The Use of Catalytic Amounts of CuCl and Other Improvements in the Benzyne Route to Biphenyl-Based Phosphine Ligands

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Abstract: Biphenyl-based phosphine ligands can be prepared on a significantly larger scale than previously possible as a result of the following discoveries and improvements to the original experimental procedure: the finding that CuCl catalyzes the coupling of hindered dialkylchlorophosphines with Grignard reagents; the development of conditions that permit $ClPCy_2$ to be prepared and utilized *in situ*; the development of a more reliable large-scale preparation of 2-dimethylaminophenylmagnesium halide.

Keywords: copper catalyzed P–C bond formation; improved synthesis; palladium catalysis; phosphine ligands

Introduction

The combination of phosphines **1** with a source of Pd(0) gives catalysts for the formation of C–N,[1] C–O,[2] and C–C[1b,3] bonds that are exceptional in terms of activity and general utility. These ligands possess a number of attributes that make them attractive to the practicing organic chemist: they are crystalline materials that are very stable to air oxidation – even in solution – and a number of derivatives of **1** are commercially available.[4] We[1–3] and others[5] have demonstrated that catalysts derived from Pd(0)/**1** enjoy an extensive substrate scope and can transform aryl chlorides as well as aryl bromides, iodides, and sulfonates. An unusual structural feature of **1** is the *o*-biphenyl moiety, which is important for efficient catalysis. Replacing the group with phenyl,[1c] *o*-cyclohexylphenyl,[1c] or *p*-biphenyl[6] gives ligands that are inferior in terms of selectivity and activity (Figure 1).

Furthermore, the effectiveness of **1** is often highly dependent on the nature of the R′ substituent on the biphenyl backbone. For example, although the parent *o*-biphenyl ligands (R′ = H; R = *t*-Bu or Cy) are very effective for a large number of C–N bond forming reactions,[1b,c] for the most challenging substrate combinations (those that are very sterically hindered or contain sensitive functional groups), higher numbers of turnovers and greater selectivities for reductive elimination (instead of β-hydride elimination) are only observed when R′ = H. Our studies to date have suggested that dimethylamino-substituted ligand **2a** is the most generally useful ligand for the Pd-catalyzed amination of aryl halides and sulfonates.[1a,6] Ligand **2a** also gives very effective catalysts for the formation of α-arylketones,[1a,3b] α-arylesters,[3c] and biaryls (*via* Suzuki coupling reactions).[1a]

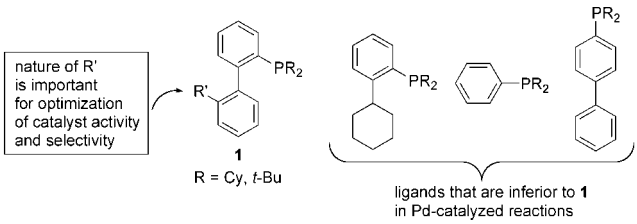
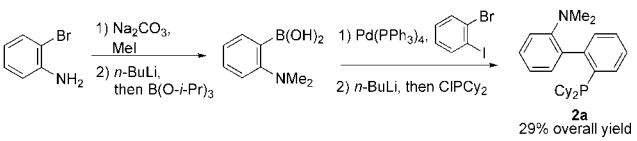


Figure 1.

Initially, the main drawback to the use of **2a** was its unavailability: its synthesis required 4 steps (Scheme 1). While in some instances (e.g., for the ketone arylation reaction) it was found that **2a** could be replaced by the more easily prepared ligand **3** (Figure 2). This was only a partial remedy, as **3** was not as useful as **2a** for other reactions, and the synthesis of **3** was still costly, time-consuming, and required chromatography. Therefore, it was significant when we discovered that *o*-metalated biphenyls generated



Scheme 1.

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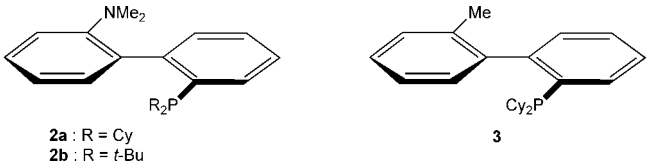
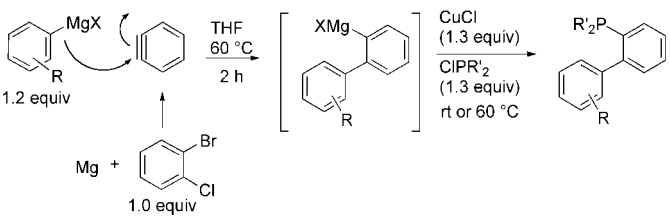


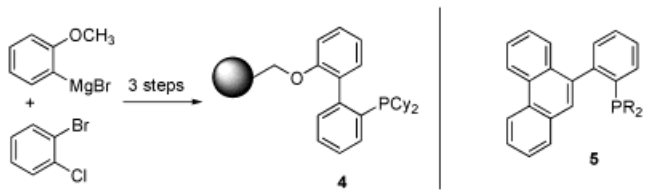
Figure 2.

by the addition of Grignard reagents to benzyne[7] could be trapped directly with chlorodialkylphosphines to give a variety of phosphines **1**.[8]

The protocol, outlined in Scheme 2, can be used to produce *o*-biphenyl-based phosphine ligands from inexpensive precursors in good yield and in large amounts relative to what is available by the reactions shown in Scheme 1. The route displayed in Scheme 2 has also facilitated the design and synthesis of new ligands. For example, polystyrene-supported ligand **4** (Scheme 3) was prepared in 3 steps from *o*-methoxyphenylmagnesium bromide and can be used for the Suzuki coupling and amination reaction of aryl chlorides and bromides; in some instances, **4** can be recycled up to 5 times without additional palladium and without significant loss in catalytic activity.[9] Also, structures **5** can be prepared in one step from 9-bromophenanthrene[6] and are extremely effective ligands for several Pd-catalyzed reactions, including the intramolecular formation of alkyl aryl ethers.[2b]



Scheme 2.



Scheme 3.

While the procedures in our previous report[8] on the synthesis of biphenyl-based ligands are satisfactory for small scale (<10 g) preparations, it became obvious that a number of problems would need to be surmounted if large quantities of ligands (>100 g) such as **2** and **3** were to become available: 1) The original procedure called for the addition of a stoichiometric amount of CuCl to the biphenylmagnesium halide prior to the addition of the dialkylchlorophosphine. While the cost of adding the CuCl to the reactions was only a minor concern, a more significant issue was the removal of copper byproducts. To remove copper that was ligated by the phosphine products, aqueous NH_4OH was added to the crude reaction mixture; an undesirable consequence was the formation of an emulsion that could be broken only by adding large amounts of solvent and brine. While filtering the emulsion through celite was beneficial, the process was extremely slow as the surface of the celite became clogged by a thick paste. Thus, the preparation of 100 grams of **1a** by our published procedure would require approximately 25 L of liquids (11 L of organic solvent, 8 L of conc. NH_4OH, and 6 L of brine). 2) To decrease the cost of the $ClPCy_2$ that is required for the synthesis of **1a** and **2**, we showed that the chlorophosphine could be used without purification when generated from PCl_5 and CyMgCl.[8] The yields obtained were similar to those with pure $ClPCy_2$. However, our procedure called for the separation of $MgCl_2$ from the chlorophosphine by filtration under argon – a manipulation that was performed so that one of the reaction components could be transferred via cannula or syringe (the biphenylmagnesium halide/CuCl mixture was also heterogeneous; our attempts to transfer either mixture with a filter cannula were not successful). However, the Schlenk filtration was time consuming and awkward on a large scale, and it was desirable to eliminate it from the protocol. 3) A problem specific to the preparations of dimethylamino ligands **2** was the amount of time required to prepare 2-dimethylaminophenylmagnesium chloride (28–48 h). After our initial publication, we observed that the formation of the Grignard reagent sometimes required even longer reaction times (we note that the Grignard formation was reproduced without event prior to publication) – and additional amounts of dibromoethane were sometimes required in order for the reaction to reach completion. It was always necessary to monitor the reaction to insure that the formation of the Grignard reagent was indeed complete.

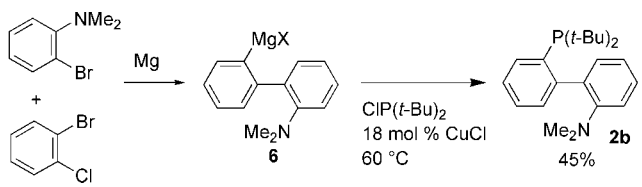
We show below how each of the aforementioned problems was ameliorated, and how ligands **2a**, **2b**, and **3** can be prepared in quantity by procedures that are very convenient.

Results and Discussion

The first issue that was addressed was the reliable formation of 2-dimethylaminophenylmagnesium chloride. In our original protocol, the Grignard reaction was initiated by slowly adding dibromoethane (over 1.5 h) to a mixture of 2-chloro-*N*,*N*-dimethylaniline and magnesium turnings in THF at reflux temperature. Adding the dibromoethane in a single

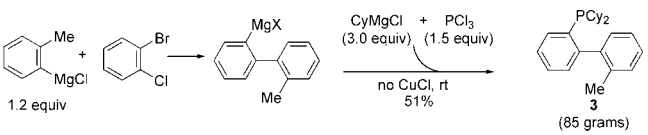
portion, either before or after the addition of the aryl chloride, was completely ineffective, as were other methods for activating Mg (adding catalytic amounts of I_2; vigorously agitating the turnings for 24 h under argon with mechanical stirring prior to use; sequentially washing the Mg with 1 M HCl, water, EtOH, and ether). Also, the formation of the Grignard reagent could not be improved by changing to a higher boiling ether solvent (dioxane, DME). However, large differences were observed when different grades of magnesium were examined. In four side-by-side experiments, dibromoethane (10 mol % relative to the aryl chloride) was added in five portions over 1.5 h to a rapidly stirred mixture (with a magnetic stirrer) of 2-chloro-*N*,*N*-dimethylaniline (0.75 M in THF) and Mg at reflux temperature. Four grades of Mg were tested – turnings, chips, 50 mesh powder, and 350 mesh powder,[10] and the reactions were monitored periodically by quenching with MeOH and measuring the ratio of *N*,*N*-dimethylaniline : 2-chloro-*N*,*N*-dimethylaniline. After 3 h, the reaction with turnings showed only trace product (< 1%), and the reaction with Mg chips had fared only slightly better (<10% conversion). However, the ratio of *N*,*N*-dimethylaniline : 2-chloro-*N*,*N*-dimethylaniline was 3 : 1 for the reaction with 50 mesh powder, and it was 48 : 1 with 350 mesh powder. A time of 4 h was sufficient for the latter reaction to proceed to completion. The formation of the 2-*N*,*N*-dimethylphenyl magnesium chloride using 350 mesh powdered Mg was reproduced more than 10 times on small scale (up to 10 grams). Unfortunately, when the scale of the reaction was increased, the length of time required to form the Grignard reagent was less reliable. An experiment that started with 46 grams of 2-chloro-*N*,*N*-dimethylaniline (0.6 M in THF) took 24 h and addition of a second charge of dibromoethane was necessary in order for the reaction to proceed to completion. Increasing the concentration to 3.0 M was beneficial on a 10 g scale (the amount of time required to form the Grignard reagent was only 1.5 h), but on a 22 g scale, the initiation of the Grignard was sluggish, and the addition of a second charge of dibromoethane resulted in a dangerous situation: the reaction initiated very suddenly and refluxed violently through the top of the condenser.[11] Because of these findings, we decided to re-examine the use of 2-bromo-*N*,*N*-dimethylaniline for the synthesis of **2a** and **2b**. We initially abandoned the bromide because, when purchased in small quantity, it is ca. 9 times more expensive than the chloride. However, the cost of the two materials is more comparable when they are purchased in bulk. More importantly, problems have never been encountered in the preparation of 2-dimethylaminophenylmagnesium bromide on any scale (up to 50 grams): no initiator is required, and its formation requires less than 30 min.

At this point, we sought to reduce the amount of CuCl that is used in the C–P bond forming reactions. That CuCl can enhance the yields of coupling reactions between biphenylmagnesium halides and chlorophosphines was first observed for the preparation of **1** (R = H, R′ = *t*-Bu) in these labs by Sadighi.[2a,12] In that preparation, a stoichiometric amount of CuCl was utilized.[13] Although there are a number of reactions of Grignard reagents for which Cu-catalysis is precedented,[14] we could find no examples in which the reaction of a halophosphine with an organolithium or Grignard reagent is catalyzed by Cu(I).[15] Thus, we were gratified to find that the CuCl could be used in catalytic amounts in the coupling reaction of Grignard reagent **6** with either *in situ* generated Cy_2PCl (*vide infra*) or $(t\text{-Bu})_2PCl$ (Scheme 4), and consequently that the volume of liquid needed to work up the reactions could be decreased dramatically because an emulsion did not form. The purification of compound **2b** is also simpler when a catalytic amount of CuCl (18 mol %) is used; filtration through celite is much faster than for reactions that employ a stoichiometric amount of CuCl. We note that the yield of **2b** has improved since our previous report because the crystallization procedure has been further optimized (not because using CuCl as a catalyst instead of a reagent provides the product in better yield).



Scheme 4.

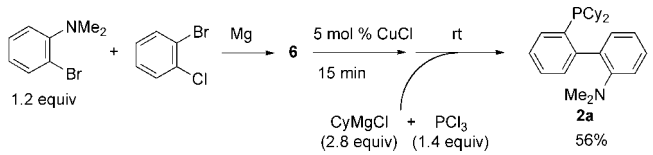
The preparation of ligand **3** proceeds smoothly when $ClPCy_2$ is generated *in situ* from CyMgCl and PCl_5 without removal of the precipitated Mg salts and, unlike **2a** and **2b**, **3** can be prepared in good yield (51%) when the copper catalyst is omitted. The latter procedure has been carried out on an 85 gram scale, and from a production standpoint has the obvious advantage that it generates no copper-containing waste (Scheme 5).



Scheme 5.

We also found that aminophosphine **2a** could be prepared in good yield (56%) with *in situ* generated $ClPCy_2$ (Scheme 6). The best results were obtained if

Grignard reagent **6** was first stirred for 10 minutes with the CuCl catalyst prior to combination with the chlorophosphine. Since the mixture of CuCl/**6** is heterogeneous, it cannot be transferred efficiently *via* cannula to the crude chlorophosphine. However, simply pouring the slurry of CuCl/**6** into the mixture of $ClPCy_2/MgX_2$ (with brief exposure to air) gave **2a** in good yield. We note that, for the *in situ* generation of $ClPCy_2$, it is important that the ratio of $CyMgCl : PCl_3$ be exactly 2 : 1 (freshly titrated CyMgCl should be used). The ^{31}P NMR spectrum of the crude $ClPCy_2$ should indicate that the reagent is > 95% pure. In experiments where we used a 2.13 : 1 ratio of CyMgCl : PCl_3, it was not trivial to separate **2a** from the PCy_3 byproduct *via* crystallization, and the product could therefore be obtained only in 40–42% yield.



Scheme 6.

Conclusion

In summary, we have described preparations of biphenyl-based phosphine ligands that can be carried out on a large scale with less time and cost than previously possible. The improvements stem from the finding that CuCl can catalyze the coupling of aryl Grignard reagents with hindered chlorophosphines, from the identification of a reliable source of 2-(2-dimethylaminophenyl)phenylmagnesium halide, and from the development of efficient conditions for the generation and *in situ* use of dicyclohexylchlorophosphine.

Experimental Section

General Remarks

THF and diethyl ether were purchased from J. T. Baker in CYCLE-TAINER® solvent delivery kegs and vigorously purged with argon for 2 h. The solvents were further purified by passing them under argon pressure through two packed columns of neutral alumina. Magnesium turnings were purchased either from Alfa-Aesar or Mallinckrodt-Baker. 1,2-Dibromoethane (99%) and 2-bromochlorobenzene (99%) were purchased from Alfa-Aesar. Magnesium powder (350 mesh, 99.5%), cyclohexylmagnesium chloride (2.0 M solution in Et_2O) and *o*-tolylmagnesium chloride (1.0 M in THF) were purchased from Aldrich Chemical Co. 2-Chloro-*N*,*N*-dimethylaniline (95%) was purchased from Karl Industries (Aurora, OH; the impurity was identified as 2-chloro-*N*-methylaniline). 2-Bromo-*N*,*N*-dimethylaniline was prepared on a 100 g scale in > 98% purity (judged by ^1H NMR) by the method of Gilman[16] from 2-bromoaniline (King's Laboratories, Blythewood, SC) and Me_2SO_4 (Aldrich). Alternatively, 2-bromo-*N*,*N*-dimethylaniline (95%) can be purchased from Karl Industries. Phosphorus trichloride was purchased either from Aldrich (99.999%) or Alfa-Aesar (99.5%), and was not purified before use. Dicyclohexylchlorophosphine (98%) was purchased from Strem Chemical Co., and was stored in a glovebox. Additions of the reagent were performed outside of the glovebox using a syringe. Di-*tert*-butylchlorophosphine (96%) was purchased in Sure-Seal® containers from Aldrich, and was not stored in the glovebox. Copper(I) chloride was either purchased from Strem (99.999%) or Aldrich (99.995%). The ligands described below were judged to be > 97.5% pure by comparing their ^1H and ^{31}P NMR spectra and GC chromatograms to those reported previously.[1a,2a,8]

Synthesis of 2-Dimethylamino-2′-dicyclohexylphosphinobiphenyl (2a) with *in situ* Prepared $ClPCy_2$

A dry, 3-necked, 500-mL, round-bottomed flask with 24/40 joints was equipped with a stirrer, a gas inlet adapter and two septa. The flask was evacuated, flame dried, refilled with argon, cooled to rt, and sequentially charged with 75 mL of diethyl ether and PCl_3 (4.9 g, 3.1 mL, 36 mmol). The flask was then cooled in a bath of ethylene glycol: ethanol (6 : 4; –40 °C),[17] and the solution was stirred rapidly. Cyclohexylmagnesium chloride (33 mL of a 2.2 M solution in diethyl ether, 72 mmol) was added to the solution via cannula over the course of 15 min. During the addition, $MgCl_2$ precipitated from solution; care was taken to maintain stirring during the entire addition. The mixture was then stirred for 20 min, at which time the –40 °C bath was replaced by an ice bath. After stirring at 0 °C for 30 min, the mixture was warmed to rt. An aliquot was taken and transferred directly to an NMR tube. The major resonance (δ = 126 ppm; > 95%) by ^{31}P NMR spectrum was attributed to $ClPCy_2$; only traces of PCy_3 (δ = 11 ppm; < 5%) were detected. The crude mixture was used directly in the reaction described below.

A dry, 100-mL, round-bottomed flask (with a 14/20 ground glass joint) was equipped with a stirrer and a gas inlet adapter with a septum,[18] and was charged with Mg turnings (1.37 g, 56.4 mmol). The flask was again evacuated and backfilled with argon, THF (30 mL) was added, and the mixture was heated in an oil bath at 70 °C. 2-Bromo-*N*,*N*-dimethylaniline (6.0 g, 3.8 mL, 30 mmol) was added in four equal portions over the course of ca. 20 min, and after the reflux caused by Grignard formation had subsided, the temperature of the oil bath was lowered to 60 °C (it took ca. 30 min for the bath to cool). 2-Bromochlorobenzene (4.9 g, 3.0 mL, 26 mmol) was then added in 4 equal portions over the course of ca. 20 min. The mixture was then stirred for 2 h 15 min at 60 °C and subsequently cooled to rt (an aliquot was quenched with MeOH and analyzed by GC: no chlorobenzene remained). CuCl (130 mg, 1.3 mmol) was then added, and the mixture stirred for 10 min. Briefly being exposed to air, this mixture was poured directly into the crude $ClPCy_2$. For this manipulation, one of the septa was removed from the 3-necked flask, and the flow rate of argon was increased. The flask that had contained the

Grignard reagent/CuCl was rinsed twice with 5 mL portions of THF, and was placed under argon while the THF was added. After stirring for 1 h at rt, the consumption of the Grignard reagent was complete (as determined by GC analysis). The reaction was quenched by pouring it directly into an Erlenmeyer flask that contained 300 mL of ice. Ethyl acetate (100 mL) and conc. NH_4OH (3 mL) were then added, and the mixture was stirred for 10 min, filtered through celite, and transferred to a separatory funnel. The aqueous layer was separated and the organic layer washed with brine. The combined washings were then extracted with ethyl acetate, and the extract was washed with additional brine. The organic layers were combined, dried (Na_2SO_4), filtered, and concentrated. Ethyl acetate (12 mL) was added to the residue, which was stirred and cooled in an ice bath. Methanol (72 mL) was added, the mixture stirred for 1.5 h at 0 °C, and filtered on a Buchner funnel. The white solid was rinsed with 30 mL of cold methanol, and dried under vacuum. The yield of the title compound was 5.9 g (58%).

An identical experiment gave 5.3 g (53%) of the title compound.

2-Dimethylamino-2′-di-*tert*-butylphosphinobiphenyl (2b)

A dry, 100-mL round-bottomed flask was charged with Mg turnings (1.37 g, 56.4 mmol) and stirrer and was equipped with a gas inlet adapter with a septum.[18] The apparatus was evacuated and backfilled with argon. THF (25 mL) was added and the mixture was stirred and heated in a bath at 70 °C. 2-Bromo-*N*,*N*-dimethylaniline (6.0 g, 3.8 mL, 30 mmol) was then added in 4 equal portions over the course of 15 min and, after the reflux caused by Grignard formation had subsided, the temperature of the oil bath was lowered to 60 °C (it took ca. 30 min for the bath to cool). 2-Bromochlorobenzene (4.9 g, 3.0 mL, 26 mmol) was then added in 4 equal portions over the course of ca. 20 min, the mixture was stirred for 2 h 15 min at 60 °C and subsequently cooled to rt (an aliquot was quenched with MeOH and analyzed by GC: no chlorobenzene remained). CuCl (450 mg, 4.5 mmol) was then added, and the mixture stirred for 15 min. Di-*tert*-butylchlorophosphine (5.4 g, 5.6 mL, 30 mmol) was then added *via* syringe over the course of 5 min, and the mixture was heated in an oil bath at 60 °C for 20 h. The reaction was quenched with water (ca. 80 mL), and transferred to an Erlenmeyer flask with 80 mL of ethyl acetate and 80 mL of hexane. Conc. NH_4OH (25 mL) was added, and the mixture was stirred for 10 min, filtered through celite, and transferred to a separatory funnel. The aqueous layer was separated, and the organic layer was washed twice with water. The combined washings were extracted with ethyl acetate, and the extract was washed twice with water. The organic layers were combined, dried (Na_2SO_4), filtered, and concentrated. The residue was suspended in 17 mL of methanol, which was stirred while cooling in an ice bath for 2 h. A spatula was used to break any large pieces. A solid was filtered on a Buchner funnel, and transferred to a round-bottomed flask. Methanol (10 mL) was added, the suspension was stirred for 1 h while cooled in an ice bath, and the solid was again filtered and transferred back to the 100 mL flask. Additional methanol (10 mL) was added, the suspension was stirred for 1.5 h at rt and then for 1.5 h while cooled in an ice bath. A white solid was filtered and dried under vacuum. The yield of the title compound was 3.86 g.

An additional crop of crystals was obtained by concentrating the mother liquor from the third crystallization, adding 5 mL of methanol to the residue, and stirring for 4 h at rt. An additional 200 mg of the title compound was obtained. The combined yield was 4.1 g (47%).

An identical experiment gave 3.8 g (43%) of the title compound.

Synthesis of 2-Methyl-2′-dicyclohexylphosphinobiphenyl (3) with *in situ* Prepared $ClPCy_2$ and without CuCl

A 5 L, 4-necked flask was equipped with an overhead stirrer, a 500 mL addition funnel, a thermocouple and a Claisen adapter fitted with a septum and an N_2 inlet. The apparatus was flushed with N_2. After the flask was charged with 1 L THF and PCl_5 (65.5 mL, 750 mmol), it was cooled to an internal temperature of ca. −14 °C with an ice/salt slurry bath. The 500 mL addition funnel was charged with CyMgCl (770 mL, 2 M in Et_2O) in 2 portions (500 mL then 270 mL). The CyMgCl solution was added into the 5 L flask over ca. 2 h via rapid dropwise addition with periodic breaks to prevent the internal temperature from rising above 0 °C. To help control the exotherm, the ice/salt slurry was refreshed periodically. After addition was completed, the ice/salt bath was removed and the reaction was allowed to warm to ambient temperature with stirring over 2 h.

A 1 L, 3-necked flask was equipped with a stirrer, a reflux condenser and a 60 mL addition funnel and was flushed with N_2. The 1 L flask was charged with oven-dried Mg turnings (12 g) and *o*-tolyl magnesium chloride (500 mL, 1 M in THF) and was placed in a 60 °C oil bath. After the solution was allowed to equilibrate for 10–15 min, the 60 mL addition funnel was charged with 2-bromochlorobenzene (53.5 mL, 458 mmol). The 2-bromochlorobenzene was added to the 1 L flask dropwise (~30–45 min). After ca. one third of the 2-bromochlorobenzene had been charged, an exotherm occurred inducing vigorous reflux for the remainder of the addition. Upon complete addition of 2-bromochlorobenzene, the reaction mixture was maintained in the oil bath for 2 h. The flask was removed from the oil bath and allowed to cool to ambient temperature with stirring (~1 h). This solution was transferred into the crude Cy_2PCl solution *via* vacuum-assisted cannula transfer. The resulting mixture was allowed to stir at ambient temperature for 14 h and then quenched with 500 mL water over ca. 20 min in order to control the exotherm. The organic phase was removed and filtered through a pad of Celite with an EtOAc wash (300 mL). After the organic phase was reduced under vacuum to ca. 250 mL total volume, it was transferred with minimal EtOAc to a 2 L, 3-necked, round-bottom flask fitted with an overhead stirrer and a 500 mL addition funnel. The solution was seeded with crystals (seeding is not necessary but tends to produce a first batch product of higher purity) and cooled with an ice bath, initiating crystallization. The addition funnel was charged with 2 × 500 mL MeOH, which was added dropwise (~30–45 min) to complete product precipitation. The solid was isolated via vacuum filtration with one wash (200 mL cold MeOH) and was dried under vacuum. Yield: 85 g (51%).

Acknowledgements

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[4] Ligands **1** (R = H, R′ = Cy or *t*-Bu), **2a**, and **3** are commercially available from Strem Chemical, Inc.

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[10] For these experiments, Mg turnings were purchased from Mallinckrodt-Baker, Mg chips (-4+30 mesh, 99.98%), 50 mesh powder (99+%) and 350 mesh powder (99.5%) were purchased from Aldrich Chemical Co.

[11] A similar incident occurred at Strem Chemical, Inc. during an attempt to prepare large amounts of 2-dimethylaminophenylmagnesium chloride.

[12] J. P. Sadighi, *Palladium Catalysis in the Synthesis of Polyaniline-Related Materials*, Ph. D. Thesis, Massachusetts Institute of Technology, Cambridge, MA, **1999**.

[13] The use of stoichiometric amounts of CuCl for the preparation of **1** (R = H, R′ = *t*-Bu) has merit, since the ligand forms an insoluble copper complex: organic impurities can be removed by washing with ether/hexanes. Subsequent treatment with conc. NH_4OH and simple work-up provides the ligand in pure form.

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[17] D. W. Lee, C. M. Jensen *J. Chem. Ed.* **2000**, *77*, 629.

[18] An adapter similar to that sold by ChemGlass, item CG-1062, was used.