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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, $PdCl_2L_2$ (L = Cy*Phine, Cy*Phine-CF_3 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 one of the most valuable contributions to synthetic chemistry.[1] In line with this, 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.[2] 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.[3] Herein, we describe the development of Pd precatalysts, $PdCl_2L_2$ (L = Cy*Phine,[3] Cy*Phine-CF_3[4] and Cy*Phine-*n*Bu[4]), 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[5]) 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.[6–9] 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 for a 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.[1k,10] However, only two

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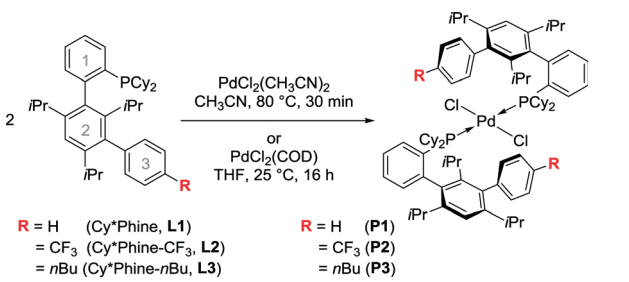
† Electronic supplementary information (ESI) available: Synthesis of palladium complexes **P1–P4**, general information, experimental procedures and copies of the NMR spectra of all the compounds. See DOI: 10.1039/c5cy00507h

examples, $PdCl_2(PCy_3)_2$ [10e,f] and $Pd(Amphos)_2Cl_2$ [Amphos = $tBu_2(p\text{-}NMe_2C_6H_4)P$],[1k,10g,h] have shown the capacity to couple challenging electron-rich substrates without the need for an 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,[3] and others,[11] to be detrimental to Sonogashira reactions. Furthermore, the presence of Cu^I salts has also demonstrated the capacity to instigate ligand transfer from Pd at elevated temperatures causing interference.[12] Thus, we envisaged that a $PdCl_2L_2$ setup using Cy*Phine as the ligand, L, could make an effective precatalyst for Cu-free Sonogashira cross-coupling.

$PdCl_2$(Cy*Phine)$_2$ (**P1**) was prepared in a facile manner by reacting 2 equivalents of Cy*Phine with $PdCl_2(CH_3CN)_2$ in CH_3CN at 80 °C for 30 minutes under an argon atmosphere. A yellow precipitate was formed, which was collected *via* vacuum filtration to obtain the $PdCl_2$(Cy*Phine)$_2$ precatalyst in high yield (85%). Optionally, $PdCl_2$(COD) can be combined with 2 equivalents of Cy*Phine in THF at room temperature to produce the equivalent precatalyst after overnight agitation.[13] 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.[14]

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).[3] 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 those 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_3PO_4 in CH_3CN 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.[2] Nonetheless, the significant response variance in the different reaction environments was not anticipated, or fully understood at this time.[15] 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**.



Scheme 1 Synthesis of preformed palladium complexes $PdCl_2L_2$ (L = Cy*Phine, Cy*Phine-CF_3, Cy*Phine-*n*Bu).

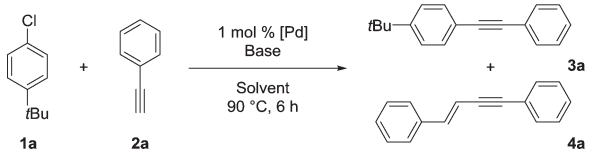
To gauge the performance level of **P1**, we evaluated it against other commercially available di-ligated palladium precatalysts for the coupling of **1a** and **2a** (Chart 1). Phosphine-based Pd systems including $PdCl_2(PPh_3)_2$, $PdCl_2(PCy_3)_2$ and the state-of-the-art $Pd(Amphos)_2Cl_2$ were selected. The N-heterocyclic carbene-based precatalyst, PEPPSI-IPr was also included to offer a broader perspective and completeness. As we were also interested in directly comparing the *m*-terarylphosphine architecture against the biarylphosphine congener, we prepared and included a new precatalyst, $PdCl_2(XPhos)_2$ (**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 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.

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.* $PdCl_2(PPh_3)_2$ and PEPPSI-IPr), the need for slow addition strategies (*e.g.* $Pd(Amphos)_2Cl_2$), and a general substrate scope limitation (*e.g.* $PdCl_2(PCy_3)_2$).

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).

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

Table 1 Optimization of reaction conditions[a]



Entry	Precatalyst	Solvent	Base	Yield[b] (%)
1	**IS-1**[c]	CH_3CN	Cs_2CO_3	91 : 9
2	**IS-1**[c]	CH_3CN	K_3PO_4	47 : 2
3	**P1**	CH_3CN	Cs_2CO_3	87 : 13
4	**P1**	CH_3CN	K_2CO_3	85 : 10
5	**P1**	CH_3CN	Na_2CO_3	56 : 6
6	**P1**	CH_3CN	K_3PO_4	94 : 6
7	**P1**	CH_3CN	CsF	78 : 12
8	**P1**	CH_3CN	Piperidine	24 : 19
9	**P1**	CH_3CN	Et_3N	24 : 22
10	**P1**	Toluene	K_3PO_4	86 : 12
11	**P1**	DMSO	K_3PO_4	15 : 8
12	**P1**	DMF	K_3PO_4	48 : 15
13	**P1**	1,4-dioxane	K_3PO_4	54 : 7
14	**P1**	1,2-DCE	K_3PO_4	32 : 13
15	**P1**	NMP	K_3PO_4	30 : 11
16	**P2**	CH_3CN	K_3PO_4	94 : 6
17	**P3**	CH_3CN	K_3PO_4	95 : 5

[a] 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 of base, 90 °C, 6 h. [b] 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. [c] **IS-1** = $PdCl_2(CH_3CN)_2$ and 2 equiv. of Cy*Phine were added separately to the reaction mixture to form the catalyst *in situ*.

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 to the electron-donating properties of the R-substituent of the third ring (R = −*n*Bu > −H > $-CF_3$). Similarly, a performance enhancement effect was also reported by Buchwald's 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.[16]

A substrate scope overview for **P1** is provided in Table 2 with a more comprehensive list found in the ESI.† 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, respectively). More sensitive substrates, like

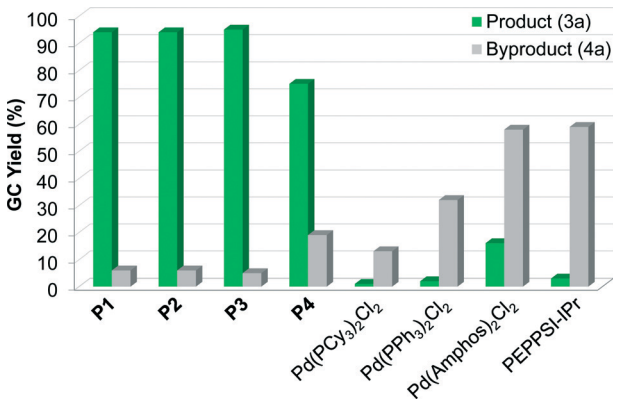


Chart 1 A performance comparison of **P1–P4** with commercially available precatalysts in the benchmark reaction using **1a** and **2a** reaction conditions: 1 mol% Pd precatalyst, 0.5 mmol of 1-*tert*-butyl-4-chlorobenzene (**1a**), 0.6 mmol of phenylacetylene (**2a**), 1 mL of CH_3CN, 1 mmol of K_3PO_4, 90 °C, 6 h. GC-FID yield of **3a** and **4a** based on 0.5 mmol of **1a** using dodecane as an internal standard.

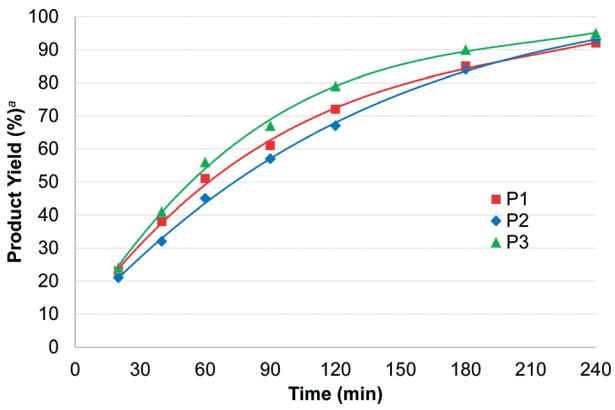
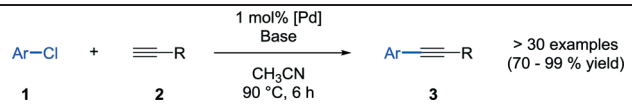
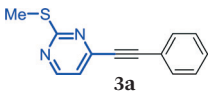
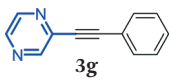
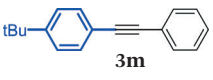
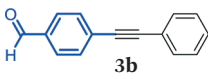
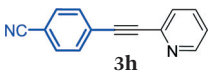
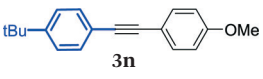
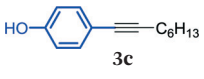
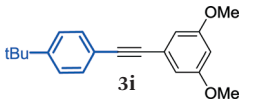
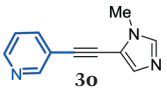
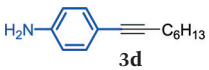
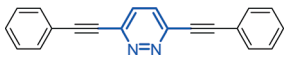
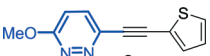
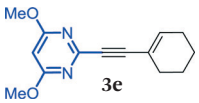
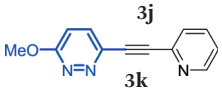
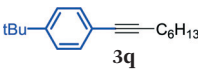
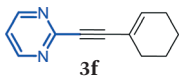
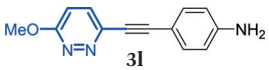
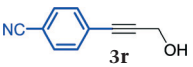


Chart 2 Kinetic profiles of precatalysts **P1–P3** for the benchmark reaction using **1a** and **2a**. Yields determined by GC-FID using dodecane as an internal standard.

Table 2 Selected substrate scope[a]



Entry		Yield[c] (%) method	Entry		Yield[c] (%) method	Entry		Yield[c] (%) method	
								P1	IS-1[d]
1	 3a	95, I	7	 3g	99, I	13	 3m	90, I	91, A
2	 3b	82, I	8	 3h	80, I	14	 3n	97, I	89, A
3	 3c	91, I	9	 3i	92, I[b]	15	 3o	85, I	90, A
4	 3d	82, I	10	 3j	84, II	16	 3p	97, I	95, B
5	 3e	75, I	11	 3k	60, II	17	 3q	93, I	99, C
6	 3f	87, I	12	 3l	90, II	18	 3r	52, I[b] 83, I[e]	95, D

[a] Reaction conditions: Method I: 1 mol% **P1** ($PdCl_2(Cy^*Phine)_2$), 0.5 mmol of aryl chloride **1**, 0.6 mmol of alkyne **2**, 1 mmol of K_3PO_4, 1.0 mL of CH_3CN, 90 °C, 6 h. [b] 12 h reaction time was used instead. Method II: as per method I, except 1 mmol of NEt_3, 1.0 mL of THF, 60 °C, and 12 h were used instead. Method A: 1 mol% **IS-1** (0.005 mmol of $PdCl_2(CH_3CN)_2$, 0.010 mmol of Cy*Phine), 1 mmol of Cs_2CO_3, 1.0 mL of CH_3CN. Method B: as per method A, except 1 mmol of Et_3N, 1 mL of THF, 60 °C, and 6 h were used instead. Method C: 1 mol% **IS-2** (0.005 mmol of $Pd(OAc)_2$, 0.015 mmol of Cy*Phine), 1 mmol of Cs_2CO_3, 1 mL of CH_3CN, 90 °C, 3–16 h. Method D: as per method C, except K_3PO_4 was used as the base. [c] Average isolated yields of two runs. [d] Isolated yield values and the conditions for methods A–D were obtained from ref. 3. [e] 1 mol% **P1** and 1 mol% additional Cy*Phine were used (LTM = 3 : 1).

chloropyridazines, required a lower reaction temperature (60 °C) and a different solvent and base combination (THF/NEt_3, Method II) to efficiently promote the alkynylation reaction (Table 2, entries 10–12).

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 difference was the LTM ratio of 3 : 1 utilized by **IS-1** as 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.[3] This augmentation effect was further verified when the experiment was repeated with 1 mol% **P1** and an extra 1 mol% 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%. Therefore, 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.[17]

Conclusions

In conclusion, we have added two *meta*-terarylphosphine ligands (Cy*Phine-CF_3 (**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 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 resulted in 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 under way, as well as the extension of their applications to other Pd-catalyzed cross-coupling reactions.

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Notes and references

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