines.<sup>3</sup> This augmentation effect was further verified when the experiment was repeated with 1 mol% of **P1** and an extra 1 mol% of Cy\*Phine was added to the reaction mixture (to bring the LTM ratio up to 3:1). The outcome was an isolated yield improvement of **3f** to 83 % from 52 %. Thereby, in cases where LTM ratios greater than 2:1 are required, the use of **IS-1** should be considered.

Nonetheless, most substrates can be transformed by **P1** using only two methods, as opposed to four methods when **IS-1** was employed. This simplified protocol for **P1** adds yet another level of convenience, in addition to its ease of handling being an air- and moisture-stable solid. Importantly, the added practicality of **P1** does not hinder its high performance and its substrate scope is inclusive of examples that contain heteroaromatic groups on both coupling partners (Table 2, Entries 8, 11-12, 15-16). These examples are of particular interest as they are representative of substrates used to prepare industrially valuable molecules.<sup>17</sup>

## Conclusions

In conclusion, we have added two *meta*-terarylphosphine ligands (Cy\*Phine-CF<sub>3</sub> (**L2**) and Cy\*Phine-*n*Bu (**L3**)) to the Cy\*Phine series and prepared several novel air- and moisture-stable precatalysts **P1** – **P3**, including **P4** as a biarylphosphine-based precatalyst derived from XPhos. In a comparison, **P1** – **P3** all



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Table 2. Selected substrate scope.<sup>a</sup>

$\text{Ar-Cl} \quad \mathbf{1} + \quad \text{R-C}\equiv\text{C-H} \quad \mathbf{2} \xrightarrow[\text{Base}]{1 \text{ mol\% [Pd]}} \text{Ar-C}\equiv\text{C-R} \quad \mathbf{3}$					
> 30 examples (70–99% yield)					
Entry	Yield (%), <sup>c</sup> Method	Entry	Yield (%), <sup>c</sup> Method	Entry	Yield (%), <sup>c</sup> Method
1	95, I	7	99, I	13	90, I 91, A
2	82, I	8	80, I	14	97, I 89, A
3	91, I	9	92, I <sup>b</sup>	15	85, I 90, A
4	82, I	10	84, II	16	97, I 95, B
5	75, I	11	60, II	17	93, I 99, C
6	87, I	12	90, II	18	52, I <sup>b</sup> 83, I <sup>d</sup> 95, D

<sup>a</sup> Reaction conditions: **Method I**: 1 mol% **P1** (PdCl<sub>2</sub>(Cy\*Phine)<sub>2</sub>), 0.5 mmol aryl chloride **1**, 0.6 mmol alkyne **2**, 1 mmol K<sub>2</sub>PO<sub>4</sub>, 1.0 mL of CH<sub>3</sub>CN, 90 °C, 6 h. <sup>b</sup> 12 h reaction time was used instead. **Method II**: As per method I except 1 mmol NEt<sub>3</sub>, 1.0 mL THF, 60 °C, 12 h used instead. **Method A**: 1 mol% **IS-1** (0.005 mmol PdCl<sub>2</sub>(CH<sub>3</sub>CN)<sub>2</sub>, 0.010 mmol Cy\*Phine), 1 mmol Cs<sub>2</sub>CO<sub>3</sub>, 1.0 mL CH<sub>3</sub>CN. **Method B**: As per method A, except 1 mmol Et<sub>3</sub>N, 1 mL THF, 60 °C, 6 h were used instead. **Method C**: 1 mol% **IS-2** (0.005 mmol Pd(OAc)<sub>2</sub>, 0.015 mmol Cy\*Phine), 1 mmol Cs<sub>2</sub>CO<sub>3</sub>, 1 mL CH<sub>3</sub>CN, 90 °C, 3–16 h. **Method D**: As per method C, except K<sub>3</sub>PO<sub>4</sub> was used as the base. <sup>c</sup> Average isolated yields of two runs. <sup>d</sup> Isolated yield values and the conditions for methods A – D were obtained from ref. 3. <sup>d</sup> 1 mol% of **P1** and 1 mol% of additional Cy\*Phine was used (LTM = 3:1).

outperformed **P4**, but relative to one another **P1**, **P2** and **P3** were equally productive in our benchmark reaction. However, the presence of an electron-donating substituent on the peripheral phenyl ring of the ligand structure conjured an incremental reaction rate enhancement. A systematic evaluation of **P1** in copper-free Sonogashira cross-coupling reactions revealed a competitive level of performance relative to **IS-1**, in general. However, differences emerged in the instances where an LTM ratio of 3:1 is necessary to furnish high yields. The employment of **P1** was found to be very convenient with its streamlined protocol compared to **IS-1**, which added practicality and increased its attractiveness as a high performance precatalyst. Furthermore, **P1** was found to be substantially more efficient than other state-of-the-art precatalyst alternatives for challenging, industrially valuable substrates. Further developments related to ligand design improvements are underway, as well as the extension of their applications to other Pd-catalyzed cross-coupling reactions.

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## Notes and references

- <sup>a</sup> *Organic Chemistry, Institute of Chemical and Engineering Sciences (ICES), Agency for Science, Technology and Research (A\*STAR), 11 Biopolis Way, Helios #03-08, Singapore 138667;*  
<sup>40</sup> *E-mail: howard\_jong@ices.a-star.edu.sg, yangyo@ices.a-star.edu.sg*  
<sup>b</sup> *School of Medical and Life Sciences, Nanyang Polytechnic, 180 Ang Mo Kio Avenue 8, Singapore 569830*  
<sup>c</sup> *Singapore Bioimaging Consortium (SBIC), Agency for Science, Technology and Research (A\*STAR), 11 Biopolis Way, Helios, #02-02, Singapore 138667*

- † Electronic Supplementary Information (ESI) available: [Synthesis of palladium complexes **P1** – **P4**, general information, experimental procedures and copies of the NMR spectra for all the compounds]. See DOI: 10.1039/b000000x/
- ‡ Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.
- For recent reviews on Pd-catalyzed cross-coupling reactions see: (a) R. R. Tykwinski *Angew. Chem. Int. Ed.* **2003**, *42*, 1566-1568. (b) R. Chinchilla, C. Nájera *Chem. Rev.* **2007**, *107*, 874-922. (c) H. Doucet, J.-C. Hierso *Angew. Chem. Int. Ed.* **2007**, *46*, 834-871. (d) H. Plenio *Angew. Chem. Int. Ed.* **2008**, *47*, 6954-6956. (e) C. Torborg, M. Beller *Adv. Synth. Catal.* **2009**, *351*, 3027-3043. (f) C. A. Fleckenstein, H. Plenio *Chem. Soc. Rev.* **2010**, *39*, 694-711. (g) N. M. Jenny, M. Mayor, T. R. Eaton *Eur. J. Org. Chem.* **2011**, 4965-4983. (h) R. Chinchilla, C. Nájera *Chem. Soc. Rev.* **2011**, *40*, 5084-5121. (i) C. C. C. Johansson Seechurn, M. O. Kitching, T. J. Colacot, V. Snieckus *Angew. Chem. Int. Ed.* **2012**, *51*, 5062-5085. (j) J.-C. Hierso, M. Beaupérin, S. Saleh, A. Job, J. Andrieu, M. Picquet *C. R. Chim.* **2013**, *16*, 580-583. (k) H. B. Li, C. C. C. Johansson Seechurn, T. J. Colacot *ACS Catal.* **2012**, *2*, 1147-1164.
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  - Y. Yang, Chew, X. Chew, C. W. Johannes, E. G. Robins, H. Jong, Y. H. Lim *Eur. J. Org. Chem.* **2014**, 7184-7192.
  - See the Supporting Information for details regarding the preparation of Cy\*Phine- $\text{CF}_3$  and Cy\*Phine-*n*Bu. Buchwald and co-workers have also recently reported the synthesis and use of a similar *n*Bu-substituted terarylphosphine ligand used in nucleophilic fluorination; see reference 16a.
  - Alkynylation reactions in the absence of copper co-catalysts were first reported by Heck and associates. However, Heck alkynylation reactions are more commonly referred to as copper-free Sonogashira reactions. H. A. Dieck, F. R. Heck *J. Organomet. Chem.* **1975**, *93*, 259-263.
  - For arylation of primary amides and aliphatic alcohols, an LTM ratio of 1:1 is effective as recently been shown by Buchwald and co-workers using their 3<sup>rd</sup> Generation Pd precatalysts. For details, see: N. C. Bruno, S. L. Buchwald *Org. Lett.* **2013**, *15*, 2876-2879.
  - N*-heterocyclic carbene (NHC)-based Pd systems frequently employ a 1:1 LTM strategy. The PEPPSI precatalysts have been effective in Negishi, Kumada-Tamao-Corriu and Suzuki-Miyaura reactions. For examples, see: E. A. Kantchev, B. C. J. O'Brien, M. G. Organ *Angew. Chem. Int. Ed.* **2007**, *46*, 2768-2813.
  - The importance of a higher LTM ratio (1.5:1, or more) to furnish good results and to prevent catalyst deactivation for reactions such as the Suzuki-Miyaura reaction and Buchwald-Hartwig amination has been shown by numerous research groups. For examples, see: (a) A. F. Littke, C. Dai, G. C. Fu *J. Am. Chem. Soc.* **2000**, *122*, 4020-4028. (b) A. F. Littke, G. C. Fu *Angew. Chem. Int. Ed.* **2002**, *41*, 4176-4211. (c) A. Zapf, A. Ehrentraut, M. Beller *Angew. Chem. Int. Ed.* **2000**, *39*, 4153-4155. (d) J. P. Wolfe, R. A. Singer, B. H. Yang, S. L. Buchwald *J. Am. Chem. Soc.* **1999**, *121*, 9550-9561. (e) E. R. Strieter, D. G. Blackmond, S. L. Buchwald *J. Am. Chem. Soc.* **2003**, *125*, 13978-13980.
  - The Buchwald group previously reported the need to add additional ligand to their monophosphine-ligated, 2<sup>nd</sup> Generation Pd XPhos precatalyst in order to achieve good results in their alkynylation reactions, see: W. Shu, S. L. Buchwald *Chem. Sci.* **2011**, *2*, 2321-2325.
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  - D. Gelman, S. L. Buchwald *Angew. Chem., Int. Ed.* **2003**, *42*, 5993-5996; J.-C. Hierso, A. Fihri, R. Amardeil, P. Meunier *Org. Lett.* **2004**, *6*, 3473-3476; C. Torborg, J. Huang, T. Schulz, B. Schäffner, A. Zapf, A. Spannenberg, A. Börner, M. Beller, M. *Chem. Eur. J.* **2009**, *15*, 1329-1336.
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  - Details for alternative method to prepare **P1**: To an oven-dried round bottom flask was added PdCl<sub>2</sub>(COD) (28.6 mg, 0.1 mmol, 1.0 equiv.) and anhydrous THF (5 mL). With rapid stirring, Cy\*Phine (110.8 mg, 0.2 mmol, 2.0 equiv.) was added. The vial was capped under argon and stirred vigorously at room temperature overnight. The solvent was concentrated *in vacuo* and pentane (10 mL) was added. The resulting yellow precipitate was filtered through a sintered glass frit, washed with pentane (3 × 5 mL), and dried under reduced pressure to afford a yellow solid (111 mg, 85%).
  - Precatalysts **P1** – **P3** have been stored on the benchtop for at least 30 days without any observable loss of catalytic activity.
  - More detailed studies will need to be conducted to elucidate the complex phenomenon. We postulate that the differences in solubility of the catalysts and bases, as well as the number of catalyst species in solution, could all potentially impact the performance.
  - (a) H. G. Lee, P. J. Milner, S. L. Buchwald *J. Am. Chem. Soc.* **2014**, *136*, 3792-3795. (b) T. J. Maimone, P. J. Milner, T. Kinzel, Y. Zhang, M. K. Takase, S. L. Buchwald *J. Am. Chem. Soc.* **2011**, *133*, 18106-18109.
  - Efficient transformations of these types of substrates is often beyond the capabilities of other catalyst systems, see: refs. (1k) and (10).