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# A new P3N ligand for Pd-catalyzed cross-couplings in water†‡

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A new "P3N" ligand, $(n\text{-Bu}_2\text{N})_3\text{P}$, derived from $PCl_3$ and three equivalents of $n\text{-Bu}_2\text{NH}$ is reported. When complexed to palladium, it readily participates in homogeneous (copper-free) Heck–Cassar–Sonogashira and Suzuki–Miyaura couplings. Reliance on relatively low loadings of Pd is documented under aqueous micellar conditions; *i.e.*, in water containing micelles using the well-established and inexpensive anionic surfactant SDS. Comparisons are shown with several commonly used, representative ligands which, by contrast, are made typically in a number of steps that involve environmentally egregious conditions, and can typically be quite expensive. These issues can now be avoided for these very important reactions using this P3N ligand. Quantum calculations showed the conformational, steric, and electronic nature of P3N ligands and the energetics of their binding to Pd.



## Introduction

Phosphine ligands are a ubiquitous part of homogeneous catalysis, serving as fundamental catalytic components in key transformations such as coupling reactions.[1] While there are occasional examples of Pd catalysis proceeding under "ligandless" conditions, the vast majority of reactions, particularly cross-couplings, rely on the careful selection of an appropriate ligand.[2–17] These reactions are not just academically significant but also serve as essential tools in the synthesis of pharmaceuticals, complex organic molecules, and advanced materials.[18–20] In particular, cross-couplings such as Suzuki–Miyaura (SM) and Heck–Cassar–Sonogashira[21–23] have played a pivotal role in the development of innovative pharmaceuticals and bioactive natural products, further emphasizing the need for efficient metal–ligand systems[24] (Fig. 1). Triphenylphosphine is an example of a ligand with a rich history of use in organic synthesis. While it remains widely available and inexpensive, it is an example whose synthesis involves resource-intensive steps, generating a significant environmental burden[25,26] (Fig. 2). Performance-wise, it is by today's standards limited in effectiveness.[27,28] This has driven research toward the development of more electronically and sterically controlled phosphines, which have significantly advanced the field by improving several features associated with the catalytic processes involved.[29–35]

The complexity of synthesizing these advanced ligands raises concerns not only about their scalability and cost, but also about the broader implications associated with their production. Thus, while extensive progress has been made over the past several decades to fine-tune ligands for catalytic

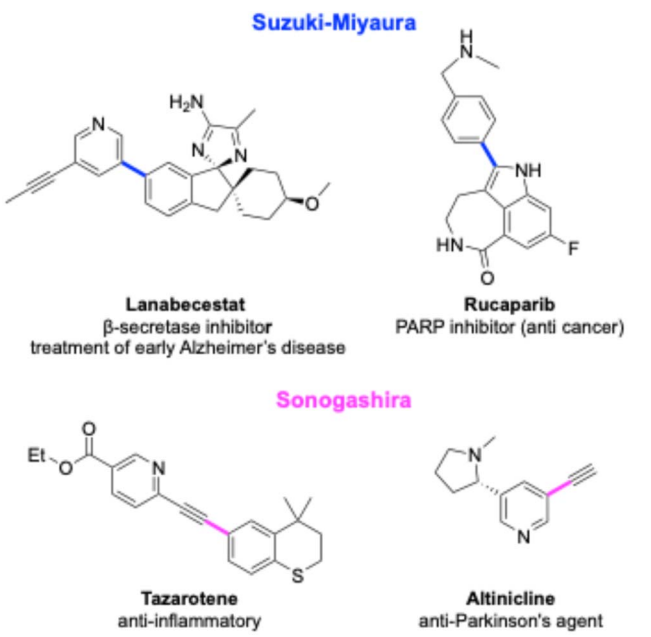


Fig. 1 Examples of bioactive molecules assembled *via* key cross-couplings.

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† This contribution is dedicated to the memory of Aunt Shahla and Dr Alex B. Wood.

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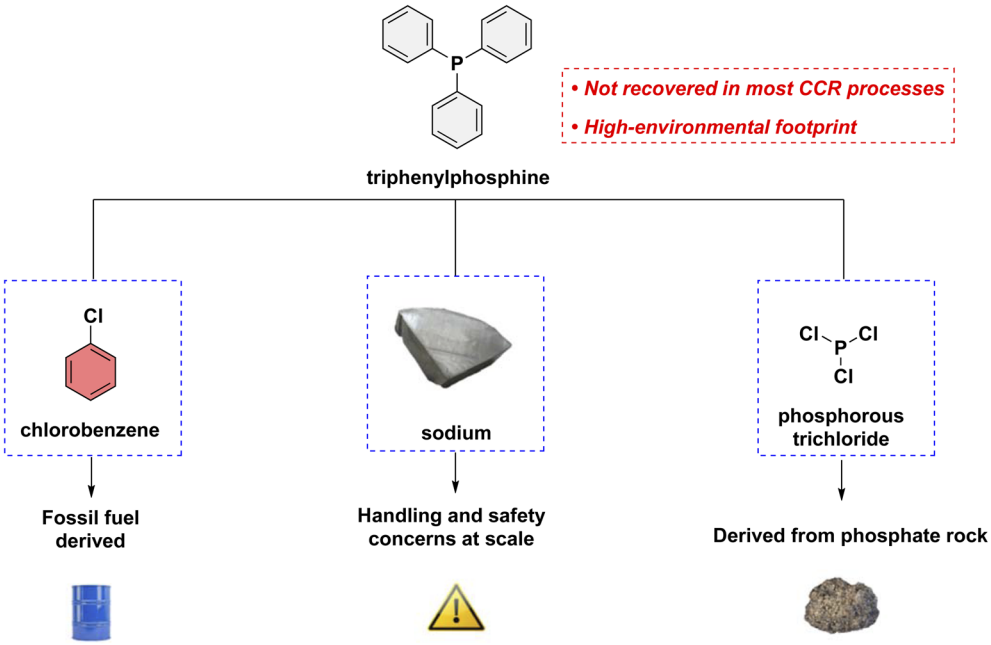



Fig. 2 Conventional synthetic and sustainability issues involving triphenylphosphine ligands composed of P–N bonds, as originally disclosed,[47] especially those containing three such arrays (*i.e.*, "P3N" ligands, or $(R_2N)_3P$) have led to extensive research in attempts to understand their structure and reactivity.[48] Since the first synthesis of an aminophosphine by Michaelis and Luxembourg in 1895,[49] significant advances have enhanced both their applicability and practical value. Their unique electronic properties and steric arrangements have made them valuable ligands in transition metal complexes, in addition to being important intermediates in various transformations.[50–55]

performance, far less attention has been given to the chemistry required for their synthesis. As a result, many ligands are designed with a singular focus in mind: achieving a targeted reaction outcome, oftentimes forgoing environmental and practical constraints associated with their preparation. The preparation of these ligands oftentimes relies on harsh reagents, multi-step procedures, and hazardous waste generation, raising concerns about their long-term sustainability.[36–39] However, times have changed, and there is now a growing awareness of the processes behind reagent, and especially ligand development, the analyses of which include sustainability benchmarks such as Life Cycle Assessments (LCA) and "cradle-to-grave" evaluations.[25,34,40–43] In this context, aminophosphines have resurfaced as a potential alternative to traditional phosphines. Their status is reflected by their expanding roles across several disciplines, such as in coordination chemistry,[44] catalysis,[45] and to a limited extent, organic synthesis.[46] This versatility can be attributed to their unique molecular

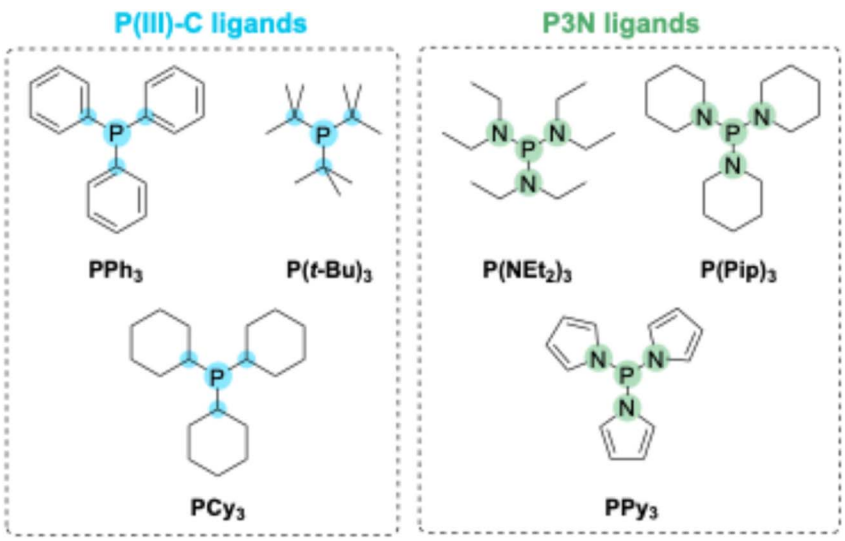



Fig. 3 Representative examples of P–C and P–N ligand frameworks.

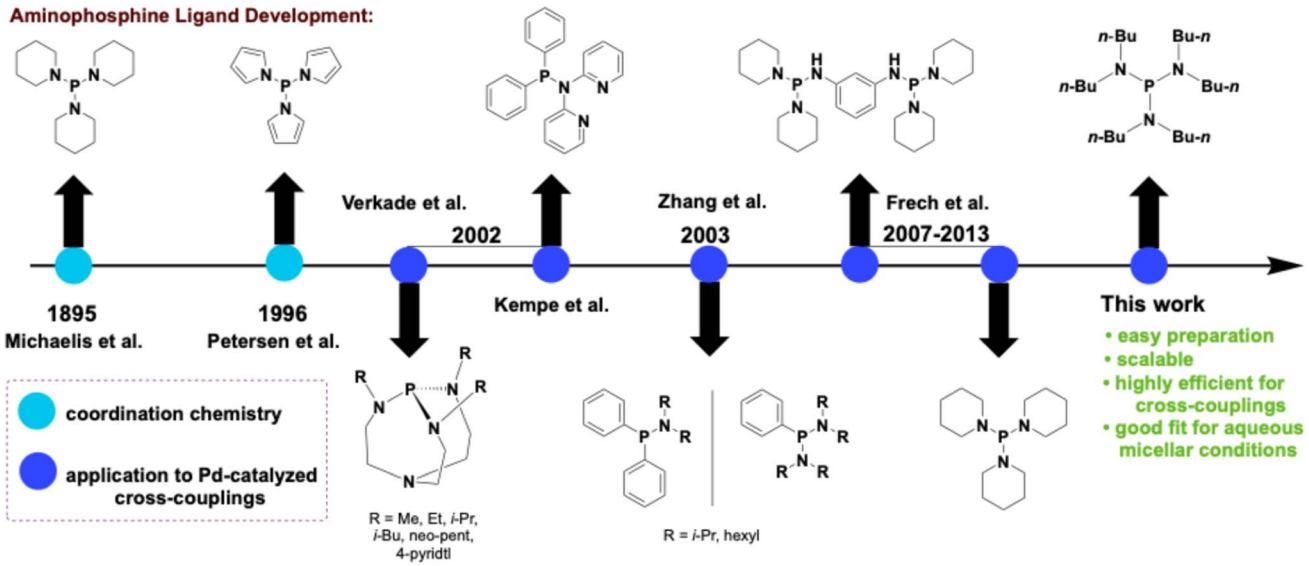



Fig. 4 Evolution of aminophosphines as ligands.

structure, as aminophosphines are characterized by phosphorus being directly attached to each nitrogen (P–N), setting them apart from both "P,N-ligands" as well as conventional phosphines that primarily contain phosphorus–carbon (P–C) bonds.

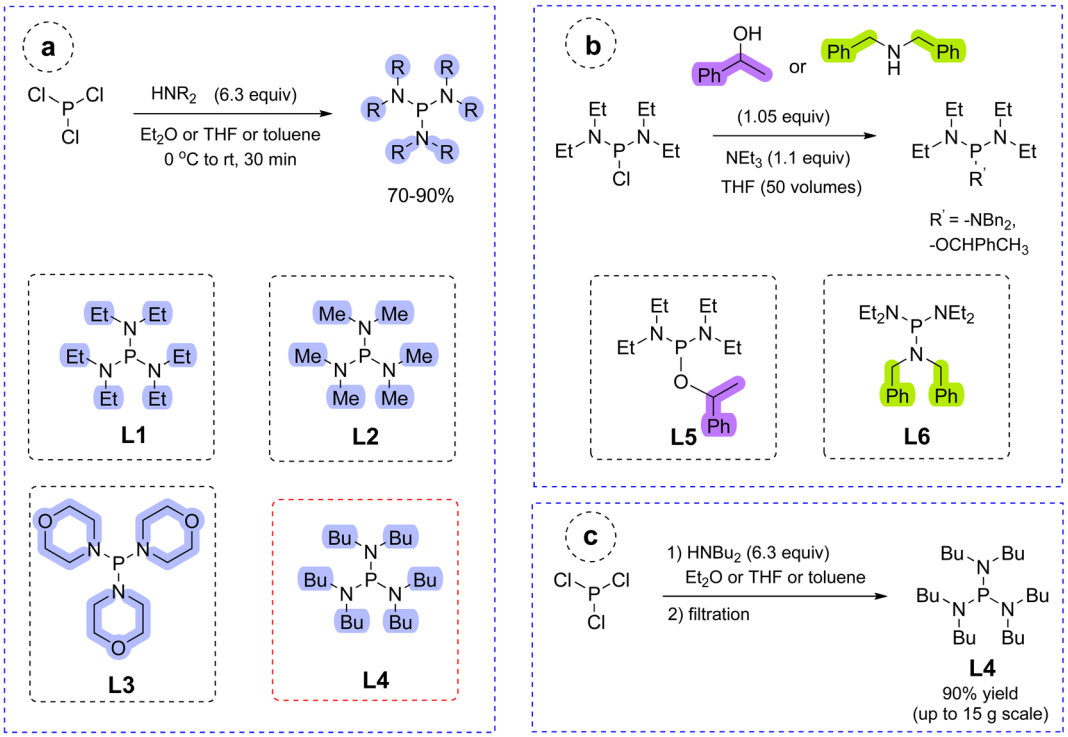
Aminophosphine ligands, however, have only recently gained attention in catalysis. Thus, while their origins can be traced back to the mid-1990s (Fig. 4), a foundational study by Petersen introduced examples of aminophosphines employing *N*-pyrrolylphosphines as a class of phosphorus–nitrogen ligands characterized by unusual steric features and uncommon π-acceptor properties (Fig. 3).[44] Although initially limited to coordination studies, P–N ligands were later investigated in metal-catalyzed transformations; *e.g.*, Verkade and co-workers showed that bicyclic triaminophosphines (see Fig. 4) serve as ligands in Pd-catalyzed Suzuki–Miyaura cross-couplings,[56] work that coincided with the emergence of mono- and di-aminophosphine variants.[53,57,58] In some cases, water in place of traditional organic solvents led to improved selectivity in SM reactions by suppressing homocouplings.[59] A report on 1,3-diaminobenzene-based aminophosphine pincer complexes from Frech and co-workers then followed, which included a limited number of P–N ligands applied to Pd catalysis.[60–62] Subsequently, the same group described aminophosphine ligands with flexible coordination geometries, likewise being utilized in Pd-catalyzed cross-couplings and other metal-catalyzed reactions.[63–66] Notwithstanding these noteworthy advances, significant challenges remained regarding their use as ligands in modern Pd catalysis, in particular from the sustainability perspective.

Herein, we describe the preparation and use of a triaminophosphine ligand, $(n\text{-}Bu_2N)_3P$, designed to address these factors *via* a combination of synthetic simplicity, reaction efficiency, and environmental compatibility. Thus, P3N ligands, in general, can be prepared in a single step utilizing (in several cases) essentially cost-free, commercially available precursors under mild and safety-conscious conditions and hence, suitable for scale up. This simple approach, which readily accommodates single solvent recovery, therefore also leads to a low E-Factor (*e.g.*, cEF), especially when compared to ligands made decades ago.[67] When complexed to Pd, catalysis of both Suzuki–Miyaura and Heck–Cassar–Sonogashira reactions take place under environmentally respectful conditions in aqueous micellar media, and with low catalyst loadings.

## Results and discussion

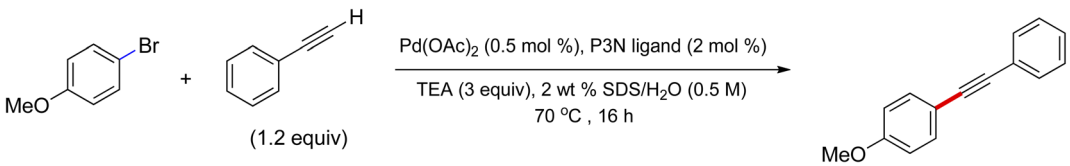
The investigation began by screening several bench-mark ligand-containing Pd catalysts currently in use to effect copper-free Heck–Cassar–Sonogashira reactions.[68] Only an aminophosphine ligand bearing three diethylamino groups (bis(diethylamino)phosphine; **L1**; Scheme 1) led to detectable product formation (see ESI and Table S1‡). The performance of XPhos aligned with previous reports demonstrating its utility in Sonogashira reactions conducted in aqueous media.[68] The modest activity observed with this Pd-complexed P3N ligand **L1** suggested that, with further refinement, a more effective catalyst matched to the new rules[69] associated with chemistry in water might be identified.

The commercially available aminophosphine, tris(dimethylamino)phosphine (HMPT; **L2**) was not pursued given its precursor status to its oxidized version, HMPA. Using **L1**, therefore, a limited screening was performed which revealed that improvements could be achieved using triethylamine as base under aqueous micellar medium, albeit by increasing the reaction temperature. Reducing the Pd loading to 0.5 mol% had minimal impact on efficiency (Table 1, entries 1 and 2; also see ESI, Table S2‡). Increasing the ligand lipophilicity was also anticipated to assist the process by enhancing the binding




Scheme 1 (a) Different variations of synthesized symmetrical aminophosphines. (b) Unsymmetrical variation of aminophosphines. (c) Scaled-up synthesis of **L4**.

Table 1 Evaluation of ligands **L1** to **L6** (see below table) as their Pd complexes in Sonogashira couplings




| Entry | Ligand | Conversion[a] (%) | Yield[b] (%) |
|---|---|---|---|
| 1 | **L1** | 10 | 6 |
| 2 | **L2** | 56 | 45 |
| 3 | **L3** | 44 | 36 |
| **4** | **L4** | **full** | **92** |
| 5 | **L5** | 86 | 79 |
| 6 | **L6** | NR | — |

[a] GCMS conversion. [b] Isolated yields.

constant between the Pd-containing catalyst and inner cores of the nanomicelles in which the coupling is taking place.[70,71]

Inspired by the earliest known aminophosphine ligand, tris(piperidinyl)phosphine, used by Frech and co-workers in Heck–Cassar–Sonogashira couplings,[49,62] the analog tris(morpholino)phosphine (**L3**) was prepared and then tested in the same coupling. This ligand was chosen as a more polar variant with the aim of improving solubility and performance under aqueous micellar conditions. However, when evaluated under the same optimized reaction conditions, **L3** afforded an unacceptable level of conversion and hence, isolated yield (Table 1, entry 3).

In order to evaluate new ligands featuring increased steric bulk and lipophilicity in Heck–Cassar–Sonogashira reactions in micellar media, two variants were prepared by simply modifying the sequence. Hence, starting with bis(diethylamino)phosphorus monochloride, 1-methylbenzyl alcohol or dibenzylamine was added to arrive at **L5** and **L6**, respectively (Scheme 1b). Evaluation of **L4** *vs.* **L5**, and **L6** as ligands complexed to Pd revealed notable differences in reactivity (Table 1). Phosphine

ligand **L4** led to full conversion and thus, the highest yield, likely benefiting from its steric bulk, which could enhance ligand stability and allow greater temperature tolerance, as well as facilitating reductive elimination.[72,73] Its increased lipophilicity improved micellar compatibility and likely contributes to the observed improvement. Unsymmetrical aminophosphine **L5** derived from dibenzylamine also performed well. Mixed ligand **L6**, incorporating a P–O bond showed no catalytic activity, possibly due to an unfavorable coordination profile or more likely, its electronic nature. These results highlight the significant role that both structure and electronics can play in modulating reactivity in derived P3N-Pd catalysts towards cross-couplings in aqueous micellar media.

Using $[Pd(allyl)Cl]_2$ as the palladium source, a variety of surfactants were investigated, although the best results were anticipated to be found using either nonionic vitamin E-based TPGS-750-M[74] or Savie.[75] However, as the results in Table 2 show, in fact it was the micellar array (and not a nanoemulsion) derived from anionic surfactant sodium dodecylsulfate (SDS)[76,77] that gave the highest yield of acetylenic product. Switching to $Pd(OAc)_2$ (see ESI, Table S7‡) led to the same outcome: SDS outperformed the other surfactants screened (Table 2). Closer examination of the palladium source using two aryl bromides with different electronic properties; 4-bromoanisole and 2-bromobenzonitrile indicated that $Pd(OAc)_2$ is preferred, and hence, it was used in all subsequent studies (see ESI, Tables S4 and S5‡).

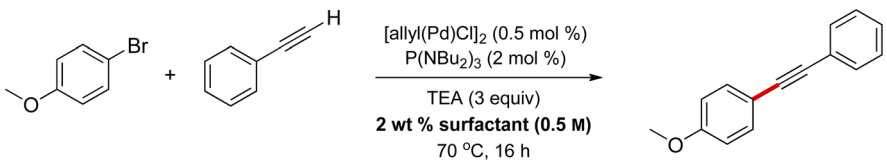
Organic co-solvents were then evaluated in combination with SDS in order to address the likelihood of limited solubility of advanced, highly functionalized substrates (*i.e.*, "brick dust") in the aqueous micellar medium. A sulfonamide derivative, notorious for its poor aqueous solubility,[78] was selected as a test case. Significant improvements in the extent of conversion were observed, relative to SDS in water alone, screening various ether-based solvents, with cyclopentyl methyl ether (CPME)[79] providing the best outcome (see ESI, Table S6‡).

Bases of both the organic and inorganic types was examined under micellar conditions. Organic bases generally performed best, and between triethylamine and those derived from guanidine affording the best results, the former was selected for use due to its low cost, availability, and consistent performance (see ESI, Table S8‡).

Several other reaction parameters were studied in an effort to determine optimum conditions for use of this P3N ligand in Pd-catalyzed Heck–Cassar–Sonogashira couplings. Variations in global concentration had minimal impact on the outcome (see ESI, Table S8‡). The loading of palladium was determined to be 0.25 mol% of dimeric catalyst (thus 0.5 mol% Pd) (see ESI, Tables S9 and S10‡), with a 1 : 4 ratio of this Group 10 metal to P3N ligand (see ESI, Tables S11 and S12‡). Also, while the reaction temperature varied by substrate (see ESI, Table S13‡), reaction times can vary from minutes to usually two hours, although this depends upon both the electronic configuration of the aryl/heteroaryl halide and substrate complexity (see ESI, Tables S14 and S15‡).

As illustrated in Table 3, a wide variety of substrate types readily participate in Heck–Cassar–Sonogashira couplings using this new catalytic system derived from a P3N ligand ($n$-$Bu_2N)_3P$ complexed to (low loadings of) Pd, thereby forming a catalyst that functions well under aqueous micellar conditions. These included unprotected products containing amines (**1**, **12**), secondary amides (**3**, **4**, **8**), and sulfonamides (**3**). Additionally, several alkyne-containing heteroaromatics such as products containing a pyridine (**7**, **9**), oxazole (**4**), quinoline (**10**), benzothiophene (**12**), oxadiazole (**6**), and indole (**2**) were all readily formed. Acetylenes bearing ester groups (**1**, **5**, **11**) were also obtained, as were several bearing carbamates such as Boc-protected amines (**2**, **11**) and Cbz-derivatized amine (**5**). Aldehyde **9** could also be isolated in modest yield. Notably, some highly functionalized aryl bromides from the Merck informer library (**X4** and **X8**) were well tolerated, leading in excellent yields to products **5** and **11**. Single-crystal X-ray diffraction of

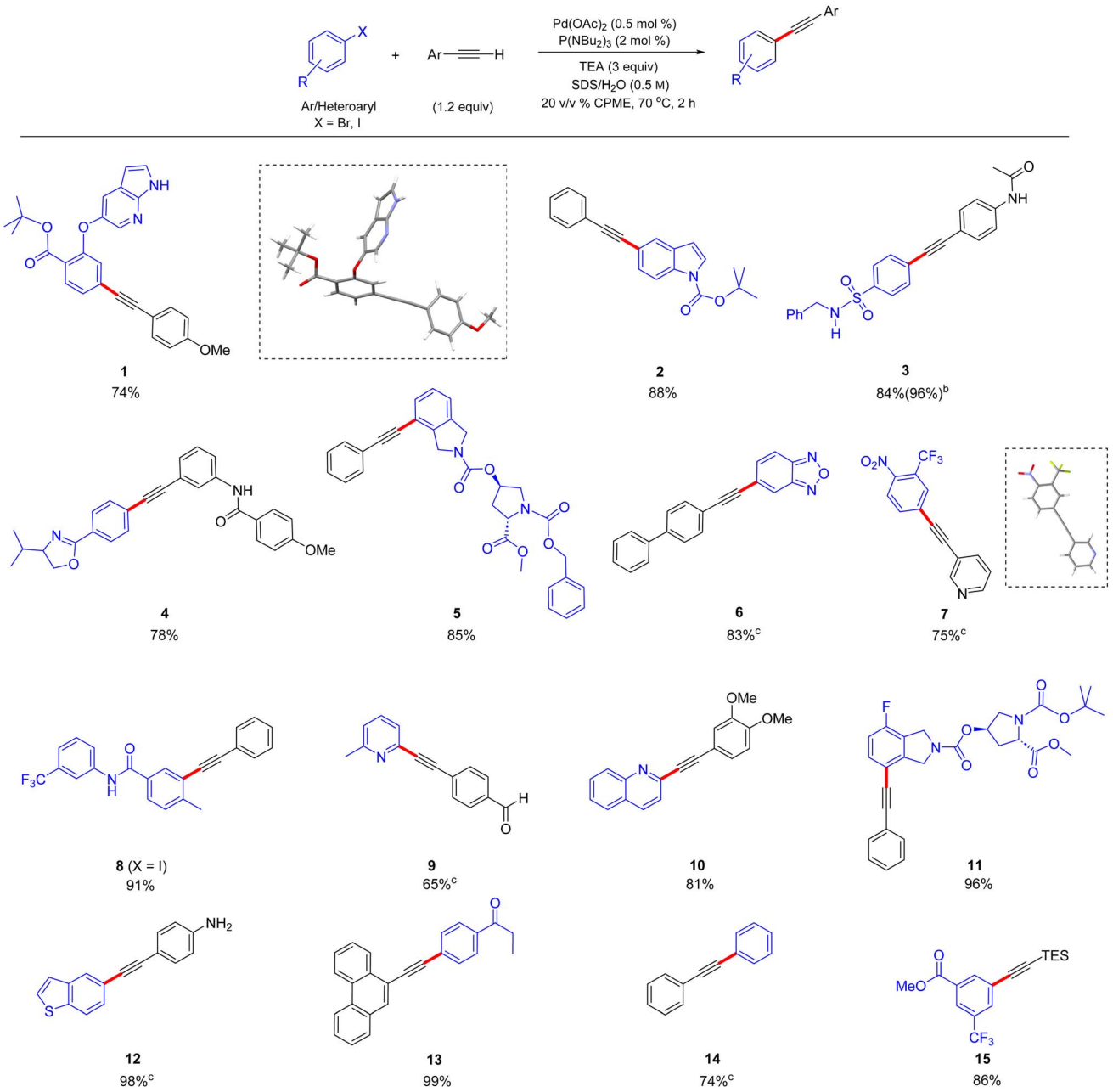
Table 2 Screening surfactants




| Entry | Surfactant | Yield[a] (%) |
|---|---|---|
| a | none (on $H_2O$) | 35 |
| b | TPGS-750-M | 71 |
| c | Tween-100 | 57 |
| d | Savie | 61 |
| e | TTAB | 73 |
| f | SDS | 84 |
| g | Brij-56 | 81 |

[a] qNMR yield using 1,3,5-trimethoxy benzene as an internal standard.

Table 3 Representative products from Heck–Cassar–Sonogashira couplings using the P3N ligand $(n\text{-}Bu_2N)_3P$[a]



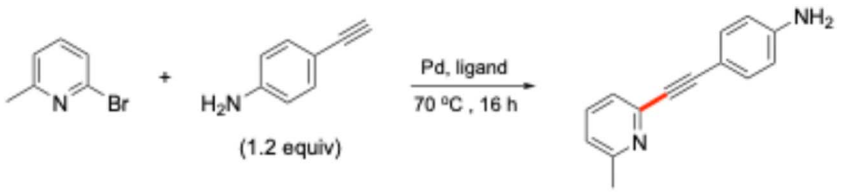

[a] Isolated yields. [b] 1 mol% Pd used. [c] Reaction time: 20 min.

products **1** and **7** (see ESI, Tables S31 and S32‡) confirmed their structure.

The comparative performance of the P3N aminophosphine **L4** to other well-established phosphine ligands was investigated for Heck–Cassar–Sonogashira couplings under identical conditions. Thus, in addition to their simplicity of preparation and very modest cost, as well as their use under aqueous micellar conditions in the total absence of an organic solvent, the results are shown in Table 4. These were obtained using 0.5 mol% of $Pd(OAc)_2$ in the presence of ligand **L4**, indicating that comparable or better yields (by qNMR) are to be expected relative to those screened, including ferrocenyl, N-heterocyclic carbenes, and biaryl phosphine ligands.

Using the optimized coupling conditions applied to Heck–Cassar–Sonogashira couplings (see Table 3), various ligands were screened in this case for use in Suzuki–Miyaura cross-coupling reactions.[80] Aminophosphine **L4** again displayed good performance (see ESI, Table S15‡). Lowering the Pd loading to 0.125 mol% had minimal effect on reaction outcome (see ESI, Table S16‡). A surfactant screening confirmed that SDS

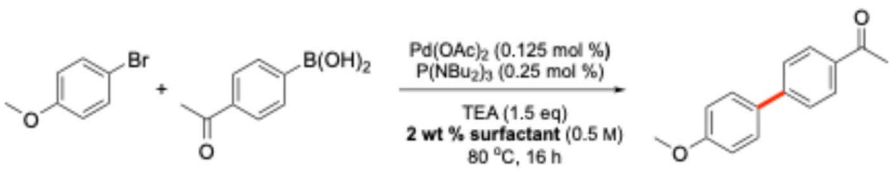
Table 4 Comparative study of ligands on Pd in Heck–Cassar–Sonogashira cross-coupling reactions[a]




| Entry | Ligand | Yield[b] (%) |
|---|---|---|
| 1 | SPhos | 77 |
| 2 | XPhos | 58 |
| 3 | dppf | 79 |
| 4 | DTBPF | 87 |
| 5 | $CyPPh_2$ | 90 |
| 6 | **$P(NBu_2)_3$(L4)** | **92** |
| 7 | IPr | 15 |

[a] Reaction conditions: $Pd(OAc)_2$ (0.50 mol%), **L4** (2 mol%), triethylamine (3 equiv.), 2 wt% SDS/$H_2O$ (0.5 M) 70 °C, 16 h. [b] By quantitative NMR using 1,3,5-trimethoxybenzene as the internal standard.

Table 5 Surfactant screen for Suzuki–Miyaura couplings




| Entry | Surfactant | Yield[a] (%) |
|---|---|---|
| a | none (on $H_2O$) | 33 |
| b | TPGS-750-M | 42 |
| c | Savie | 40 |
| d | SDS | 92 |

[a] qNMR yield using 1,3,5-trimethoxybenzene as an internal standard.

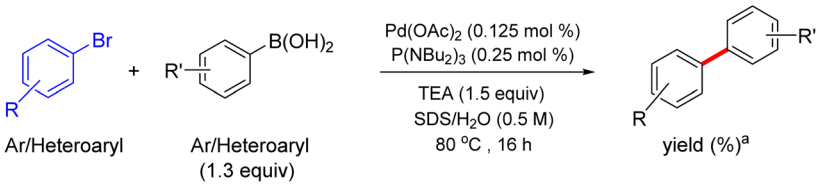
provided considerably higher yields compared to nonionic surfactants, revealing a potential benefit from the sodium counterion in SDS, which may play a role in the transmetalation step[81] (Table 5).

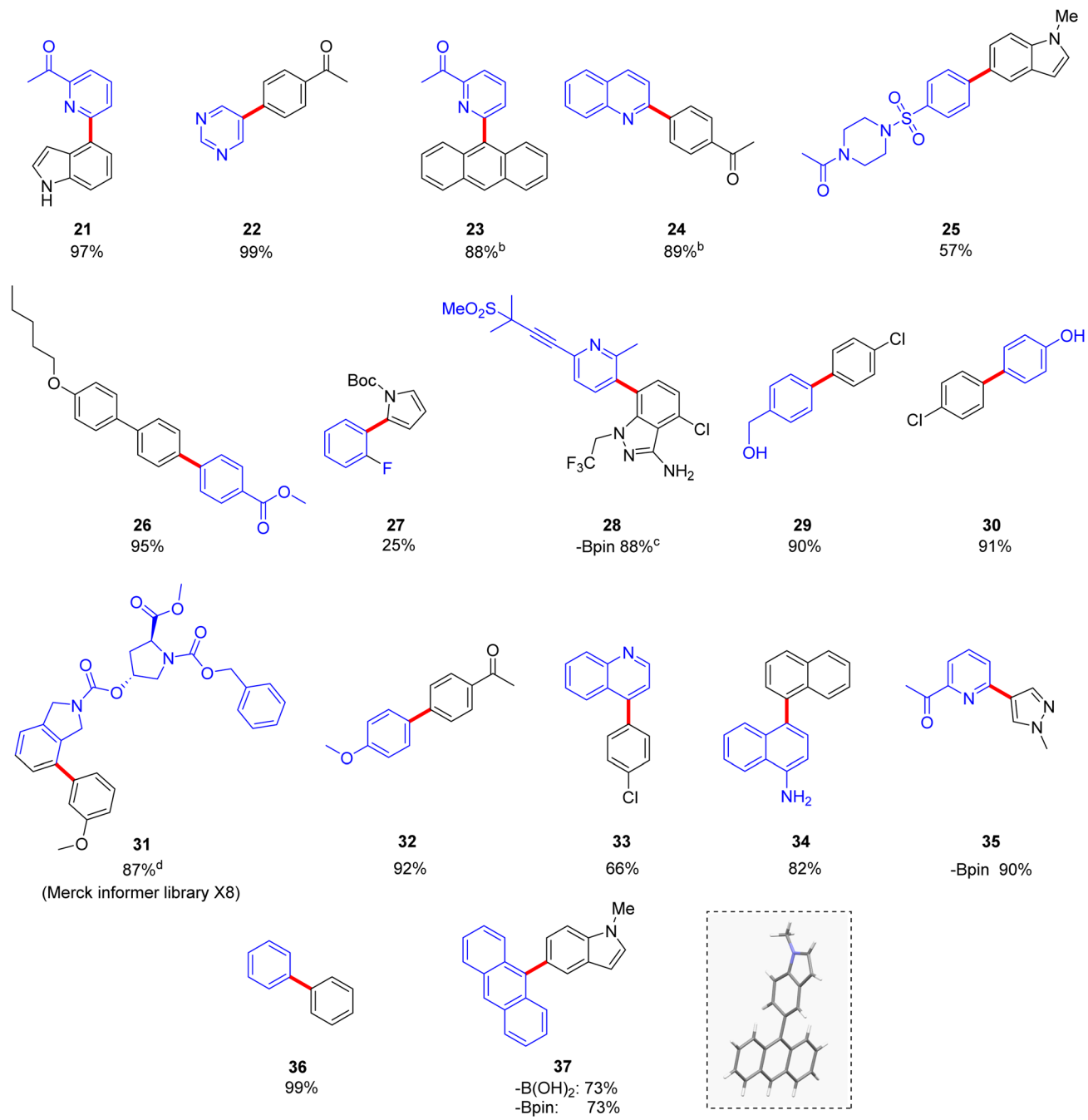
Here, too, relatively inexpensive $Pd(OAc)_2$ was found to be an excellent source of this Group 10 metal. It is worth noting that using the alternative (albeit more costly) commercially available, pre-ligated $Pd(PPh)_2Cl_2$, along with ligand **L4** led to a nearly quantitative yield of the desired product, indicative of a lack of interference of $Ph_3P$ given its presence in the medium (see ESI, Table S18‡).

Finding a compatible co-solvent with potential solubility challenges in mind did not lead to a clear choice (see ESI, Table S19‡), indicating a potential dependence dictated by the substrate. Reaction temperatures of 70–80 °C consistently afforded high catalytic activity. And while use of lower temperatures may suffice, more complex cases appear to require these somewhat elevated temperatures, especially given the low loadings of catalyst (see ESI, Table S24‡).

The scope shown in Table 6 indicates, as with Heck–Cassar–Sonogashira coupling products (see Table 3), that a wide range of functionality is tolerated in these SM reactions using **L4** as the ligand on palladium. Heterocyclic aryl bromides leading to products containing pyridine (**16**, **18**, **23**, **30**), pyrimidine (**17**), quinoline (with leaving group at positions **2** and **4**; **19**, **28**), pyrazole (**30**), indole (**32**) and isoindoline (**26**) are all preserved under these reaction conditions. Unprotected amines present in products **16**, **23**, and **29** are also compatible. Additionally, poorly water-soluble substrates worked efficiently, except in a few cases where a minimal amount of co-solvent was needed to increase the levels of conversion and hence, maintain efficiency (**19**, **23**, **26**). Most, however, worked well in the absence of any co-solvent, leading to products **18**, **20**, **21**, **29**, and **32**. Several representative cases demonstrated that a bromide reacts selectively in the presence of an aryl chloride, which remains for

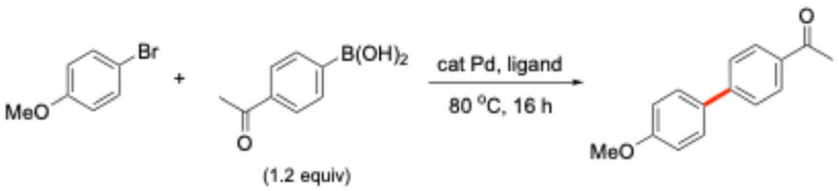
Table 6 Representative examples of Suzuki–Miyaura couplings using the P3N ligand $(n\text{-}Bu_2N)_3P$



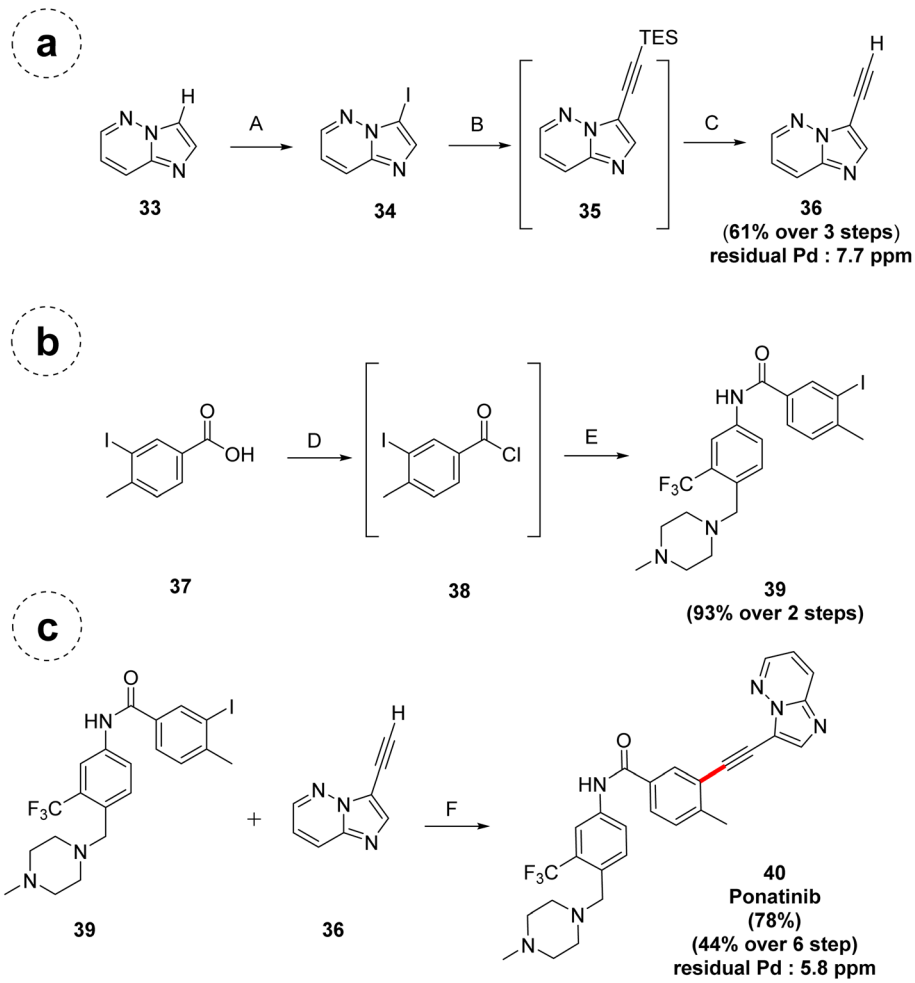

[a] Isolated yield. [b] 20 v/v% CPME as co-solvent. [c] 0.5 mol% Pd, 1 mol% ligand, 20 v/v% CPME, 2 equiv. of boronic ester and 3 equiv. of $NEt_3$ were used. [d] 0.2 mol% Pd, 0.4 mol% ligand, 20 v/v% CPME and 3 equiv. of $NEt_3$ were used.

Table 7 Comparative study of ligand **L4** performance in a SM coupling[a]




| Entry | Ligand | Yield[b] (%) |
|---|---|---|
| 1 | SPhos | Quant |
| 2 | Xphos | Quant |
| 3 | dppf | 94 |
| 4 | $CyPPh_2$ | 95 |
| 5 | $(n\text{-}Bu_2N)_3P$ (**L4**) | **92** |

[a] Reaction conditions: aryl bromide (0.25 mmol), boronic acid (1.2 equiv.; 0.3 mmol), $Pd(OAc)_2$ (0.125 mol%), **L4** (0.25 mol%), triethylamine (1.5 equiv.), 2 wt% SDS/$H_2O$ (0.5 M), 80 °C, 16 h. [b] By quantitative NMR using 1,3,5-trimethoxybenzene as internal standard.

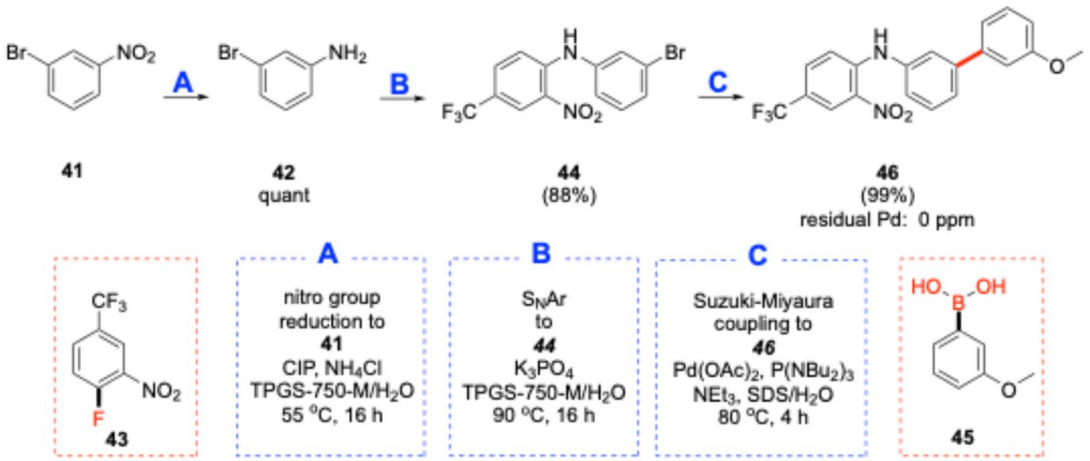



Scheme 2 Multi-step synthesis of ponatinib; reaction conditions: (a) step A: **33** (1 equiv.), NIS (3 equiv.), $I_2$ (5 equiv.), ACN (1.8 M), 80 °C, Ar, 30 min. Step B: **34** (1 equiv.), TES-acetylene (1.5 equiv.), $Pd(OAc)_2$ (0.5 mol%), **L4** (2 mol%), $NEt_3$ (3 equiv.), 2 wt% SDS/$H_2O$ (0.5 M), CPME (20 v/v%), 70 °C, Ar, 16 h. Step C: **35** (1 equiv.), TBAF (1 equiv.), THF (0.02 M), 0 °C to rt, 16 h. (b) Step D: **37** (1 equiv.), $(COCl)_2$ (3 equiv.), EtOAc (0.25 M), 0 °C to rt, 2 h. Step E: **38** (1 equiv.), 4-[(4-methyl-1-piperazinyl)methyl]-3-(trifluoromethyl)aniline (1 equiv.), EtOAC (0.18 M), $NEt_3$ (3 equiv.), 0 °C to rt, 2 h. (c) Step F: **39** (1 equiv.), **36** (2 equiv.), $Pd(OAc)_2$ (0.75 mol%), **L4** (3 mol%), $NEt_3$ (3 equiv.), 2 wt% SDS/$H_2O$ (0.5 M), CPME (20 v/v%), 70 °C, Ar, 16 h.

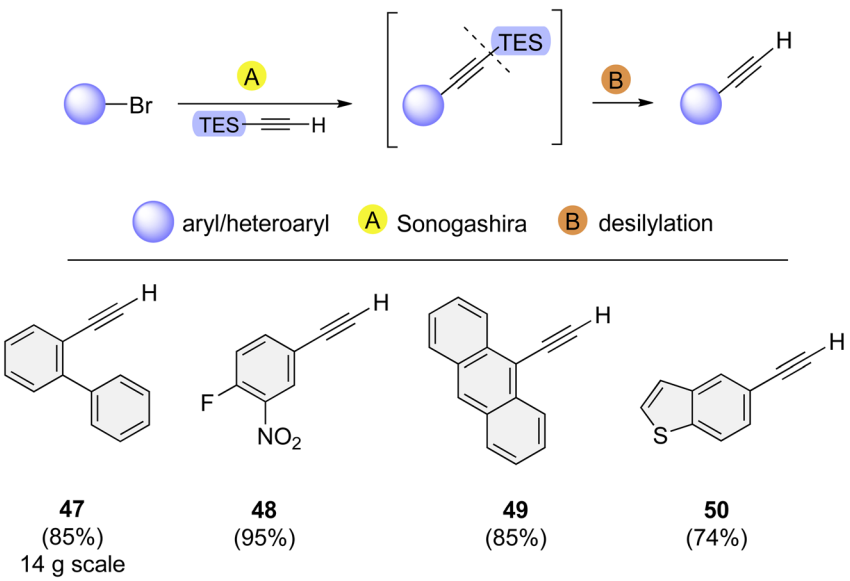
further functionalization (**23–25**, **28**). Other functional groups such as products containing a methyl ketone (**16–19**, **27**, **30**), an unprotected benzylic alcohol (**24**), fluorides (**22** and **23**), methyl esters (**21** and **26**), a sulfonamide (**20**), carbamate (**16**), phenol (**25**), and internal alkyne (**23**) were all well-tolerated. On the other hand, product **27** was unexpectedly obtained in low yield. Importantly, both boronic acids and esters all appeared to be compatible with this methodology (see products **28**, **35**, and **37**). The X-ray crystal structure of **37** further confirmed a successful coupling (see ESI and Table S33‡).

By way of comparison of various ligands commonly associated with Suzuki–Miyaura couplings (Table 7), all led to the product biaryls in high yields using the standard 1 : 2 ratio of Pd : ligand, with a loading of only 0.125 mol% $Pd(OAc)_2$. However, considering the complexity and the number of required steps to synthesize traditional phosphines, P3N ligand **L4** still deserves serious consideration as an inexpensive, easy-to-make, and effective ligand that appears to be competitive with other common phosphine ligands used on palladium for SM cross-coupling reactions.

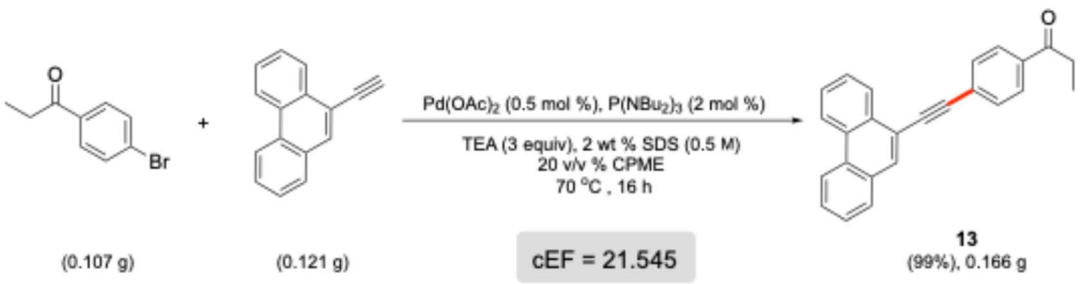
Focus then shifted towards use of aminophosphine **L4** as a ligand on Pd as catalyst in a late-stage application, selecting synthesis of the unsymmetrical alkyne ponatinib, an FDA-approved tyrosine-kinase inhibitor (Scheme 2).[82] To obtain terminal alkyne intermediate **35**, imidazo[1,2-*b*]pyridazine **33** was initially treated with iodine/NIS to obtain iodinated product




Scheme 3 3-Step sequence; reaction conditions: step A: **41** (1 equiv.), CIP (5 equiv.), $NH_4Cl$ (3 equiv.), 2 wt% TPGS-750-M/$H_2O$ (0.5 M), 10 v/v% THF, 55 °C, 16 h. Step B: **42** (1 equiv.), **43** (1.1 equiv.), $K_3PO_4 \cdot H_2O$ (2 equiv.), 2 wt% TPGS-750-M/$H_2O$ (1 M), 90 °C, 16 h. Step C: **44** (1 equiv.), **45** (1.3 equiv.), $Pd(OAc)_2$ (0.125 mol%), **L4** (0.25 mol%), $NEt_3$ (1.5 equiv.), 2 wt% SDS/$H_2O$ (0.5 M), 80 °C, Ar, 4 h.




Scheme 4 Synthetic approach to terminal alkynes using **L4** as the ligand; reaction conditions: step A: aryl bromide (1 equiv.), TES acetylene (1.2 equiv.), $Pd(OAc)_2$ (0. 5 mol%), **L4** (2 mol%), $NEt_3$ (3 equiv.), 2 wt% SDS/$H_2O$ (0.5 M), CPME (20 v/v%), 70 °C, Ar, 16 h. Step B: TBAF (1 M in THF, 1.5 equiv.), DCM (0.1 M), 0 °C to rt, 2 h.




Scheme 5 Complete E-Factor for the preparation of **13**.

**34**.[83] (Triethylsilyl)acetylene was then coupled to form the corresponding protected alkyne **35**. Deprotection afforded terminal alkyne **36**.[84] This 3-step sequence (Scheme 2a) led to an overall yield of 61%. Analysis of **36** *via* ICP-MS revealed the presence of only 7.7 ppm Pd to be present, notwithstanding the lack of any "clean up" involved that is required under typical Heck–Cassar–Sonogashira conditions where higher loadings of catalyst are utilized in organic solvents. Since the FDA limit for Pd is only 10 ppm/dose/d, use of low loadings of a Pd complexed by a very low-cost ligand may translate into considerable catalyst cost savings on scale up, especially when this is a major factor in drug synthesis earmarked for distribution in low-income countries. Synthesis of the coupling partner **39** was straightforword (2-steps; 93% overall yield; Scheme 2b).[85] The final Heck–Cassar–Sonogashira coupling between fragments **36** and **39** (Scheme 2c) afforded ponatinib (**40**) (78% isolated yield). The overall 6-step sequence took place in 44% yield, while the ICP-MS on the API itself showed it to contain only 5.8 ppm of palladium.

An additional 3-step sequence highlighting a SM coupling catalyzed by the same Pd catalyst containing ligand **L4** is shown in Scheme 3. Thus, starting with *meta*-bromonitrobenzene (**41**), treatment with carbon iron powder (CIP)/ammonium chloride led to aniline **42**. Simple filtration to remove the CIP followed by an $S_NAr$ reaction using crude material with **43** afforded **44**. SM coupling of **44** with boronic acid **45** gave biaryl **46**, which was obtained in an overall yield of 87% over three steps. As expected, when using low loadings of a Pd catalyst under aqueous micellar conditions, ICP-MS analysis in this case failed to show any residual Pd to be present in final product **46**.

Terminal alkynes, as either targets or reaction partners, are readily fashioned in 1-pot using this new methodology. Heck–Cassar–Sonogashira couplings using TES-acetylene (as employed *en route* to ponatinib; see Scheme 2a) followed by an in-flask desilylation with TBAF at 0 °C-rt arrives at each of the terminal acetylenic products **47–50** (Scheme 4). This sequence included the biaryl containing alkyne **47**, 14 grams of which was prepared in 85% isolated yield suggesting that scaling up these couplings should be straightforward.

Complete environmental factors (cEF) is a common metric used to assess a methodology's greenness.[86] For the synthesis of compound **13** (Scheme 5) a cEF was calculated to be 21.5 (see the ESI,‡ page 42 for calculations). Recycling the aqueous medium containing SDS twice was accompanied by a moderate decrease in conversion, and hence, isolated yield, to the desired product.

## Ligand studies

The reasons for the efficacy of the P3N ligands are not immediately obvious. The nature of these ligands has been explored with quantum calculations. The electronic properties of the P–N bond and the lone pair on phosphorus are unique and are revealed, for example, in calculated gas-phase electronic proton affinities (PAs) of the very simple model ligand, $P(NH_2)_3$ shown in Table 8 for protonation on phosphorus along with related molecules for comparison. To compensate for well-known polarization effects of substituents in the gas phase[87] the PAs of the model ligands $P(NH_2)_3$ and $N(NH_2)_3$ are compared with those of $PMe_3$ and $NMe_3$, respectively. Where the methyl substituents are of comparable polarizability to the amino substituents. Thus, the relative electronic PAs in Table 8 will reflect the remaining effects on the basicities, such as inductive and other effects, after the polarization effects from charge-induced dipole stabilization of the phosphonium and ammonium ions are subtracted out. In the case of $N(NH_2)_3$, the interpretation seems simple: the 17 kcal mol$^{-1}$ difference in electronic PA relative to that of trimethylamine in Table 8 is almost surely due to a quite strong short-range inductive effect of the three amino substituents.

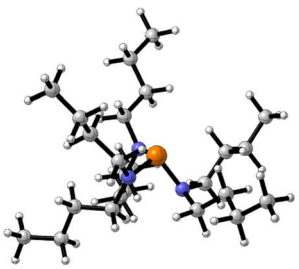
For $P(NH_2)_3$, interpreting the PA data is more complicated. Its electronic PA is remarkably much higher, by almost 20 kcal mol$^{-1}$, than that for $N(NH_2)_3$, in spite of the fact that protonation on N is slightly favored over P in trimethylamine *versus* trimethylphosphine. Why? The 4.33 kcal mol$^{-1}$ higher

Table 8 Computed electronic proton affinities energies, $\Delta E^\circ_{e,rel}$, for protonation at the central phosphorus (or nitrogen) at the G4 level of theory. Energies in kcal mol$^{-1}$

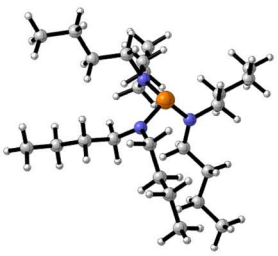
| | Electronic PA | Rel. Electronic PA |
|---|---|---|
| | $\Delta E^\circ_{e,rel}$, $G_4$ | $\Delta\Delta E^\circ_{e,rel}$, *vs.* $Me_3P$ or $Me_3N$ |
| $P(NH_2)_3$ | 237.73 | 4.22 |
| $PMe_3$ | 233.51 | 0.00 |
| $N(NH_2)_3$ | 216.33 | −2.13 |
| $NMe_3$ | 218.46 | 0.00 |

Table 9 Calculated electronic energies, enthalpies, and free energies in kcal mol$^{-1}$ at 298 K for reactions of ligand conformers **A** and **B** with Pd and oxidative additions to bromobenzene at B3LYP/6-31G(d) and B3LYPD3BJ/6-31+G(d,p) levels of theory, with a SDD basis for Pd and Br, in the gas phase and in toluene solvent using solvation free energies from the SMD method

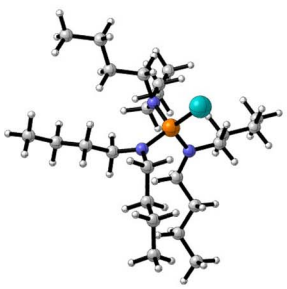
| | B3LYP | B3LYPD3BJ | | | |
|---|---|---|---|---|---|
| Structure | $\Delta E_e^\circ$ | $\Delta E_e^\circ$ | $\Delta H_{298K}^\circ$ | $\Delta G_{298K}^\circ$ | $\Delta G_{298K,tol}^\circ$ |
| **A** to **B** | −0.57 | 0.88 | 0.95 | 1.42 | 1.68 |
| **PdA** to **PdB** | −0.23 | 2.96 | 3.14 | 3.04 | 3.25 |
| **PdPhBrA** to **PdPhBrB** | −1.86 | −0.94 | −0.68 | −0.85 | −1.04 |
| **Pd** + **B** to **PdB** | −41.92 | −50.74 | −52.52 | −43.36 | −43.55 |
| **PdB** + **B** to **PdB$_2$** | −34.90 | −52.03 | −53.47 | −37.08 | −34.39 |
| **PdB** + **PhBr** to **PdPhBrB** | −38.55 | −53.91 | −52.17 | −37.83 | −31.19 |
| **PdB$_2$** + **PhBr** to **PdPhBrB$_2$** | −11.00 | −33.52 | −28.80 | −11.52 | −6.30 |
| **PdPhBrB** + **B** to **PdPhBrB$_2$** | −7.35 | −31.63 | −30.10 | −10.77 | 2.05 |



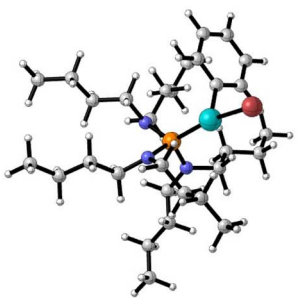
**A** Ligand conformer, $C_3$, all *anti*



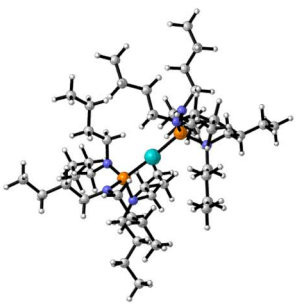
**B** Ligand conformer



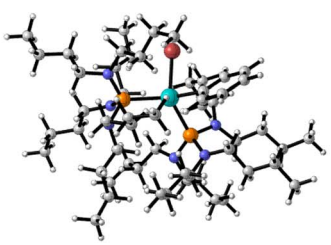
Pd**B** (Ligand + Pd)



**PdBPhBr** (oxidative addition product with PhBr)



**PdB$_2$** Two P3N ligands on Pd



**PdB$_2$PhBr**, oxidative addition product with PhBr

Fig. 5 Structures of tris-(di-*n*-butylamino)phosphine ligand and Pd complexes at the B3LYPD3BJ/6-31+G(d,p) and B3LYPD3BJ/6-31+G(d,p)/SDD(Pd,Br) levels of theory. Color key: teal: palladium, orange: phosphorus, brown: bromine, blue: nitrogen.

basicity relative to $PMe_3$, must result from more than one effect. The strong 17 kcal $mol^{-1}$ inductive effect in $N(NH_2)_3$, should be felt in $P(NH_2)_3$ in near equal force. So, there must be another, even stronger, base-strengthening effect(s) of 21 kcal $mol^{-1}$ operating! Looking at the calculated structures gives a hint of what this might be (see Fig. S1 in ESI-2‡ for structures). The computed PNH bond angles in $P(NH_2)_3$ at the amino nitrogens lie well above 109.5°, up to 116.3° and 119.1°, and the computed natural bond orbital analysis shows $sp^{1.98}$ and $sp^{2.84}$ hybridizations at N for the localized orbitals. The structure for $N(NH_2)_3$ shows no such behavior. It has near-tetrahedral geometry at the amino nitrogens and computed hybridizations near $sp^3$. This seems to point directly to d-orbital involvement in the phosphorus-containing model ligand, though, interestingly, little documentation of such a large d-orbital effect seems to appear in the aminophosphine literature.[88] Although one might expect the three amino substituents would exert a strong inductive electron withdrawal from the phosphorus, as in $N(NH_2)_3$, it would appear that considerable electron density may be donated back from the nitrogen lone pair to appropriately-oriented empty d-orbital(s) on P *via* a P–N pi bond, a type of "back bonding". This would explain the shift toward $sp^2$ hybridization on the amino nitrogens to provide a nearly p lone-pair orbital on N. Looking at the computed charge on phosphorus and P-31 chemical shifts of aminophosphines, however, it does not appear that the inductive effect of the amino groups has fully been mitigated by p–d back bonding in $P(NH_2)_3$. Looking at the computed structure of the protonated aminophosphine, $HP^+(NH_2)_3$, shows another, more remarkable, bond-angle change. There the amino nitrogens have assumed nearly trigonal geometry and a nearly 0.1 Å shorter P–N bond length than in $P(NH_2)_3$.[88a] Thus, the large effect of d-orbitals is not just in the neutral $P(NH_2)_3$, but appears to exert a much stronger effect on the stabilization of the protonated species $HP^+(NH_2)_3$. This is not unexpected since P now has a full formal plus charge that can be very strongly stabilized by electron donation from three N lone-pair p orbitals. One would expect this to also affect the Pd–P bonding as electrons are donated from P to Pd in catalysts derived from P3N ligands. We are actively exploring this question.

The structure of the tris-(di-*n*-butylamino)phosphine ligand in Fig. 1 was optimized at the B3LYPD3BJ/6-31+G(d,p) level of theory with an unsymmetrical $C_1$ conformation **A** and an all-anti arrangement of the *n*-butyl groups chosen to have the groups arranged to have a minimum steric energy and keep the *n*-butyl groups away from the face of the phosphine to allow binding to palladium and it's oxidative addition substrate. A second reasonable conformation **B** like this was of $C_3$ symmetry, but a bit less hindered sterically on the face of the phosphine, had about a 1.7 kcal $mol^{-1}$ higher free energy at 298 K in the gas phase and in toluene solvent, which mimics the solvation environment in the micelles (see ESI-2‡). The *n*-butyl groups could adopt numerous other conformations, but conformations **A** and **B** both appear to be reasonably low energy and representative. Other conformations were not explored. Reaction energies for various reactions of **A** and **B** are shown in Table 9 (see Fig. 5 for structures).

Attachment of Pd to conformers **A** and **B** led to formation of **PdA** and **PdB**, which were optimized at the B3LYP/6-31G(d)/SDD(Pd,Br) and B3LYPD3BJ/6-31+G(d,p)/SDD(Pd,Br) levels of theory, in this case, with the **PdA** conformer more stable by 3.3 kcal $mol^{-1}$ in toluene. The ligand addition has a free energy of reaction of about −44 kcal $mol^{-1}$. A second ligand could be added on the **PdB** to give $\mathbf{PdB_2}$, with a free energy of −35 kcal-$mol^{-1}$. Oxidative addition of bromobenzene to **PdB** gave the intermediate **PdPhBrB** that is strongly downhill by −39 kcal $mol^{-1}$. In spite of a good deal of steric hindrance, we find that $\mathbf{PdB_2}$ might also undergo oxidative addition with bromobenzene with a somewhat negative free energy of −12 kcal $mol^{-1}$ in the gas phase and −6 kcal $mol^{-1}$ in toluene. That product $\mathbf{PdPhBrB_2}$, however, is predicted to be vulnerable to lose one ligand in toluene, though more stable in the gas phase. Thus, it appears that both the di-ligated and mono-ligated palladium molecules are candidates for catalytic activity with substrates that are not too sterically demanding, in which case the monoligated catalyst should be preferred.

## Conclusions

A new P3N ligand has been shown to be effective when complexed to Pd in a 2 : 1 ratio, forming a very inexpensive catalyst useful for both Sonogashira and Suzuki–Miyaura couplings run under environmentally respectful conditions using water as the reaction medium. This ligand, $(n\text{-}Bu_2N)_3P$, is formed by adding the secondary amine $n\text{-}Bu_2NH$ to $PCl_3$ at ambient temperatures, a trivial process amenable to scale-up, thereby allowing for its straightforward multi-gram preparation. Both types of couplings using this P3N ligand-derived catalyst led to excellent isolated yields of desired products, relying on relatively low loadings of palladium. Comparisons under aqueous micellar conditions with other commonly used ligands (normally performed in waste-generating organic solvents) indicate that $(n\text{-}Bu_2N)_3P$ is equally effective, or even more so, for these couplings. Two sequences illustrative of these commonly used Pd-catalyzed cross-couplings are presented: one that results in a streamlined route to the unsymmetrical alkyne-containing pharmaceutical ponatinib, while the second features a Suzuki–Miyaura coupling as part of an overall high-yielding sequence, leading to a product containing an undetectable level of residual Pd. Calculations of E-Factors document the attention to "greenness" associated with this ligand development.

*Ab initio* calculated structures and proton affinities of the model ligands $P(NH_2)_3$ and $N(NH_2)_3$ give strong evidence of a previously little-known phenomenon in aminophosphines. The aminophosphine has p–d pi bonding and donation of lone-pair electrons into empty d orbitals on phosphorus that especially stabilizes the phosphonium ion after protonation. This effect should make the aminophosphine particularly effective as a donor ligand on palladium. DFT calculations on the P3N ligand $(n\text{-}Bu_2N)_3P$ gives a set of structures and relative energies for the ligand, its palladium binding complexes, and oxidative-addition products. These results reveal possible intermediates in the catalytic pathways of this P3N ligand. Many structures are

sterically crowded and include moderately stable candidates as intermediates with two $(n\text{-Bu}_2\text{N})_3\text{P}$ ligands on Pd.

## Data availability

There are 2 files containing ESI-1 and ESI-2‡ that contain all the data.

## Author contributions

E. O. designed the project and performed the ligands synthesis and characterizations along with experiments related to H–C–S with the assistance of M. S. L. L. and S. F. and M. B. designed, optimized and characterized the ponatinib synthesis and the intermediates with the assistance of S. F. M. O. contributed to the experimental, characterization and optimization of S.-M. with the assistance of E. B. and K. M. contributed to the optimization work on H–C–S. E. B. contributed to the synthesis and characterization of terminal alkynes. E. O. N. designed, optimized and characterized the 3-Step sequence and the intermediates. D. H. A. conducted the computational study. E. O. and D. H. A. wrote the ms. E. O. wrote the ESI-1‡ with the assistance of M. B., M. O. and E. O. N. DHA carried out all computations, wrote the ESI-2,‡ and contributed to the writing of the manuscript B. H. L. supervised the work and assisted in revising the ms and ESI-1.‡ All authors have given approval to the final version of the manuscript.

## Conflicts of interest

There are no conflicts to declare.

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