CHEMISTRY
A European Journal

A Journal of
ChemPubSoc Europe

Accepted Article

Title: Palladium Complexes based on Ylide-Functionalized Phosphines (YPhos): Broadly Applicable High-Performance Precatalysts for the Amination of Aryl Halides at Room Temperature

Authors: Jens Tappen, Ilja Rodstein, Katie McGuire, Angela Großjohann, Julian Löffler, Thorsten Scherpf, and Viktoria H. Gessner

To be cited as: *Chem. Eur. J.* 10.1002/chem.201905535

Link to VoR: http://dx.doi.org/10.1002/chem.201905535

Supported by
ACES

WILEY-VCH

Palladium Complexes based on Ylide-Functionalized Phosphines (YPhos): Broadly Applicable High-Performance Precatalysts for the Amination of Aryl Halides at Room Temperature

Jens Tappen[a], Ilja Rodstein[a], Katie McGuire[a], Angela Großjohann[a], Julian Löffler[a], Thorsten Scherpf[a] and Viktoria H. Gessner*[a]

Dedicated to Prof. Dr. Manfred Scheer on the Occasion of his 65th Birthday.

Abstract: Palladium allyl, cinnamyl and indenyl complexes with the ylide-substituted phosphines Cy_3P^+-C^-(R)PCy_2 (with R = Me (**L1**) or Ph (**L2**)) and Cy_3P^+-C^-(Me)P*t*Bu_2 (**L3**) were prepared and applied as defined precatalysts in C–N coupling reactions. The complexes are highly active in the amination of 4-chlorotoluene with a series of different amines. Higher yields were observed with the precatalysts in comparison to the *in-situ* generated catalysts. Changes in the ligand structures allowed for improved selectivities by shutting down β-hydride elimination or diarylation reactions. Particularly, the complexes based on **L2** (joYPhos) revealed to be universal precatalysts for various amines and aryl halides. Full conversions to the desired products are reached mostly within 1h reaction time at room temperature, thus making **L2** to one of the most efficient ligands in C-N coupling reactions. The applicability of the catalysts was demonstrated for aryl chlorides, bromides and iodides together with primary and secondary aryl and alkyl amines, including gram-scale applications also with low catalyst loadings of up to 0.05 mol%. Kinetic studies further demonstrated the outstanding activity of the precatalysts with TOF over 10.000 h^{-1}.

Introduction

Palladium-catalyzed cross coupling reactions have become one of the most powerful methods in organic synthesis, both in academic research as well as industrial processes. They are widely used for the preparation of pharmaceuticals, fine chemicals, and precursors for materials chemistry.[1] This success is mainly based on the high efficiency of the catalysts and the development of reliable and reproducible reaction protocols that are applicable to a large variety of substrates and processes. Thereby, the design of potent ligands has decisively contributed to this progress. In general, Pd complexes with electron-rich and bulky phosphines[2] or *N*-heterocyclic carbenes (NHCs)[3] are the most active catalysts in coupling reactions. Major advances in this field are often connected with the development of new specialized ligands that easily accomplish the crucial steps in the catalytic cycle and prevent undesired side-reactions. This for example also holds true for Buchwald-Hartwig amination reactions (BHA).[4] While first amination protocols used simple monophosphines and rather harsh reaction conditions,[5] the continuous development of more electron-rich and customized ligands - such as Buchwald's bulky dialkylbiaryl phosphines[6] or other electron-rich di- or trialkyl phosphines (Figure 1)[7] or NHCs[8] - led to highly active catalysts that operate at low temperatures and allow the coupling of sterically demanding substrates. Despite these developments in BHA, significant challenges remain. For example, deactivated aryl chlorides are still challenging substrates and usually require high temperatures, which however are often not compatible with complex functionalized compounds commonly seen in pharmaceutical industry.[4] Only few catalysts are known which efficiently couple aryl chlorides under mild conditions.[8a, 9] However, these tailor-made catalysts are often highly specialized and expensive, need high catalyst loadings, are only applicable for few substrates and/or are highly reactive and thus difficult to apply in large scale.

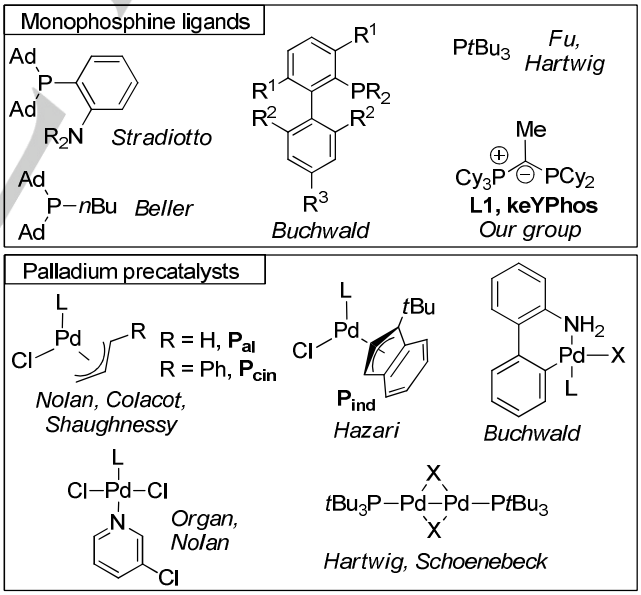


Figure 1. Monophosphines and palladium precatalysts used in Pd-catalyzed coupling reactions.

Recently, we reported on the ylide-functionalized phosphine (YPhos) $Y_{Me}PCy_2$ (**L1**, keYPhos) as an excellent ligand for Buchwald-Hartwig aminations of aryl chlorides at room temperature.[10] In combination with $Pd_2(dba)_3$ or $Pd(OAc)_2$ as metal sources, high activities were observed also with challenging substrates without elaborate tailoring of the ligand design. To further evaluate the potential and improve the design of YPhos ligands for broader applications, we became interested

[a] J. Tappen, I. Rodstein, K. McGuire, A. Großjohann, J. Löffler, Dr. T. Scherpf, Prof. Dr. V. H. Gessner
Faculty of Chemistry and Biochemistry, Chair of Inorganic Chemistry II, Ruhr University Bochum, Universitätsstr. 150, 44801 Bochum (Germany)
E-mail: viktoria.gessner@rub.de

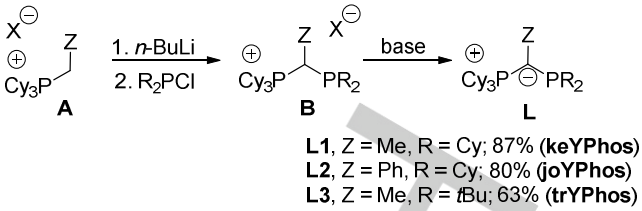
Supporting information for this article is given via a link at the end of the document.

in the impact of the ylide moiety and phosphine substituent on the catalytic activity. Both moieties determine the electron density at the phosphorus atom and thus the donor property of the ligand.[11] Furthermore, we were also interested in the effect of the use of defined palladium complexes as precatalysts in the coupling reactions. Various studies on palladium catalyzed coupling reactions have shown that the use of defined pre-catalysts with a Pd to ligand ratio of 1:1 can be beneficial for catalysis due to the more facile and selective formation of the active LPd(0) species compared to catalysts prepared from Pd_2dba_3, which often differs in quality.[12,13] Moreover, Pd(II) complexes are usually stable towards air and moisture and thus easier to apply also in larger scale compared to catalysts *in situ* generated from the more sensitive free phosphine ligands. A series of different types of complexes have been successfully applied, both with carbenes and phosphines over the past years. Prominent examples are shown in Figure 1.[14,15] In case of phosphines, particularly η^3-allyl and cinnamyl Pd(II) complexes of type $\mathbf{P_{al}}$ and $\mathbf{P_{cin}}$ developed by Nolan, Shaughgnessy and Colacot[16,17] and *tert*-butyl indenyl complexes developed by Hazari[18] have been successfully employed in coupling reactions with a series of different monophosphines and thus should also be tested here.

Results and Discussion

Ligand Synthesis and Properties. To study the impact of different substitution patterns in the YPhos ligands on the catalytic performance, we addressed the use of the *tert*-butyl analogue $Y_{Me}PtBu_2$ (**L3**, trYPhos) of **L1** as well as $Y_{Ph}PCy_2$ (**L2,** joYPhos) with a phenyl group in the ylide-backbone (Scheme 1). Due to the more electron-releasing property of the *tert*-butyl substituent compared to the cyclohexyl group, we expected **L3** to be a stronger donor and thus provide in an even more active catalyst. Furthermore, the increased steric bulk should further stabilize the catalytically active mono-ligated LPd species relative to the usually inactive L_2Pd species and thus also results in higher activities. This was already shown in case of α-arylation reactions, where **L3** showed a higher activity at room temperature albeit being more sensitive.[19] In contrast, we expected **L2** to be less electron-donating than **L1** since the phenyl substituent in the ylide backbone should stabilize the negative charge at the carbanionic centre. Therefore, we expected **L2** to yield more stable catalysts in comparison to **L1** and **L3**.

The new YPhos ligand joYPhos (**L2**) was prepared *via* a similar synthetic procedure as previously reported for **L1** and **L3** (Scheme 1, see ESI for details),[10,11] starting from the simple phosphonium salt **A** (with Z = Ph) and its reaction with the chlorodicyclohexylphosphine after deprotonation. Deprotonation of the formed phosphino phosphonium salt **B** was accomplished by an additional equiv. of base (KO*t*Bu). **L2** was thus isolated as colorless solid in yields of 80 % and characterized by multi-nuclear NMR and IR spectroscopy, XRD and EA analysis (Figure 2). The ligand is characterized by two doublets in the $^{31}P\{^1H\}$ NMR spectrum at –5.2 and 21.6 ppm with coupling constants of 132.1 Hz. It should be noted that **L2** possesses a remarkable stability in the solid state. No decomposition or oxidation was observed after 1 month when stored under air.



Scheme 1. Preparation of the YPhos ligands **L1**-**L3**.

Next, the steric and electronic properties of the ligands were measured by determination of the Tolman electronic parameters (TEP) and the buried volumes (%V_{bur}) of the ligands in order to get a first estimation of the ligand properties. The buried volumes were calculated from the geometries of the isolated **L**·AuCl complexes (XRD analysis, Figure 2), which were prepared by treatment of the YPhos ligands with (tht)AuCl (tht = tetrahydrothiophene). With %V_{bur} = 47.9%, **L2** holds an intermediate position between the smaller **L1** (%V_{bur} = 45.2%)[10] and bulkier **L3** (%V_{bur} = 51.3%). The increased size of **L2** compared to **L1** can be explained by the increased steric demand of the phenyl substituent in the ylide backbone, which results in a smaller P-C-P angle (114.1(1)° in **L2** compared to 119.1(2) **L1**) thus forcing the PCy_3 moiety closer towards the metal. Overall, all YPhos ligands are sterically bulky ligands, which are more demanding than classical phosphines (e.g. %V_{bur}($PtBu_3$) = 26.7 % or %V_{bur}(PAd_3) = 40.5 %).[20]

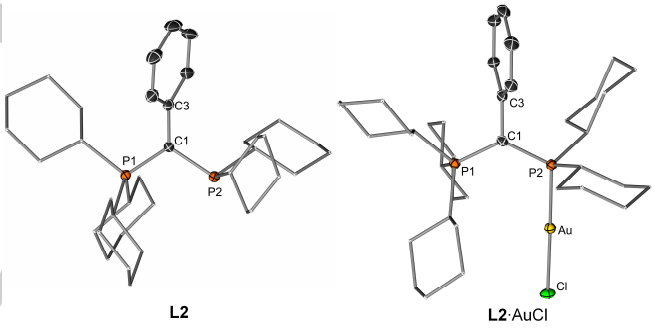
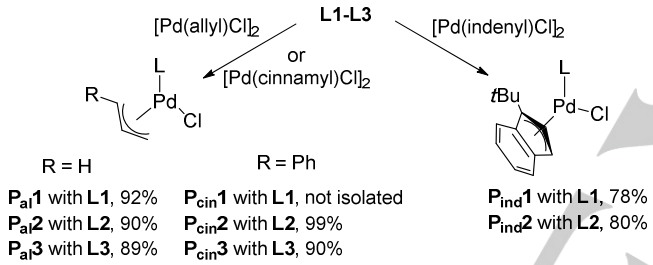


Figure 2. Molecular structures of **L2** and **L2**·AuCl in the solid state.

Surprisingly, determination of the TEP value of **L2** by measurement of the CO stretching frequency in the rhodium complexes Rh(acac)(CO)(L) revealed that **L2** is more electron-rich than expected. With a TEP of 2049.3 cm^{-1} it is comparable to **L1** (TEP = 2050.1 cm^{-1})[10] and the *N*-heterocyclic carbene IMes (IMes = 1,3-dimesitylimidazol-2-ylidene, IMes: TEP=2050.7 cm^{-1}).[21] This can be explained by the molecular structures of **L2** as well as its AuCl complex. In contrast to our initial assumption, the phenyl group in the ligand backbone is not in plane with the PCP linkage but perpendicularly arranged (Figure 2). Hence, no charge delocalization into the phenyl ring is possible as expected for this system and thus explains the rather low TEP value of **L2**. We believe that this arrangement of the phenyl group is due to steric congestions by the bulky PCy_3 and PCy_2 moiety forcing the Ph group out of the P-C-P plane.

Preparation of Palladium Complexes. Next, we addressed the isolation of Pd(II) complexes as suitable and easy-to-handle precursors for catalysis. We chose the allyl and cinnamyl

complexes of type $\mathbf{P_{al}}$ and $\mathbf{P_{cin}}$ as well as the η^3-indenyl system $\mathbf{P_{ind}}$ as first test complexes, since they have already been applied with a series of other monophosphines.[14-16] In general, the cinnamyl and indenyl complexes have been reported to perform superior to the allyl complexes due to a more facile reduction to the active Pd(0) species, which prevents the formation of Pd(I) compounds, that are often assumed to be detrimental to catalysis.[22] The complexes [L·Pd(η^3-allyl)Cl], [L·Pd(η^3-cinnamyl)Cl] and [L·Pd(η^3-1-*t*Bu-indenyl)Cl] with **L1-L3** were synthesized by reaction of the dimeric palladium precursors and the free ligands (Scheme 2). All complexes could be isolated as solids in good to excellent yields of 78 to 99 %. Sole exceptions are the cinnamyl complex with **L1** and the indenyl complex of **L3**. The latter was found to only slowly form upon mixing of the ligand and the palladium precursor, so that decomposition started before the reaction was complete. Thus, $\mathbf{P_{ind}3}$ was not further investigated as potential precatalysts. However, $\mathbf{P_{cin}1}$ formed cleanly upon mixing of the starting materials as judged by NMR spectroscopic studies (see Figure S19 and S20) but was found to be difficult to isolate in analytically pure form due to its high solubility and the decomposition in the course of extended washing processes. Due to its clean formation it was also tested as precatalyst, yet not as isolated but as in situ formed complex.



Scheme 2. Synthesis of palladium complexes with **L1-L3**.

The complexes were characterized by multi-nuclear NMR and IR spectroscopy, elemental and XRD analysis. The molecular structures of $\mathbf{P_{al}3}$, $\mathbf{P_{cin}2}$, $\mathbf{P_{cin}3}$ and $\mathbf{P_{ind}1}$ are depicted in Figure 3, the structure of $\mathbf{P_{al}1}$ is shown in the SI (Figure S70). Interestingly, all structures feature the same geometry/ orientation of the YPhos ligands in the palladium complexes with the bulky PCy_3 moiety always being oriented on the same side as the metal fragment. Thus, the PCy_3 group retains its orientation as found in the free ligand and does not undergo any P-C rotation upon metal coordination. In case of the Pd(0) dba complexes of **L1** and **L3** this orientation led to an agostic interaction between the metal and one of the cyclohexyl groups of the PCy_3 unit.[10,19] Such an interaction is – as expected – not present in the Pd(II) systems. However, the preserved geometry of the ligand in all structures suggests that the active Pd(0) species forms without the necessity to undergo any conformational changes. The Pd-P distances amount between 2.3168(11) and 2.406(1) Å and are thus on the longer side of Pd-P bond lengths described in literature.[23]

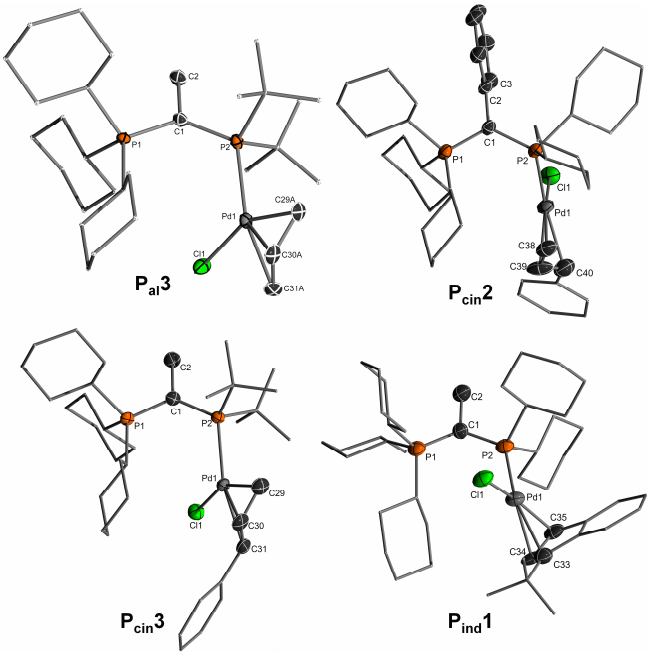


Figure 3. Molecular structures of $\mathbf{P_{al}3}$, $\mathbf{P_{cin}2}$, $\mathbf{P_{cin}3}$ and $\mathbf{P_{ind}1}$. Pictures of the structures of the other Pd complexes are given in the SI together with further crystallographic details.

Comparison of the Catalytic Activity. To study the impact of the steric and electronic properties of the new YPhos ligands on their catalytic ability, **L1**-**L3** were applied in C-N coupling reactions at room temperature. We compared the activities of the catalysts in situ generated from **L1-L3** and $Pd_2(dba)_3$ with those of the isolated precatalysts $\mathbf{P_{al}}$, $\mathbf{P_{cin}}$ and $\mathbf{P_{ind}}$. The C-N coupling reaction of *p*-chlorotoluene with different amines using 0.5 mol% of catalyst (based on Pd) and KO*t*Bu as base was chosen as test reaction. Previous studies on the amination reactions with **L1** showed that this catalyst is compatible with a large variety of aryl chlorides but showed some limitations in the amine scope, particularly when using primary and secondary alkyl amines. These amines are generally more difficult to couple because of possible side-reactions such as diarylation and β-hydride elimination. Thus, a series of alkyl amines of different steric demand was chosen to challenge our newly designed ligands and precatalysts and to provide insights into the impact of the steric and electronic properties on the activity and productivity of the catalysts. We also included *N*-methyl aniline **2a** as amine to also test whether the high activity for aryl amines was retained. The results are summarized in Figure 4, which shows the final yields obtained for all ligands and complexes after an optimal reaction time (see ESI for further details).

Comparison of the three different ligands shows that all render highly active Pd species. Since all YPhos ligands are strong donors,[24] the electronic difference between the cyclohexyl and *t*Bu groups seems to be only of minor importance. However, marked differences in the performance can be seen in cases where the different steric bulk of the ligands becomes important or side-reactions (β-hydride elimination, diarylation) play a role. In case of the *in situ* prepared catalysts (first three sets of results in Figure 4), **L3** gives lower yields than its cyclohexyl analogue **L1** for most of the amines. This is particularly true for the

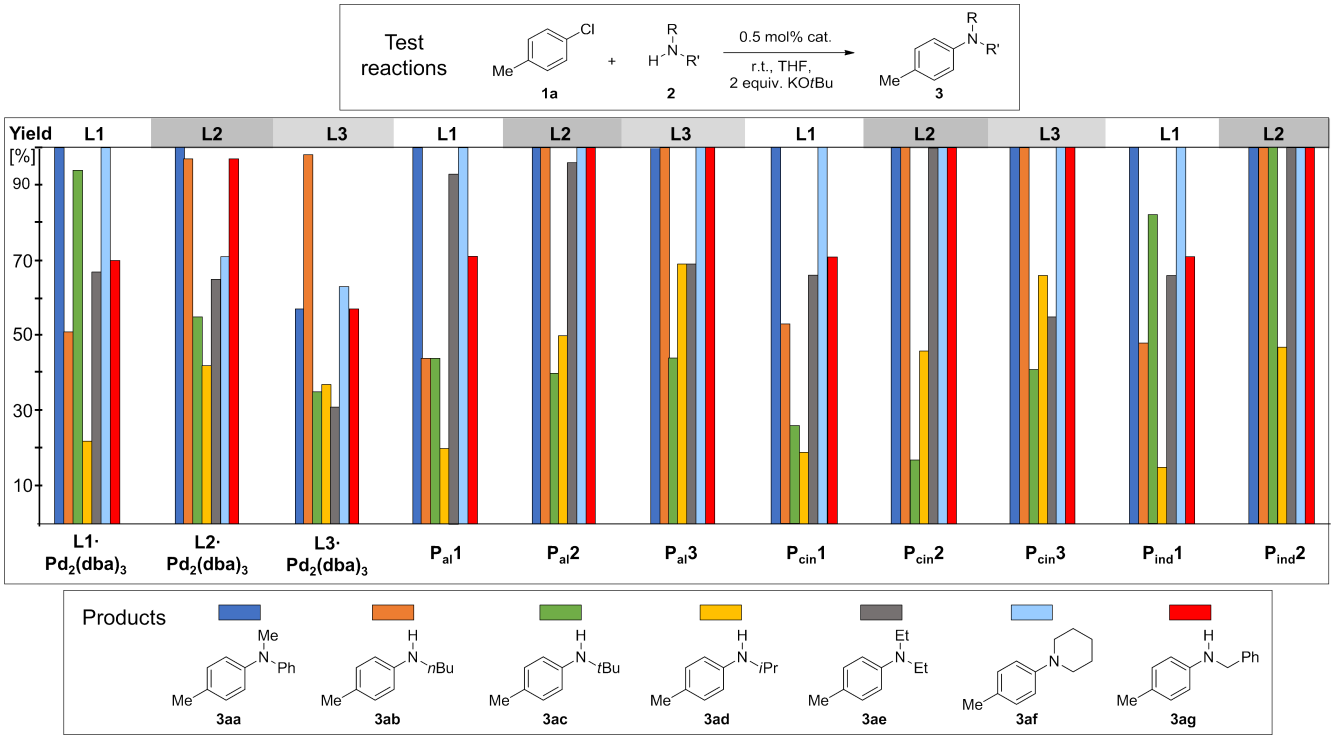
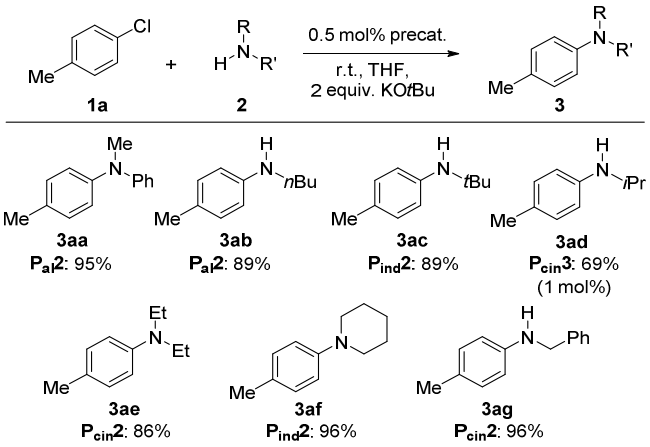


Figure 4. Results of the C-N coupling reactions with ligands **L1**, **L2** and **L3** and the corresponding complexes **3** and **4**. Reaction conditions: 0.85 mmol **1**, 0.92 mmol **2**, 0.5 mol% [Pd], 2.0 equiv. base, 3.0 mL THF, RT, optimal reaction time (see ESI for details). Yields are determined by NMR spectroscopy with 1,3,5-trimethoxybenzene as internal standard. Values are average values of at least two runs.

sterically more encumbering, secondary amines (Et_2NH, *N*-methylaniline). Here, the reduced productivity is presumably due to a slower reaction rate caused by the steric bulk and the competing decomposition of the active species under the reaction conditions.[19] Despite this disadvantage of **L3** compared to **L1**, it also offers an important advantage with respect to selectivity. In this context, the coupling with *n*-butylamine to **3ab** is most informative. In this reaction, **L1** delivers considerable amounts of the diarylated compound (3-5%), while **L3** selectively provides the desired monoarylated product in quantitative yield. Thus, the steric bulk of the *tert*-butyl group prevents a second arylation reaction of the formed aryl amine. Further selectivity issues with **L1** were observed in the coupling reactions with Et_2NH and benzyl amine. Here, significant amounts of the β-hydride elimination products were formed. In contrast, no such side-reactions were observed with **L3**. We believe that this improved selectivity of **L3** is solely due to steric effects. Previous studies by our group have shown that Pd(0) complexes with YPhos ligands are stabilized by agostic interactions between the metal and the PCy_3 moiety.[25] This interaction might be further strengthened through the increased steric bulk at the phosphine moiety, which might result in a smaller (or less flexible) P-C-P angle in the ligand backbone, which ultimately should force the cyclohexyl groups in closer proximity to palladium centre. The thus strengthened agostic interaction should hamper β-hydride elimination. With this in mind, we hypothesized that the incorporation of the phenyl group in the ylide backbone of **L2** should have an even more pronounce effect. To our delight, **L2** indeed combines the advantageous properties of both ligands, thus showing higher selectivities and even higher activities and productivities than **L1**. Neither diarylation, nor β-hydride elimination products were observed with **L2** and similar good yields were reached compared to **L1** in case of the *in situ* formed catalysts.

Motivated by the already excellent results of the *in situ* prepared catalysts with Pd_2dba_3, we next turned our attention towards the the isolated precatalysts. Recent mechanistic studies on the BHA with keYPhos (**L1**) and Pd_2dba_3 revealed the presence of an initiation period which we attributed to the time required for replacement of the dba ligand and the formation of the catalytically active phosphine-ligated palladium species.[25] This suggested that a further improvement should be possible by using defined precatalysts. To our delight, indeed higher yields could be reached when using the complexes under the same reaction conditions. Except for iPr_2NH all amines could be completely converted into the corresponding aryl amines **3** with at least one of the precatalysts. In general, the allyl complexes $\mathbf{P_{al}}$ were slightly less effective than the cinnamyl indenyl analogues $\mathbf{P_{cin}}$ and $\mathbf{P_{ind}}$. Particularly, the indenyl and cinnamyl complexes of **L2** – despite of the low solubility of $\mathbf{P_{cin}2}$ – showed an outstanding performance. Full conversion to the products was observed for all substrates (except for $iPrNH_2$) mostly within only 1 h reaction time using $\mathbf{P_{ind}2}$. Thus, not only the yield but also the reaction time could be improved with this precatalyst (see ESI). Accordingly, compounds **3aa-3ag** could all be isolated in high yields using these precatalysts (Scheme 3).[26] Overall, the precatalysts with joYPhos (**L2**) seem to form a rather universal catalyst for the C-N coupling of a variety of different amines. As such, primary as well as secondary amines are readily converted into the aryl amines, while otherwise often different ligands are needed for these two classes of substrates.[14f]



Scheme 3. Amine and scope. Reaction conditions: 0.5 mol% cat, RT, 6 h, aryl chloride:amine 1:1.1, yields are isolated yields.

The lower efficiency of the allyl complexes **P_{al}** is in line with previous reports by Hazari.[18,22] This was explained by the slower precatalyst activation and the facile formation of a Pd(I) μ-allyl dimer of the form (μ^3-allyl)(μ-Cl)$Pd_2(L)_2$, which is less likely to be formed with the more bulky η^3-cinnamyl or indenyl complexes. The μ-allyl dimer is generated by comproportionation between the corresponding LPd(0) species and the precatalysts **P_{al}.** This leads in a reduction of the active Pd(0) species and hence in a reduced catalytic efficiency. Indeed, we also observed the formation of the μ-allyl dimer with **L2** thus suggesting that this is also responsible for the lower efficiency of **P_{al}2** compared to **P_{cin}2** and **P_{ind}2**. Small amounts of (μ-allyl)(μ-Cl)Pd_2(**L2**)$_2$ were obtained from crystallization attempts with [(η^3-allyl)PdCl]$_2$ and **L2**.[17c,27] The dimer crystallizes in the triclinic space group *P*-1 with three molecules in the asymmetric unit (only one is shown in Figure 5). The complex features an almost linear P–Pd–Pd–P linkage with P–Pd–Pd angles of 162.4(1) and 168.0(1)° and a Pd-Pd bond of 2.627(1) Å and Pd-P distances of 2.315(2) and 2.318(2) Å, respectively.

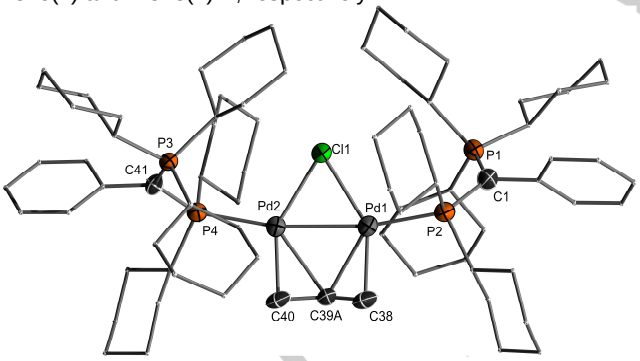


Figure 5. Molecular structure of (μ^3-allyl)(μ-Cl)Pd_2(**L2**)$_2$. See the SI for structural details.

Catalyst Activity and Productivity. In general, the precatalysts deliver highly active catalysts as demonstrated by the fast catalysis at room temperature (see section 1.4.2 in the ESI). The reactions to the compounds shown in Scheme 3 are typically finished within less than 1h using **P_{ind}2** as precatalysts, thus suggesting that turnover frequencies (TOF) of 200 h^{-1} and more can easily be reached. To further examine the activity of our catalysts we performed kinetic studies using the amination of *p*-chlorotoluene with piperidine with 0.5 mol% **P_{ind}2** as test reaction. Monitoring of the process of a reaction mixture with an aryl chloride concentration of 0.33 M showed that already 10 % conversion were reached right after addition of the catalyst and the full conversion after only 1 min reaction time (Figure 6). This corresponds to a turnover frequency of 12.000 h^{-1}. More dilute reaction conditions (0.04 M) allowed for more detailed kinetic studies. Here, a steady increase of conversion was observed with a reaction rate of 0.04 M·min^{-1} (see SI for details) and a TOF of 1.200 h^{-1}. We also examined the productivity of the two best precatalysts **P_{ind}2** and **P_{cin}2**. The down-scaling was probed with the amination of 4-chlorotoluene with piperidine. While with the cinnamyl complex only 66% conversion could be reached with 0.1 mol% catalyst loading after 3h, **P_{ind}2** gave full conversion (TON = 1000) under the same reaction conditions. Further reduction of the catalyst loading to 0.05 mol% still gave 83% yield and thus a TON of 1660 after 3h. Lower loadings unfortunately only gave poor conversion, which however might be overcome when reactions are performed on larger scale.

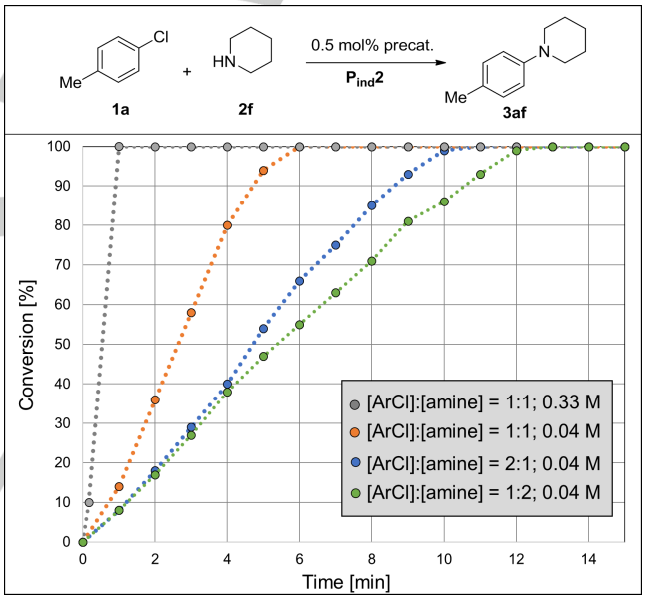


Figure 6. Conversion-time plots for the amination of *p*-chlorotoluene with piperidine with **P_{ind}2** as catalyst at different concentrations. Conditions: 0.5 mol% **P_{ind}2**, room temperature, THF. Conversion was determined by NMR spectroscopy with 1,3,5-methoxybenzene as standard.

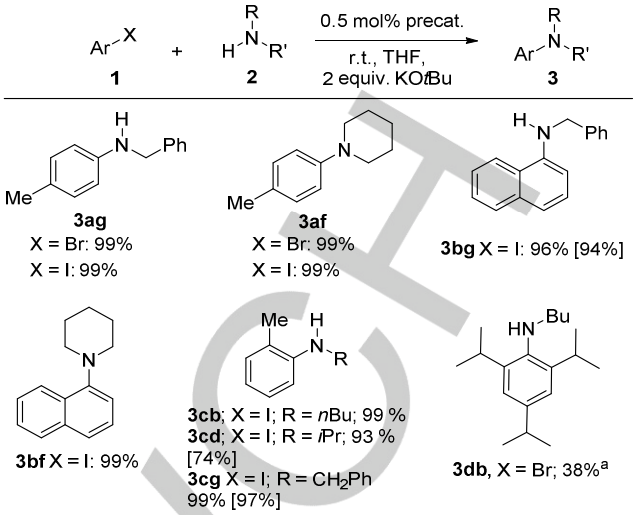
To probe the performance of **P_{ind}2** compared to other ligands/ precatalysts we compared its activity with that of two reported precatalysts. We chose (i) the indenyl complex of P*t*Bu_3 (**P_{ind}·P*t*Bu_3**), since it contains the same type of precatalyst as **P_{ind}2** and thus nicely compares with **P_{ind}2** and (ii) the Buchwald catalyst RuPhos-PdG3, which is known to be one of the best catalyst for the coupling of secondary amines.[14a] Under the same conditions used for **P_{ind}2** (0.04 M, RT, 0.5 mol% catalyst) only minor amounts of product were formed within 1 h reaction time. After 24 h, **P_{ind}·P*t*Bu_3** delivered 28 % and RuPhos-PdG3 27 % yield. This further demonstrates the high activity of the YPhos-based precatalysts at room temperature.

It is interesting to note that in contrast to our previous observations with **L1** and Pd_2dba_3 no induction period was observed in the catalysis with **P_{ind}2** (Figure 6).[25] This confirms

that the use of the precatalyst facilitates the formation of the active species and thus speeds up catalysis. Catalyst formation now presumably does not impact the rate-determining step as was found for the catalysis with **L1** and Pd_2dba_3. To probe the nature of the rate-limiting step we performed further kinetic studies including a variable time normalization analysis (VTNA) as previously reported by Burés.[28] To this end, the kinetic studies with **P$_{ind}$2** at low concentrations were repeated with two equiv. of aryl chloride and two equiv. of amine. As shown in Figure 6, doubling of the aryl chloride concentration results in a distinct increase of the reaction rate, while an increase of the amine concentration slightly reduced the reaction rate particularly at low aryl chloride concentrations (i.e. with increasing reaction time). Overlaying of the progress concentration profiles (VTNA, see SI for details, Figure S3) suggests that the reaction is first-order in [ArCl] and almost zeroth-order in [amine]. Thus, oxidative addition still is the rate-limiting step. The slight decrease of the reaction rate at low ArCl concentrations with 2 equiv. of amine probably results from the more difficult formation of the LPd(ArCl) complex under these reaction conditions.[29] Recent DFT studies have shown that the amine complex LPd(amine) is similar in energy than LPd(ArCl).[25] However, due to the high amine and low ArCl concentration at the end of the catalysis the formation of the active LPd(ArCl) species will become less favorable.

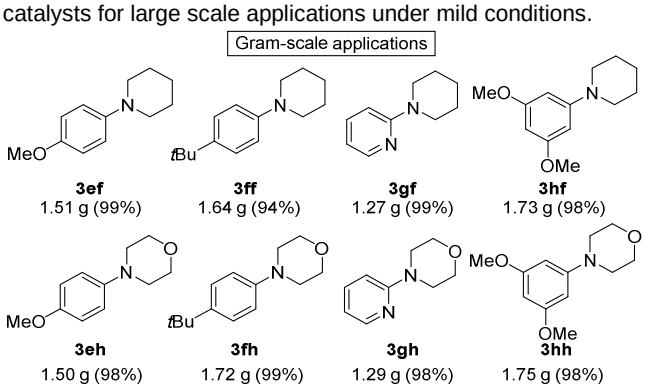
Aryl bromides and iodides. To examine the scope of our catalysts, we tested **P$_{ind}$2** in the coupling of further amines as well as aryl bromides and aryl iodides (Scheme 4). While aryl bromides are usually easy substrates, aryl iodides have repeatedly been described to be difficult to couple despite of the more facile oxidative addition.[30] This has been explained by an inhibitory effect of the formed metal iodide caused by the binding of the iodide to the Pd(II) oxidative addition or amido complex, thus slowing down amine binding and/or reductive elimination.[30b]

Fortunately, with **P$_{ind}$2** as catalyst also *p*-bromo and iodotoluene were successfully coupled to **3ag** and **3af** within only 1h reaction time at room temperature (Scheme 4). The coupling of the iodide is particularly remarkable, since to the best of our knowledge only few room temperature Pd-catalyzed C-N couplings of ArI are known until today, particularly in polar solvents.[30b,31] The latter have shown to be less compatible with the amination of ArI due to the higher solubility of the formed metal iodide and the thus increased inhibition. Besides *p*-iodotoluene also 1-iodonaphthalene and the more demanding *o*-iodotoluene were almost quantitatively coupled with different alkyl amines. In case of *o*-iodotoluene, the reaction with the secondary amine *i*PrNH$_2$ revealed to be more facile compared to *p*-chlorotoluene, giving **3cd** in 73% isolated yield. Sole limitations have so far been observed with sterically bulky aryl halides. For example, 2,4,6-tri-*iso*-propylphenylbromide only delivered 38% conversion with *n*-butylamine after 24h with 0.5 mol% catalyst loading (**3db**).



Scheme 4. Amine and halides scope. Reaction conditions: 0.5 mol% cat, RT, 1 h, aryl halide:amine 1:1.1, **P$_{ind}$2** as catalyst, NMR yields with 1,3,5-trimethoxybenzene as internal standard. Isolated yields after 2h reaction time are given in brackets. [a] after 24h.

Gram-Scale Applications. Although all precatalysts perform excellently in C-N coupling reactions, the activity of the systems based on the phenyl-substituted ligand **L2** are particularly impressive. **L2** clearly delivers the most active and most efficient catalyst and performs superior to most palladium catalysts reported in literature.[5-9] Given the facile synthesis of **L2** and its palladium complexes this catalyst is certainly competitive to established systems also applied in industry. Encouraged by this activity we became thus interested in the potential of **P$_{ind}$2** for large scale applications. Thus, we attempted the synthesis of a series of substrates in gram-scale. Since piperidine and morpholine are common moieties in pharmaceuticals and agrochemicals, we chose these two amines as well as four aryl chlorides including challenging electron-rich substrates such as the methoxy and *tert*-butyl substituted compounds **1b** and **1c** as well as an heteroaryl compound, 2-chloropyridine **1d** (Scheme 5). To our delight, **P$_{ind}$2** also performed outstandingly in these reactions, always giving full conversion to the desired products at room temperature within 6 h reaction time with 0.5 mol% catalyst loading. All compounds could be isolated in excellent yields of close to 100%, thus highlighting the potential of our catalysts for large scale applications under mild conditions.



Scheme 5. Gram-scale applications of precatalysts with **L2**. Reaction conditions: 0.5 mol% cat, RT, 6 h, aryl chloride:amine 1:1.1, yields are isolated yields.

Conclusion

In conclusion we have synthesized three different ylide-functionalised phosphines (**L1-L3)** and their corresponding palladium allyl, cinnamyl and indenyl complexes in order to study the impact of the ligand substitution pattern and the use of defined precatalysts on the catalytic activity in C-N coupling reactions. All ligands gave way to highly active catalysts that are competent in the amination of aryl chlorides at room temperature. While replacement of the cyclohexyl groups at phosphorus by *tert*-butyl groups did not result in higher yields due to steric congestions, introduction of a phenyl group in the ylide-backbone (**L2**, joYPhos) led to considerable improvements, particularly with respect to selectivity. A further improvement was accomplished by employment of the isolated palladium precatalysts, particularly when using the cinnamyl and indenyl complexes $\mathbf{P_{cin}}$ and $\mathbf{P_{ind}}$. The indenyl complex with **L2** gave full conversion to almost all aryl amines tested with 0.5 mol% catalyst loading and kept its high activity also in gram-scale applications as well as at low loadings up to 0.05 mol%. Besides, aryl chlorides also bromides and the often more tenacious iodides were successfully coupled with $\mathbf{P_{ind}2}$ at room temperature. The high activity of $\mathbf{P_{ind}2}$ was further confirmed by kinetic studies, which showed that the active species is formed without induction period giving way to turnover frequencies higher than 10.000 h^{-1}. Hence, $\mathbf{P_{ind}2}$ is one of the most active and universal catalyst for the amination of aryl halides which are known to date. Overall, these results demonstrate that the catalytic ability of the YPhos-based catalysts – despite of their already remarkably high activity – can further be increased by ligand design.

Conflicts of Interest

The authors have filed patent WO2019030304 covering the YPhos ligands and precatalysts discussed, which is held by UMICORE and products will be made commercially available from.

Acknowledgements

Funded by the European Research Council (Starting Grant: YlideLigands 677749). We thank UMICORE for the donation of chemicals. Gefördert durch die Deutsche Forschungs-gemeinschaft (DFG) im Rahmen der Exzellenzstrategie des Bundes und der Länder – EXC 2033 – Projektnummer 390677874 – RESOLV. We also thank Umicore for financial support.

Keywords: Phosphines • Ligand design • structure activity relationship • coupling reactions • Palladium

Notes and References

[1] a) J. Magano, J. R. Dunetz, *Chem. Rev.* **2011**, *111*, 2177–2250; b) K. C. Nicolaou, P. G. Bulger, D. Sarlah, *Angew. Chem. Int. Ed.* **2005**, *44*, 4442–4489; c) J.‑P. Corbet, G. Mignani, *Chem. Rev*. **2006**, *106*, 2651–2710; d) P. Ruiz-Castillo, S. L. Buchwald, *Chem. Rev*. **2016**, *116*, 12564–12649.

[2] a) R. Martin, S. L Buchwald, A*cc. Chem. Res.* **2008**, *41*, 1461–1473; b) G. C. Fu, *Acc. Chem. Res.* **2008**, *41*, 1555–1564.

[3] a) N. Marion, S. P. Nolan, *Acc. Chem. Res*. **2008**, *41*, 1440–1449. b) S. Würtz, F. Glorius, *Acc. Chem. Res*. **2008**, *41*, 1523–1533.

[4] For reviews, see: a) M. M. Heravi, Z. Kheilkordi, V. Zadsirjan, M. Heydari, M. Malmir, *J. Organomet. Chem*. **2018**, *861*, 17-104; b) S. L. Buchwald, C. Mauger, G. Mignani, U. Scholz, *Adv. Synth. Catal*. **2006**, ***348***, 23-39; c) J. F. Hartwig, *Synlett* **2006**, 1283-1294; d) P. Ruiz-Castillo, S. L. Buchwald, *Chem. Rev*. **2016**, *116*, 12564; e) R. Dorel, C. P. Grugel, A. Haydl, *Angew. Chem. Int. Ed.* **2019**, *58*, 17118-17129.

[5] a) M. S. Driver, J. F. Hartwig, *J. Am. Chem. Soc.,* **1996**, *118*, 7217-7218; b) J. P. Wolfe, S. Wagaw, S. L. Buchwald, *J. Am. Chem. Soc*., **1996**, ***118***, 7215-7216; c) G. Mann, J. F. Hartwig, M. S. Driver, C. Fernández-Rivas, *J. Am. Chem. Soc*. **1998**, *120*, 827-828.

[6] a) J. P. Wolve, S. L. Buchwald, *Angew. Chem. Int. Ed.* **1999**, *38*, 2413-2416; b) B. P. Fors, D. A. Watson, M. R. Biscoe, S. L. Buchwald, *J. Am. Chem. Soc*., **2008**, *130*, 13552–13554. c) J. M. Dennis, N. A. White, R. Y. Liu, S. L. Buchwald, *J. Am. Chem. Soc*. **2018**, *140*, 4721-4725; d) N. H. Park, E. V. Vinogradova, D. S. Surry, S. L. Buchwald *Angew. Chem. Int. Ed.* **2015**, *54*, 8259-8262; e) P. Ruiz-Castillo, D. G. Blackmond, S. L. Buchwald, *J. Am. Chem. Soc.* **2015**, *137*, 3085.

[7] a) R. J. Lundgren, B. D. Peters, P. G. Alsabeh, M. Stradiotto, *Angew. Chem. Int. Ed.* **2010**, *49*, 4071-4074; (b) L. L. Hill, L. R. Moore, R. Huang, R. Craciun, A. J. Vincent, D. A. Dixon, J. Chou, C. J. Woltermann, K. H. Shaughnessy, *J. Org. Chem.* **2006**, *71*, 5117-5125. c) A. Zapf, A. Ehrentraut, M. Beller, *Angew. Chem. Int. Ed.* **2000**, *39*, 4154; d) A. Köllhofer, T. Pullmann, H. Plenio, *Angew. Chem. Int. Ed.* **2003**, *42*, 1056; e) F. Rataboul, A. Zapf, R. Jackstell, S. Harkal, T. Riermeier, A. Monsees, W. Dingerdissen, M. Beller, *Chem. Eur. J.* **2004**, *10*, 2983-2990. f) K. D. Hesp, R. J. Lundgren, M. Stradiotto, *J. Am. Chem. Soc*. **2011**, *133*, 5194. g) A. Tewari, M. Hein, A. Zapf, M. Beller, *Tetrahedron* **2005**, *61*, 9705-9709. h) Q. Shen, T. Ogata, J. F. Hartwig, *J. Am. Chem. Soc.* **2008**, *130*, 6586-6596. i) L. Ackermann, R. Born, *Angew. Chem. Int. Ed.* **2005**, *44*, 2444-2447.

[8] a) N. Marion, O. Navarro, J. Mei, E. D. Stevens, N. M. Scott, S. P. Nolan, *J. Am. Chem. Soc.* **2006**, *128*, 4101-4111. b) M. G. Organ, M. Abdel-hadi, S. Avola, I. Dubovyk, N. Hadai, E. A. B. Kantchev, C. J. O'Brien, M. Sayah, C. Valente, *Chem. Eur. J.* **2008**, *14*, 2443-2452.

[9] For example: a) J. P. Stambuli, R. Kuwano and J. F. Hartwig, *Angew. Chem. Int. Ed.* **2002**, *41*, 4746-4748. b) Q. Shen, S. Shekhar, J. P. Stambuli, J. F. Hartwig, *Angew. Chem. Int. Ed.* **2005**, *44*, 1371-1375. c) C. A. Wheaton, J.-P. J. Bow, M. Stradiotto, *Organometallics* **2013**, *32*, 6148-6161. d) J. F. Hartwig, M. Kawatsura, S. I. Hauck, K. H. Shaughnessy, L. M. Alcazar-Roman, *J. Org. Chem.* **1999**, *64*, 5575-5580. (e) M. G. Organ, M. Abdel-Hadi, S. Avola, I. Dubovyk, N. Hadei, E. A. B. Kantchev, C. J. O'Brien, M. Sayah, C. Valente, *Chem Eur. J.* **2008**, *14*, 2443-2452. (f) Y. Zhang, V. César, G. Storch, N. Lugan, G. Lavigne, *Angew. Chem. Int. Ed.* **2014**, *53* 6482.

[10] P. Weber, T. Scherpf, I. Rodstein, D. Lichte, L. T. Scharf, L. J. Gooßen, V. H. Gessner *Angew. Chem. Int. Ed.* **2019**, *58*, 3203-3207.

[11] a) T. Scherpf, C. Schwarz, L. T. Scharf, J.-A. Zur, A. Helbig, V. H. Gessner, *Angew. Chem. Int. Ed*. **2018**, *57*, 12859-12864. b) C. Schwarz, T. Scherpf, I. Rodstein, J. Weismann, K.-S. Feichtner, V. H. Gessner, *Chem. Open* **2019**, *8*, 621-626. c) C. Schwarz, J. H,elmann, D. M. Baier, A. Ouissa, V. H. Gessner, *Catal. Sci. Tech.* **2019**, *9*, 6808-6815.

[12] N. Hazari, P. R. Melvin, M. M. Beromi, *Nature Rev.* **2017**, *1*, 1.

[13] a) P. Weber, A. Biafora, A. Doppiu, H.-J. Bongard, H. Kelm, L. J. Gooßen, *Org. Process Res. Dev.* **2019**, *23*, 1462-1470; b) S. S. Zalesskiy, V. P. Ananikov, *Organometallics* **2012**, *31*, 2302-2309; c) D. B. Eremin, V. P. Ananikov, *Coord. Chem. Rev.* **2017**, *346*, 2-19.

[14] For examples, see: a) N. C. Bruno, M. T. Tudge, S. L. Buchwald, *Chem. Sci*. **2013**, *4*, 916–920; b) N. C. Bruno, S. L. Buchwald, *Org. Lett*. **2013**,

15, 2876–2879. c) M. G. Organ, G. A. Chass, D.-C. Fang, A. C. Hopkinson, C. Valente, *Synthesis* **2008**, 2776–2797. d) M. R. Biscoe, B. P. Fors, S. L. Buchwald, *J. Am. Chem. Soc.* **2009**, *130*, 6696-6697; e) T. Kinzel, Y. Zhang, S. L Buchwald, *J. Am. Chem. Soc.* **2010**, *132*, 14073-14075; f) D. Maiti, B. P. Fors, J. L. Henderson, Y. Nakamura, S. L. Buchwald, *Chem. Sci.* **2011**, *2*, 57-68. g) Y. Zhang, G. Lavigne, V. César, *J. Org. Chem.* **2015**, *80*, 7666-7673; h) T. Scattolin, E. Senol, G. Yin, Q. Guo, F. Schoenebeck, *Angew. Chem. Int. Ed*. **2018**, *57*, 12425; i) C. C. C. Johansson Seechurn, T. Sperger, T. G. Scrase, F. Schoenebeck, T. J. Colacot, *J. Am. Chem. Soc.* **2017,** *139*, 5194; (j) F. Proutiere, M. Aufiero, F. Schoenebeck, *J. Am. Chem. Soc.* **2012**, *134*, 606;

[15] For reviews: a) C. Valente, S. Calimsiz, K. H. Hoi, D. Mallik, M. Sayah, M. G. Organ, *Angew. Chem. Int. Ed.* **2012**, *51*, 3314-3332; b) A. Bruneau, M. Roche, M. Alami, S. Messaoudi, *ACS Catal.* **2015**, *5*, 1386-1396.

[16] a) A. Chartoire, X. Frogneux, S. P. Nolan, *Adv. Synth. Catal*. **2012**, *354*, 1897–1901; b) G. Bastug, S. P. Nolan, *Organometallics* **2014**, *33*, 1253–1258; c) E. Marelli, A. Chartoire, G. Le Duc, S. P. Nolan. *Chem. Cat. Chem.* **2015**, *7*, 4021–4024.

[17] a) C. C. C. Johansson Seechurn, S. L. Parisel, T. J. Colacot, *J. Org. Chem.* **2011**, *76*, 7918–7932; b) A. J. DeAngelis, P. G. Gildner, R. Chow, T. J. Colacot, *J. Org. Chem*. **2015**, *80*, 6794–6813; c) L. L. Hill, J. L. Crowell, S. L. Tutwiler, N. L. Massie, C. C. Hines, S. T. Griffin, R. D. Rogers, K. H. Shaughness, G. A. Grasa, C. C. C. Johansson Seechurn, H. Li, T. J. Colacot, J. Chou, C. J. Woltermann, *J. Org. Chem.* **2010**, *75*, 6477-6488; d) G. L. Beutner, J. R. Coombs, R. A. Green, B. Inankur, D. Lin, J. Qiu, F. Roberts, E. M. Simmons, S. R. Wisniewski, *Org. Process. Res. Dev.* **2019**, *23*, 1529-1537.

[18] a) P. R. Melvin, A. Nova, D. Balcells, W. Dai, N. Hazari, D. P. Hruszkewycz, H. P. Shah, M. T. Tudge, *ACS Catal*. **2015,** *5*, 3680–3688; b) P. R. Melvin, N. Hazari, M. M. Beromi, H. P. Shah, M. J. Williams, *Org. Lett.* **2016**, *18*, 5784–5787; c) P. R. Melvin, D. Balcells , N. Hazari, A. Nova, *ACS Catal*. **2015**, *5*, 5596–5606; d) A. H. Dardir, P. R. Melvin, R. M. Davis, N. Hazari, M. M. Beromi, *J. Org. Chem.* **2018**, *83*, 469-477.

[19] X.-Q. Hu, D. Lichte, I. Rodstein, P. Weber, A.-K. Seitz, T. Scherpf, V. H. Gessner, L. J. Gooßen, *Org. Lett.* **2019**, *21*, 7558.

[20] a) H. Clavier, S. P. Nolan, *Chem. Commun.* **2010**, *46*, 841-861. b) L. Chen, P. Ren, B. P. Carrow, *J. Am. Chem. Soc.* **2016**, *138*, 6392-6395.

[21] R. Dorta, E. D. Stevens, N. M. Scott, C. Costabile, L. Cavallo, C. D. Hoff, S. P. Nolan, *J. Am. Chem. Soc.* **2005**, *127*, 2485.

[22] a) D. P. Hruszkewycz, D. Balcells, L. M. Guard, N. Hazari, M. Tilset, *J. Am. Chem. Soc*. **2014**, *136*, 7300–7316; b) D. P. Hruszkewycz, L. M. Guard, D. Balcells, N. Feldmann, N. Hazari, M. Tilset, *Organometallics* **2015,** *34*, 381–394.

[23] a) S. Filipuzzi, P. S. Pregosin, A. Albinati, S. Rizzato, *Organometallics* **2006**, *25*, 5955-5964; b) A. Chartoire, M. Lesieur, A. M. Z. Slawin, S. P. Nolan, C. S. J. Cazin, *Organometallics* **2011**, *30*, 4432-4436; c) J. W. Faller, N. Sarantopoulos, *Organometallics* **2004**, *23*, 2179-2185.

[24] Other electronrich phosphines: a) a) M. A. Wünsche, P. Mehlmann, T. Witteler, F. Buß, P. Rathmann, F. Dielmann, *Angew. Chem. Int. Ed.* **2015**, *54*, 11857; b) L. Ackermann, R. Born, *Angew. Chem. Int. Ed.* **2005**, *44*, 2444; c) D. Martin, D. Moraleda, T. Achard, L. Giordano, G. Buono, *Chem. Eur. J.* **2011**, *17*, 12729; d) L. Chen, P. Ren, B. P. Carrow, *J. Am. Chem. Soc.* **2016**, *138*, 6392; e) S. Ullrich, B. Kovačević, X. Xie, J. Sundermeyer, *Angew. Chem. Int. Ed.* **2019**, *58*, 10335.

[25] L. T. Scharf, I. Rodstein, M. Schmidt, T. Scherpf, V. H. Gessner, *ACS Catal.* **2020**, *10*, 999-1009.

[26] In case of *t*BuNH2 the yields of the amination reaction varied remarkably. We tried to figure out the origin but couldn't find any explanation so far.

[27] For other Pd(I) allyl complexes, see: a) J. Sieler, M. Helms, W. Gaube, A. Svensson, O. Lindqvist, *J. Oreanomet. Chem.* **1987**, *320*, 129; b) D. P. Hruszkewycz, J. Wu, J. C. Green, N. Hazari, T. J. Schmeier, *Organometallics* **2012**, *31*, 470; c) A. D. Finke, E. C. Elleby, M. J. Boyd, H. Weissman, J. S. Moore, *J. Org. Chem.* **2009**, *74*, 22, 8897.

[28] Nielsen, C. D.-T.; Burés, J. Visual kinetic analysis, *Chem. Sci.* **2019**, *101*, 348-353.

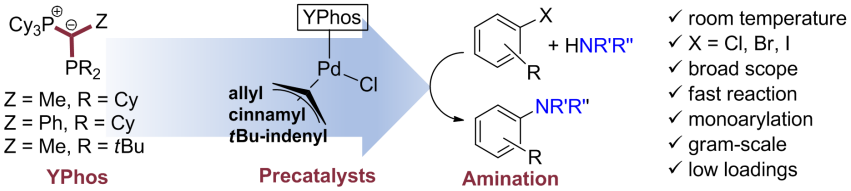
[29] Previous studies of our group [ref. 25] have shown that the complexes LPd(ArCl) and LPd(amine) are similar in energy. With the large excess of amine at the end of the reaction the amine complex presumably becomes more stable and thus prevents formation of LPd(ArCl). This results in an overall increase of the oxidative addition step and thus in a slowdown of the reaction.

[30] a) B. T. Ingoglia, C. C. Wagen, S. L. Buchwald, *Tetrahedron Lett.* **2019**, *57*, 4199-4211. b) B. P. Fors, N. R. Davis, S. L. Buchwald, *J. Am. Chem. Soc.* **2009**, *131*, 5766-5768. c) Q. Shen, T. Ogata, J. F. Hartwig, *J. Am. Chem. Soc*., **2008**, *130*, 6586–6596.

[31] M. H. Ali, S. L. Buchwald, *J. Org. Chem*. **2001**, 66, 2560-2565

10.1002/chem.201905535

Entry for the Table of Contents



User-friendly and easy accessible Pd complexes of three ylide-substituted phosphines (YPhos) were prepared and applied in C-N coupling reactions giving way to extremely active catalysts that allow for high yields and selectivities at room temperature for a wide variety of substrates. Aryl chlorides, bromides and iodides were successfully coupled also in gram-scale and with low catalyst loadings including difficult substrates such as alkyl amines.

Institute and/or researcher Twitter usernames: @ViktoriaGessner