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FULL PAPER

Synthesis, Structural Analysis and Application of Aryl-Diadamantyl Phosphine ligands in Palladium Catalyzed Cross-Coupling Reactions

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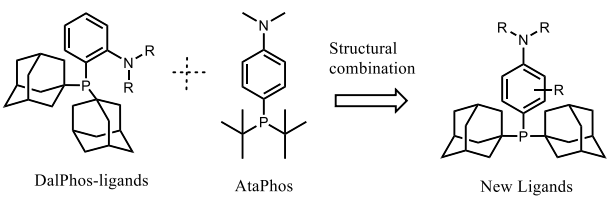
Dedication

Abstract: Synthesis, temperature dependent NMR structure investigation and utilization of a new, stable and easily accessible aryl-diadamantylphosphine ligand family is reported. The bulky and electron rich phosphorous center of the ligand enhances the catalytic activity of palladium in cross-coupling reactions of sterically demanding ortho substituted aryl halides. In our study we demonstrated the synthetic applicability of the new phosphine ligands in Buchwald-Hartwig and tosyl hydrazone coupling reactions.

Introduction

The development of new ligands for transition metal-based catalytic systems is an important task not only for academic research, but also has significance in industrial applications.[1] The use of strong sigma-donor ligands with optimized steric properties increase significantly the catalytic activity of transition metal catalysts, enabling low catalyst loadings for the desired transformations and mild conditions.[2] Taking advantage of the available ligand kits, reaction parameter optimization can be performed routinely in high throughput,[3] as well as in computational studies.[4] However, development of new ligands remains an important task of catalysis research in order to find more efficient methodologies for specific industrial applications.
Herein, we present our achievements in the development of a new, monodentate and sterically hindered phosphine ligand kit for palladium catalyzed transformations.
Steric properties and electron donor-acceptor behavior are the most important attributes of monodentate phosphine ligands from the aspects of homogeneous catalysis. Thus, design of ligands with electron rich phosphorous center and high steric demand is the key direction of the ligand developments for cross-coupling. In the last years Carrow's laboratory presented a new ligand, triadamantylphosphine which broadened the limits of the imaginable ligand properties.[5] PAd_3 seems to be bulkier than P^tBu_3, however the C-P-C bond angle and the Tolman cone angle show no significant differences. Instead, the Tolman electronic parameter shows increased electron donating property compared to P^tBu_3, as Carrow's group observed.[6] Earlier, Buchwald reported a diadamantyl-terphenyl phosphine for the formation of C-F bonds.[7,8] Other research groups also reported the development of diadamantyl phosphine derivatives as a replacement of the commonly used *tert*-butyl phosphines, Hartwig designed mono and diadamantyl-methylphosphines,[9] and Beller's diadamantyl-butylphoshine known as cataCXium A ligand proved to be highly efficient for cross-coupling of less reactive aryl halide substrates.[10] The two adamantyl groups guarantee the steric bulk and the electron rich phosphorous center, while the aryl group attached to the phosphorous atom is an easily functionalizable part of the ligand to fine tune its properties. More recently, the DalPhos ligand family developed by Stradiotto and coworkers was reported as an excellent phosphine ligand for palladium catalyzed amination, hydrazination and further carbon-carbon bond forming reactions.[11,12] The presence of two adamantyl groups around the phosphorous center and the *ortho*-phenyleneamine structural motif ensures high activity in the selected coupling reactions. Guram and coworkers reported a ligand family with similar structural features to DalPhos ligands. These phosphines were successfully applied in Suzuki-Miyaura coupling (SMC) reactions of various aryl chlorides and aryl boronic acids.[13] The most effective ligand of the collection contains two *tert*-butyl groups and a 4-dimethylaminophenyl group on the phosphine center (AtaPhos). Our ligand design was based on the merge of the structural features of DalPhos and AtaPhos ligand families, and we aimed to synthesize diadamantylphosphine ligands having para-dialkylamino substituted aryl and heteroaryl moiety in a simple manner (Scheme 1).



Scheme 1. Ligand comprises the appropriate properties from DalPhos and AtaPhos.

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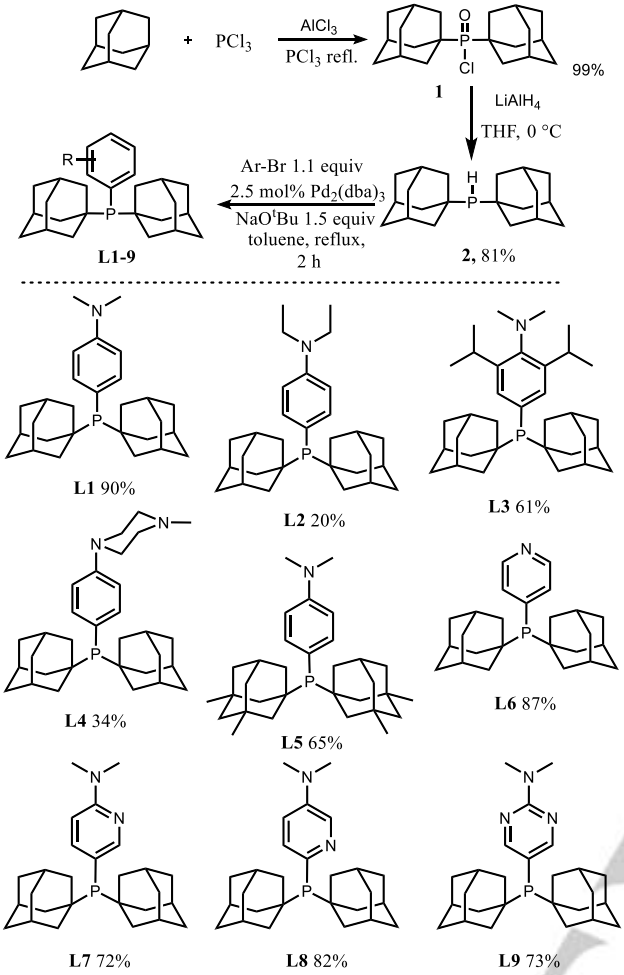


Scheme 2. The synthetic route to diadamantyl-arylphosphines and the yields of the last step of the synthetic procedure.

Results and Discussion

For the synthesis of di-1-adamantyl-arylphosphines, diadamantylphosphine was prepared on large scale in a two-step synthesis. First, the di-1-adamantylphosphinic chloride (**1**) was prepared (175g, 0.5 mol scale, 99% yield) from adamantane and phosphorus trichloride,[14] then it was reduced with $LiAlH_4$ to obtain the desired di-1-admantylphosphine (**2**) in 81% yield (121g, 0.4 mol).[15] For the formation of C(sp^2)-P bond we performed the palladium catalyzed cross-coupling of aryl- and heteroarylbromides with $HPAd_2$ in refluxing toluene in the presence of NaO^tBu base, where the phosphines also play the role of ligand to facilitate the coupling.[16] The dimethylamino derivative (**L1**) was obtained in excellent yield (90%) after a simple filtration of the reaction mixture, which makes the synthetic procedure simple and convenient. In contrast, the diethylamino analogue (**L2**) was obtained only in 20% isolated yield. This difference was attributed to different solubility properties of the phosphine ligand **L2**. This might also be the reason for the lower yield of the *N*-methylpiperazino analog **L4**. While **L1** can be isolated by simple filtration, the crystallization of **L2** and **L4** was more difficult, which caused significant drop of the yield. The phosphine bearing two isopropyl groups in its aromatic part (**L3**) was obtained in 61% yield. The introduction of two methyl groups onto the adamantane moieties was also well tolerated and **L5** was isolated in good yield. The ligand class was extended to six membered heterocyclic cores such as pyridine with (**L7**, **L8**) or without (**L6**) dimethyl amino group, and also to the pyrimidyl analog **L9**.

The structure elucidation of the products relied basically on comprehensive one- and two-dimensional NMR spectroscopy studies using widely accepted methods[17,18] to establish their ^1H, ^{13}C and ^{31}P signal assignment. However, we found unexpected complexity of spectra during the routine NMR studies of the phosphine compounds. Thus, the preparation of protonated form of the ligands was necessary[19] for the analytical investigations to simplify the assignment of the different atoms, and understand the unexpected spectral behavior of the ligands. The 30 hydrogens of the two adamantyl groups can be found in the aliphatic region between 2.24-1.72 ppm as overlapping multiplet signals. In the HSQC spectrum these hydrogens show correlation with only three carbon atoms which is in agreement with the three-fold rotational symmetry of the adamantyl moieties. Hence, the multiplet signal at δ_H =2.10 ppm can be assigned to the CH group (δ_C = 27.7 ppm), the diasteretopic hydrogens at δ_H = 1.84+1.81 ppm and δ_H = 2.21+2.08 ppm to the symmetrically two different CH_2-s at δ_C = 35.2 and 38.3 ppm respectively. In the ^1H NMR spectrum at δ_H = 5.70 ppm a doublet signal can be observed with a large coupling constant (J = 455 Hz). The same coupling constant was detected in the coupled ^{31}P NMR spectrum at δ_P = 39 ppm, i.e. this signal can be identified as the acidic hydrogen which is localized on the phosphorous atom. The unprecedented coupling constant is therefore the one bond interaction between the acidic ^1H and the ^{31}P atoms. In the aromatic region a broad signal can be observed at δ_H = 6.90 ppm and two more broad signals close to each other at δ_H = 7.56/7.41 ppm. The altogether 4 H intensity suggested that these signals belong to the *para*-substituted benzene moiety, however the expected AA'XX' spin system could not be identified. By elevating the temperature in the probehead to 350K, the two signals at δ_H = 7.56/7.41 ppm collapsed into one, and also the fine structure of the signals appeared, proving the *para*-substitution of the aromatic ring in case of protonated form of **L1**. This behavior was observed in case of all the analogous compounds. The aromatic protons proximal to the phosphorous atom showed much stronger line broadening/splitting effect than the farther ones, which suggested that this phenomenon can be explained by a hindered rotation around the bond connecting the phosphorus atom and the aromatic ring. By recording a series of ^1H NMR spectra at different temperatures the coalescence temperature of this exchange process was found to be between 310-320 K [Figure 1].

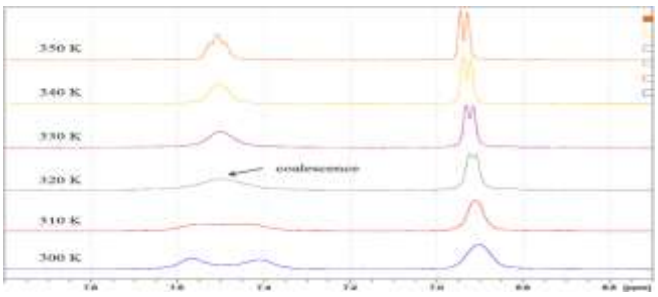


Figure 1. Temperature dependent 1H NMR spectra of **L1-H$^+$** (aromatic section).

Taking into consideration the initial split of the aromatic signals at room temperature (80 Hz) an approximate 15.0 – 15.5 kcal/mol free activation enthalpy can be calculated for the hindered rotation.[20]

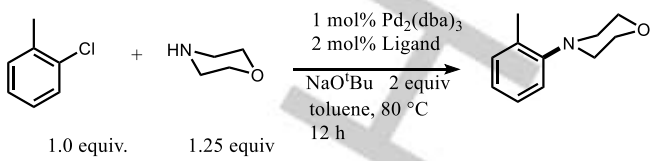
The structure of diadamantylphosphine **L1** was also determined by X-ray crystallography (Figure 2). The C-N distance for **L1** is 1.4021(15) Å and the distance of the nitrogen from the C-C-C- plane is 0.002 Å. The fact that the nitrogen atom is in the C-C-C plane can be explained by conjugation. The C11-P1-C21 angle is 119.1(1) deg supporting the very high steric demand of **L1**.

Figure 2. ORTEP view of protonated L1 at 50% probability level. BF4-counter ion is omitted for clarity. Selected bond length (Å) and bond angle (o) data: P1-C1 1.7795 (10); P1-C11 1.8226 (9); P1-C21 1.8397 (9); C1-P1-C11 112.52 (5); C11-P1-C21 119.14 (4); C1-P1-C21 110.80 (5). CSD number for structure L1 is 1941994. Tolman angle: 181°.

After the synthesis of the collection of new phosphine ligands we aimed to explore their applicability in Buchwald-Hartwig amination and tosylhydrazone couplings. The palladium catalyzed Buchwald-Hartwig coupling is a powerful tool for the amination of aromatic and heterocyclic halides.[21] Amongst these halides and halide alternatives (triflates, mesylates, tosylates, imidazylates etc.) the chlorides are the most easily accessible and cheapest substrates, but their reactivity toward palladium is the lowest.[22] As a novel alternative ligand we tested our aryldiadamantylphosphines in this palladium catalyzed transformation to produce substituted arylamines which could be of interest on the field of medicinal chemistry.

For the optimization studies we chose 2-chlorotoluene as sterically congested substrate to evaluate the catalytic power of the ligand-palladium system in the transformation. The model coupling reaction was performed with morpholine in toluene at 80 °C in the presence of 1 mol% Pd_2dba_3 and 2 mol% ligand. The reactions were conducted for 12 hours, then the desired *N*-tolylmorpholine was isolated in each case. The results show that each new ligand works efficiently in the coupling, only the *N*-methyl-piperazine substituted derivative (**L4**) showed moderate activity (55% yield). These results underlined that **L1** is a good candidate for the palladium catalyzed amination of aryl halides considering its activity and its easy preparation. In the presence of the structurally similar Me-DalPhos, Mor-DalPhos and ^{t}BuMeDalPhos ligands the desired coupling product was not detected or was present only in traces even after 16 hours reaction, while the reaction in the presence of AtaPhos ligand gave the product in a comparable 79% yield.

Table 1. The efficiency of the ligands.

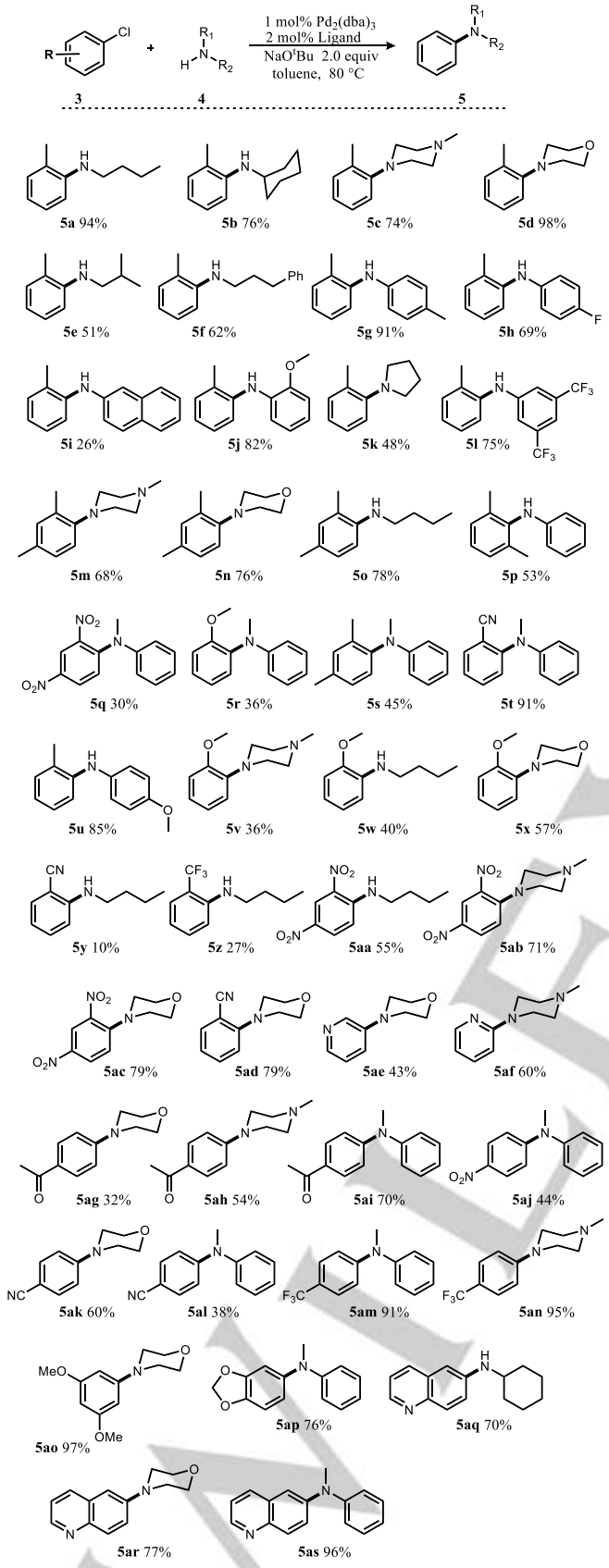


Entry	ligand	yield[a]	Entry	ligand	yield[a]
1	L1	*85%*	**8**	L8	*78%*
2	L2	*92%*	**9**	L9	*90%*
3	L3	*94%*	**10**	AtaPhos	*79%*
4	L4	*55%*	**11**	Me-DalPhos	*0%*
5	L5	*92%*	**12**	Mor-DalPhos	*5%[b]*
6	L6	*82%*	**13**	^{t}BuMe-DalPhos	*8%[b]*
7	L7	*87%*			

[a] Isolated yields. [b] GC-conversions. General procedure: 4.6 mg (5 µmol) $Pd_2(dba)_3$, 10 µmol ligand and 96 mg (1 mmol) NaO^{t}Bu was added to a 4 mL screw capped vial. The vial was purged with argon, and 2.5 mL toluene, 58.4 µL (0.5 mmol) 2-chlorotoluene and 54.1 µL (0.625 mmol) morpholine was added. The reaction mixture was stirred at 80°C for 12 hours. Purified by chromatography on silica with hexane / ethyl acetate eluent.

After the ligand screening, we explored the scope and limitations of the Buchwald-Hartwig reaction with different aromatic and heteroaromatic chlorides and primary alkyl and aryl amines using **L1** as our ligand of choice due to its straightforward availability and high activity. In these scope exploration studies 2-chlorotoluene was efficiently coupled with various primary and secondary amines such as *n*-butylamine, cyclohexylamine, *N*-methylpiperazine, morpholine, isobutylamine, phenylpropylamine, *p*-toluidine, *p*-fluoroaniline, 2-naphthylamine, *o*-anisidine, pyrrolidine and 3,5-bis(trifluoromethyl)phenylamine. The desired products **5a-l** were isolated in 26-98% yield range. Similarly, sterically hindered chloroxylenes showed comparable reactivity under the applied catalytic conditions and the appropriate products **5m-5o** were obtained in 68-78% yield. Even the sterically more hindered 2,6-dimethylchlorobenzene reacted with aniline under the catalytic conditions, and **5p** was isolated in 53% yield. It is of note that the utilization of a sterically more hindered amine such as *N*-methylaniline also allowed the coupling with *ortho*-substituted chlorobenzenes, and we obtained products **5q-t** in 30%, 36%, 45% and 91% yields respectively.

Coupling with electron rich anisidines provided the diarylamines **5u** and **5j** in 85% and 82% yields respectively. 2-Chloroanisole was also coupled with *N*-methylaniline, *N*-methylpiperazine, *n*-butylamine and morpholine obtaining the expected products in moderate yields from 36 to 57% (**5r**, **5v-x**). Ortho substituted electron deficient aryl chlorides bearing CF_3, nitro or cyano groups were also aminated using the novel Pd-phosphine ligand system and the appropriate secondary or tertiary amines (**5y-5ad**) were isolated in poor to excellent yields depending on the structure of the coupling partners.



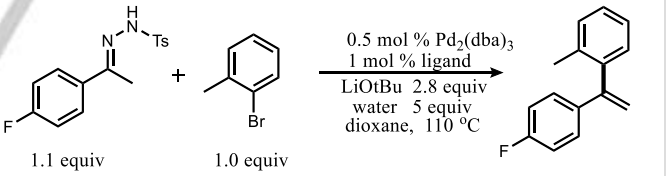
Scheme 3. Coupling method for C-N bond formation.

Starting from 3-chloropyridine the morpholine derivative (**5ae**) was isolated in 43% yield, while the coupling of this substrate with *n*-butylamine failed. In contrast to 3-chloropyridine the amination of 2-chloropyridine gave good results with *N*-methylpiperazine (60%, **5af**). Finally, *para*-substituted chlorobenzene derivatives were coupled with morpholine, *N*-methylpiperazine and *N*-methylaniline under the optimized conditions and the products were isolated in 32%, 54% and 70% yield respectively (**5ag**-**ai**). Nitro- (**5aj**) and nitrile (**5ak**-**al**) derivatives were also coupled successfully, and 4-trifluoromethyl chlorobenzene gave excellent yields (91-95%, **5am**-**an**). Nevertheless, electron rich dimethoxy derivative was also used successfully (97% **5ao**) and benzodioxole was coupled in 76% (**5ap**) as well.

Amongst the heterocyclic systems, the amination of 6-chloroquinoline was tested with three different amines, such as cyclohexylamine, morpholine and *N*-methylaniline. The appropriate products were obtained in 70%, 77% and 96% yield respectively (**5aq**-**as**). In conclusion we can state that the novel ligand, **L1** was efficient in the Buchwald-Hartwig coupling of a diverse set of sterically demanding substrates of varying electronic properties.

In parallel with the study of the Buchwald-Hartwig amination reaction, we examined the applicability of the ligands in the coupling reactions of ortho substituted aryl halides and tosylhydrazones, which are versatile reagents for synthetic transformations.[23] These are the key reagents for producing alkene derivatives in Bamford-Stevens[24] and in Shapiro[25] reactions. Moreover, the application of tosylhydrazones in palladium catalyzed cross-coupling reactions opened a new synthetic possibility for the synthesis of arylalkene derivatives.[23b] Due to the increasing interest in 1,1-diarylalkenes we aimed to study the applicability of our phosphine ligands in this novel cross-coupling reaction.

Table 2. Ligand scope in the coupling with tosylhydrazones.

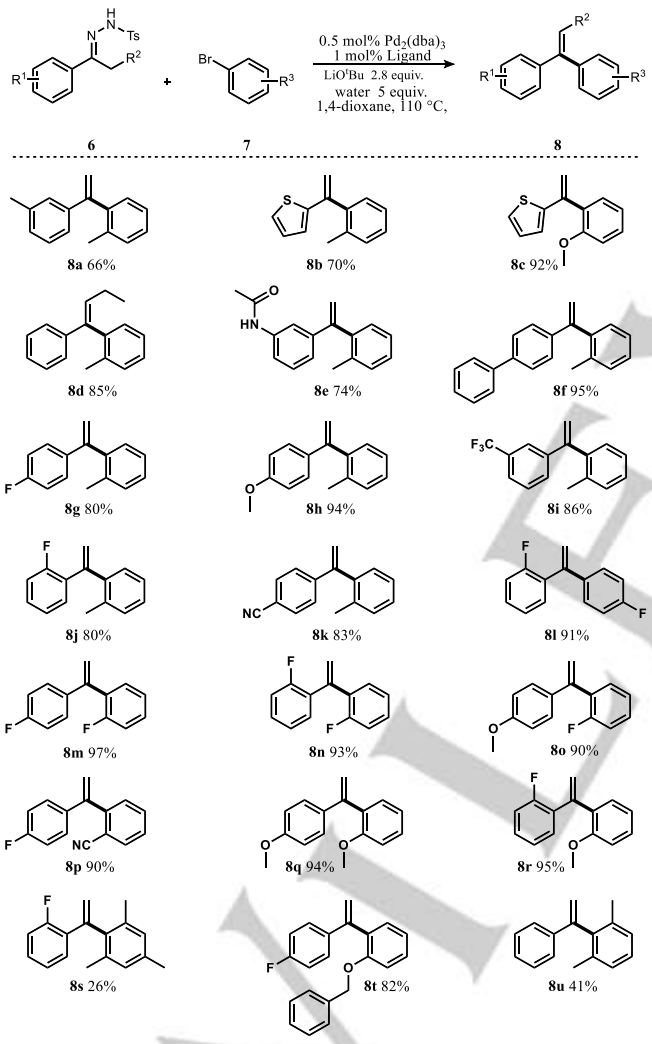


Entry	ligand	yield[a]	Entry	ligand	yield[a]
1	**L1**	87%	**8**	**L8**	10%
2	**L2**	90%	**9**	**L9**	92%
3	**L3**	90%	**10**	AtaPhos	92%
4	**L4**	88%	**11**	Me-DalPhos	0%
5	**L5**	95%	**12**	Mor-DalPhos	7%
6	**L6**	81%	**13**	^{t}BuMe-DalPhos	0%
7	**L7**	93%			

[a] Isolated yields. General procedure: 168 mg (0.55 mmol) 4'-fluoroacetophenone-tosylhydrazone, 2.3 mg (2.5 µmol) Pd_2dba_3, 5 µmol ligand, 112 mg (1.4 mmol) LiO^{t}Bu were measured in a screw capped vial. Argon atm. was used. 1.5 mL 1,4-dioxane and 45 µL (2.5 mmol) water was added, followed by 60 µL (0.5 mmol) 2-bromotoluene. Stirred at 110 °C, overnight. Purified by chromatography on silica with hexane / ethyl acetate eluent.

This transformation usually requires the presence of bulky and electron rich phosphine ligands, therefore it could be the field of coupling reaction where the new ligand family could serve as beneficial addition to the existing ones.

In the first step we studied the ligand effect on the chosen model reaction of 2-bromotoluene and 4-fluoroacetophenone-tosylhydrazide. These coupling were performed in dioxane at 110 °C in the presence of 0.5 mol% Pd_2dba_3 and 1 mol% ligand. We found that the transformation took place smoothly in case of our ligands. Only the 2-pyridyl based adamantylphosphine ligand (**L8**) proved to be ineffective in the coupling reaction. In all other cases the desired diarylalkene product was isolated typically in high yield (> 90%). For comparison we repeated the reaction with some commercially available ligands with similar structure. DalPhos ligands proved to be ineffective, however the *tert*-butyl substituted AtaPhos gave similarly good results.



Scheme 4. The coupling method of tosylhydrazones with aryl bromides.

For the exploration of the substrate scope we coupled ortho substituted aryl bromides with structurally different tosylhydrazone derivatives. The aryl group of the reactants were decorated with electron withdrawing and electron donating groups in different positions. The coupling reactions were performed under the optimized reaction conditions with the utilization of *N*,*N*-dimethylaminophenyl-diadamantylphosphine ligand (**L1**). We tested the reactivity of 2 bromotoluene (**8a**-**b**, **d**-**k**), 2-bromoanisole (**8c**, **q**-**r**), 2-bromobenzonitrile (**8p**), 2- and 4-fluorobromobenzene (**8l**-**o**) with aromatic and heteroaromatic (thiophene) tosylhydrazones. After the workup of the reaction mixtures the desired products were obtained in high yields (66-97%). Additionally, starting from the more hindered bromomesitylene, we observed difficulties presumably due to the steric hindrance of the neighboring methyl groups on the aromatic ring, and the coupled products **8s** and **8u** were obtained only in moderate 26% and 41% yields respectively.

Conclusion

A new phosphine ligand kit was developed, which could be efficiently used in cross-coupling reactions. The advantage of the new ligands is the easy synthetic accessibility from cheap reagents on multigram scale. To exploit this beneficial feature, we efficiently synthesized a collection of aryl-diadamantyl phosphine ligands containing different aryl, heteroaryl, and adamantyl motifs. Detailed spectroscopic analysis was performed to describe the structure of the new ligands, and explain their spectral characteristics. The catalytic applicability of the new ligand class was examined in Buchwald-Hartwig and tosylhydrazone couplings of ortho substituted aryl halides. In our synthetic studies we found that the new aryl-diadamantyl phosphines served as efficient ligands for the selected palladium catalyzed cross-coupling reactions, and versatile sterically congested molecular structures could be obtained through their utilization. The designed ligand class could provide good alternative to the existing ligands and offer new and efficient catalytic system for frequently performed organic transformations in diverse fields.

Experimental Section

^{1}H (500.13 MHz), ^{13}C (125.6 MHz) and ^{31}P NMR (161.99 MHz) spectra were recorded at 300 & 350 K on Bruker 500 & 400 Avance III spectrometers equipped with cryo NMR probehead & Prodigy probehead and processed using Topspin 3.2 software. Chemical shifts are given on the δ-scale and are referenced to the solvent (CD_3CN: δ_C = 1.4 and δ_H = 1.94 ppm; THF-d_8: δ_C = 67.6 and δ_H = 3.58 ppm). Pulse programs of all experiments (^{1}H, ^{13}C, ^{31}P, gs-HSQC, gs-HMBC (optimized for 10 Hz), were taken from the Bruker software library. For 1D measurements, 64K data points were used to yield the FID. For 2D measurements, sweep width in F_2 was 4000 Hz; all data points (t_2 x t_1) were acquired with 2 K x 128. For F_1, linear prediction was applied to enhance the resolution.

General procedure for the preparation of the phosphine ligands: Phosphine compound (1.0 equiv.) and aryl bromide (1.0 – 1.1 equiv.) were measured in a flame dried round bottom flask. $Pd_2(dba)_3$ (0.025 equiv.) and NaO^tBu (1.5 equiv.) were added in. The flask was charged with argon. Anhydrous toluene (3.25 mL/ 1 mmol phosphine) was added. The reaction mixture was stirred at 100°C overnight. Aryl bromides in liquid state was added after the addition of toluene. The reaction was followed by GC-MS. After completion, the reaction mixture was concentrated under reduced pressure. Unless otherwise indicated, the residue was suspended in deoxygenated ethanol in ultrasonic bath. The precipitate was filtered and washed with ethanol. Argon atmosphere was used. The product was dried in vacuum. Stored under argon.

General procedure for the substrate scope of Buchwald-Hartwig reactions: A 4 mL screw-capped vial was charged with 9.2 mg (0.01 mmol, 0.01 equiv.) $Pd_2(dba)_3$, 192.2 mg (2.0 mmol, 2.0 equiv.) NaO^tBu and 8.4 mg (0.02 mmol, 0.02 equiv.) Ligand (L1). The vial was purged with argon, and 2 mL toluene, 1.0 mmol (1.0 equiv.) halogenated compound and 1.25 mmol (1.25 equiv.) amine was added via septa. The reaction mixture was stirred at 80 °C under argon atmosphere. After completion, the reaction mixture was poured into 40 mL H_2O and was extracted with 3×15 mL CH_2Cl_2. The combined organic phases were washed with 2×10 mL 5 w/w% $NaHCO_3$ solution and 15 mL H_2O, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel with hexane / ethyl acetate.

General procedure for the coupling with tosylhydrazones: A 7ml screw-capped vial was charged with 0.55 mmol (1.1 equiv.) tosylhydrazone, 2.3 mg (0.0025 mmol, 0.5 mol%) $Pd_2(dba)_3$, 0.005 mmol (1 mol%) ligand and 112 mg (1.4 mmol, 2.8 equiv.) LiO^tBu, then purged with argon. 1.5 mL 1,4-dioxane and 45 µL (2.5 mmol) water was added, followed by 0.5 mmol (1 equiv.) aryl halide and the vial was purged once again with argon. The reaction mixture was placed into oil bath and stirred at 110°C, overnight. After reaching full conversion the reaction mixture was diluted with 10 mL DCM, the mixture was concentrated to celite and the product was isolated with column chromatography (silica gel, eluent: hexane / ethyl acetate).

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Keywords: Palladium; Phosphine; Cross-coupling; Amination; Tosylhydrazone.

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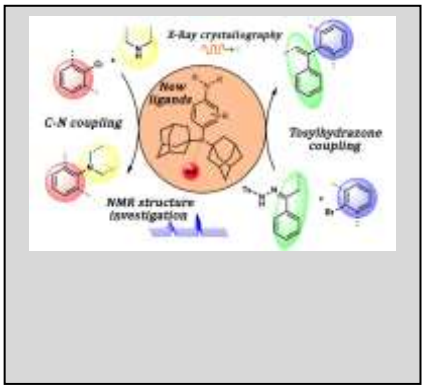

Bulky diadamantyl aryl phoshine ligands were synthesized and utilized in Buchwald-Hartwig coupling of sterically demanding ortho substituted aryl chlorides. Additionally, the ligands showed enhanced catalytic activity in the coupling of tosyl hydrazones and aryl halides.