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View Article Online
DOI: 10.1039/C9DT00159J

Dalton Transactions

ARTICLE

Facile Buchwald-Hartwig coupling of sterically encumbered substrates effected by diphosphinoamine as ligands

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

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The diphosphinoamine ligands [$(Ph_2P)_2N(Ar)$; **1** (Ar = C_6H_5), **2** (Ar = 2,6-$iPr_2C_6H_3$)] were effectively utilized in Buchwald-Hartwig coupling of a range of sterically demanding substrates. The reaction was carried out using conventional as well as microwave route while the later reduces the reaction time from 3d to 15-30 min. A broad substarte scope was achieved in this protocol and most of the coupling products are isolated in mutligram scale. DFT calculations were carried out to elucidate the reaction mechanism.

Introduction

The discovery of palladium catalyzed C-N cross coupling, namely Buchwald-Hartwig coupling, is a significant breakthrough in organic chemistry due to its importance in the synthesis of pharmaceutical drugs, dyes, polymers and natural products etc.[1-6] While the Migita and coworkers commenced the Pd catalyzed cross coupling reactions,[7] the more accessible routes were established by the groups of Buchwald and Hartwig.[8] The most common ligands for the C-N coupling reactions are BINAP,[9] dppf,[10] Xantphos,[11] Josiphos,[12] Xphos,[13] N-heterocyclic carbenes[14] and several phosphines.[15-26] Nevertheless, there are very few ligands available for the coupling of bulky substrates but their substrate scope is very limited and sometimes the yield of the reactions are also not very high (vide infra).[17,23,26] Moreover, the synthesis of ligand itself is challenging in many cases.[23,26] A further encouragement comes from the recent works by Buchwald and coworkers stating the importance of developing new ligands which can provide a broad substrate scope especially for sterically demanding groups.[8e] Hence, it is deemed desirable to have easily accessible ligands in C-N coupling reactions which can be used for a broad substrate scope for bulky substituents along with high isolated yields of the coupling products.

Recently, we have reported diphosphinoamine [$(Ph_2P)_2N(Ar)$] based ligands to make luminescent Au(I) and Cu(I) complexes.[27-28] Since bidentate phosphine ligands have already shown their potentials in the C-N coupling reactions, we also got motivated to explore our bidentate PNP ligands [$(Ph_2P)_2N(Ar)$] in such catalytic system. These PNP-ligands [$(Ph_2P)_2N(Ar)$; **1** (Ar = C_6H_5), **2** (Ar = 2,6-$iPr_2C_6H_3$)] (Chart 1) are very easy to prepare in bulk scale (90-93% yields). Herein Herein, we report C-N coupling of sterically demanding substrates by using ligands **1** and **2** in combination with a palladium source by conventional method as well as under microwave assistance (15-30 min). Our ligands **1** and **2** were found very efficient even in the coupling of very bulky amine Ar*NH_2 [Ar*= 2,6-{$C(H)Ph_2$}$_2$-4-MeC_6H_2][29a] with various bromo substrates (79-98% yields), which were obtained in very low yields (~30-65%) with the previously reported ligands (vide infra).[29b] Moreover, -CF_3 substituted bromo derivatives also afforded ~85-97% yields of coupled products, which were otherwise obtained in ~28-58% yields respectively.[30]

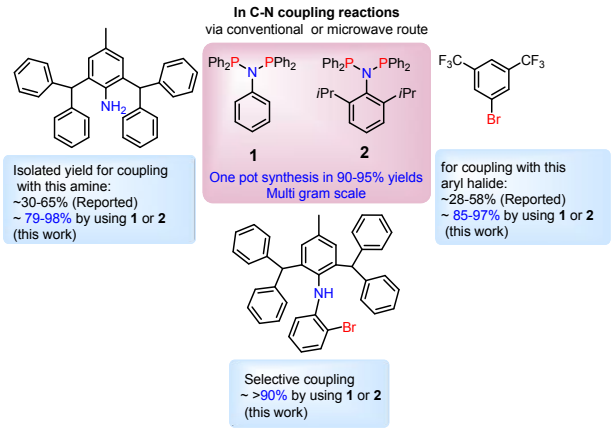

Chart 1. Ligands (**1** and **2**) used for coupling reactions and selected examples of this work.

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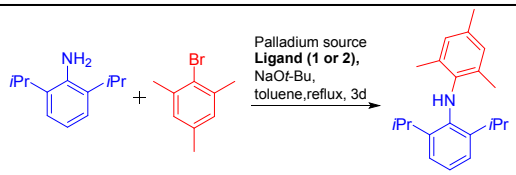
Electronic Supplementary Information (ESI) available: Experimental details, NMR data and computational details. CCDC no. for **3d**, **3h** and **3i**: 1872189-1872191. See DOI: 10.1039/x0xx00000x.

To evaluate the performance of **1** and **2,** a model coupling reaction of bulky 1-bromo 2,4,6-triisopropyl benzene with 2,6-diisopropyl aniline (Scheme 1) under optimized conditions (Table 1) was carried out and compared with the reported examples.[17,23,26] A range of phosphine ligands (Chart 2) were used in the coupling of 1-bromo-2,4,6-triisopropylbenzene with 2,6-diisopropylaniline (Scheme 1) and few of them found to be efficient (Table 2).

Gratifyingly, our ligands were found to be very efficient and gave excellent isolated yields for such sterically hindered substrates (Entry 21 and 22). Other than **1** and **2**, ligands **A**[17] and **C**[17] (Table 2, Entry 1 and 2) were also reported to give excellent isolated yields for **3j**. However, the synthetic access to our ligand is much simpler than **A** and **C**. Although the conversion yield is found to be quantitative for entry 11 and 16, their isolated yields have not been reported. Moreover, in all above mentioned cases, the substrate scope is very limited. We also performed microwave assisted synthetic route keeping the reaction conditions same, and the reaction completion time gets reduced drastically to 15-30 min. Subsequently, we accessed the substrate scope for a broad variety of sterically demanding aryl halides and amines including the bulkier amine Ar*NH_2 using both conventional and microwave techniques and their isolated yields are given in Table 3.

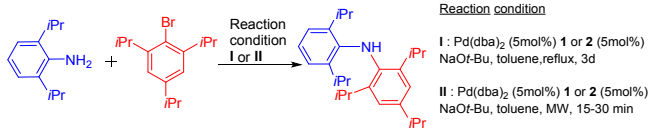
Table 1. Optimization of Palladium source and mol %.**



Entry	Palladium source*	Ligand	Mol %	Yield[a] (%)
1	$Pd(dba)_2$	**1**	5	88
2	$Pd(dba)_2$	**2**	5	90

Reaction conditions: Aryl amine = 2,6-diisopropyl aniline, (1 mmol), Aryl bromide = Mesityl bromide (1 mmol) sodium tert-butoxide (2.8 mmol). [a]Isolated yields (average of two runs) dba = dibenzylideneacetone.*Blank reaction with only Pd source afforded <10% yield.**see SI for details.

We investigated variation of aryl bromides with electron withdrawing groups like, fluoride and CF_3, to check the potential of the catalyst (Table 3). It was observed that, aryl bromides with alkyl substituents lead to very good isolated yields of coupling products **3a-3j** (83-98%). However, fluoride substituted aryl bromides give moderate to high yield of the coupling products (65-80%). It is noteworthy to mention that CF_3 substituted aryl bromides (**3p-3r**) were found to give very good isolated yields (~85-97%) compared to the previously known catalytic systems (~30-60%).28b,30 When 1,2-di-bromobenzene is used, it gives selectively mono-substituted coupling product, **3n** in >90% yields. The coupling of this very bulky amine Ar*NH2 with other halides was also found very effective (**3k**, **3i**, **3n-p**; ~79-98% isolated yields). The crystal structures of some of the coupling products are given in Table 3. Higher yields were observed in case of ligand **2**, compared to that of ligand **1** for cross-coupling products and the reason behind such behavior might be the steric bulk on the backbone of ligand 2.[9a,22,23]



Scheme 1. Coupling of 1-bromo-2,4,6-triisopropylbenzene with 2,6-diisopropyl aniline.

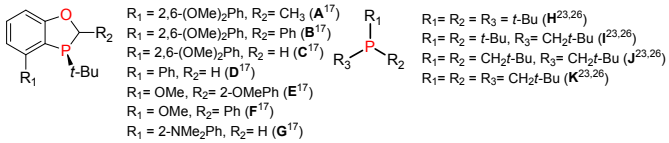


Chart 2. Some P-based ligands used for the cross coupling of 1-bromo-2,4,6-triisopropylbenzene with 2,6-diisopropyl aniline.

Table 2. Screening of various ligands for the coupling of 1-bromo-2,4,6-triisopropylbenzene and 2,6-diisopropylaniline

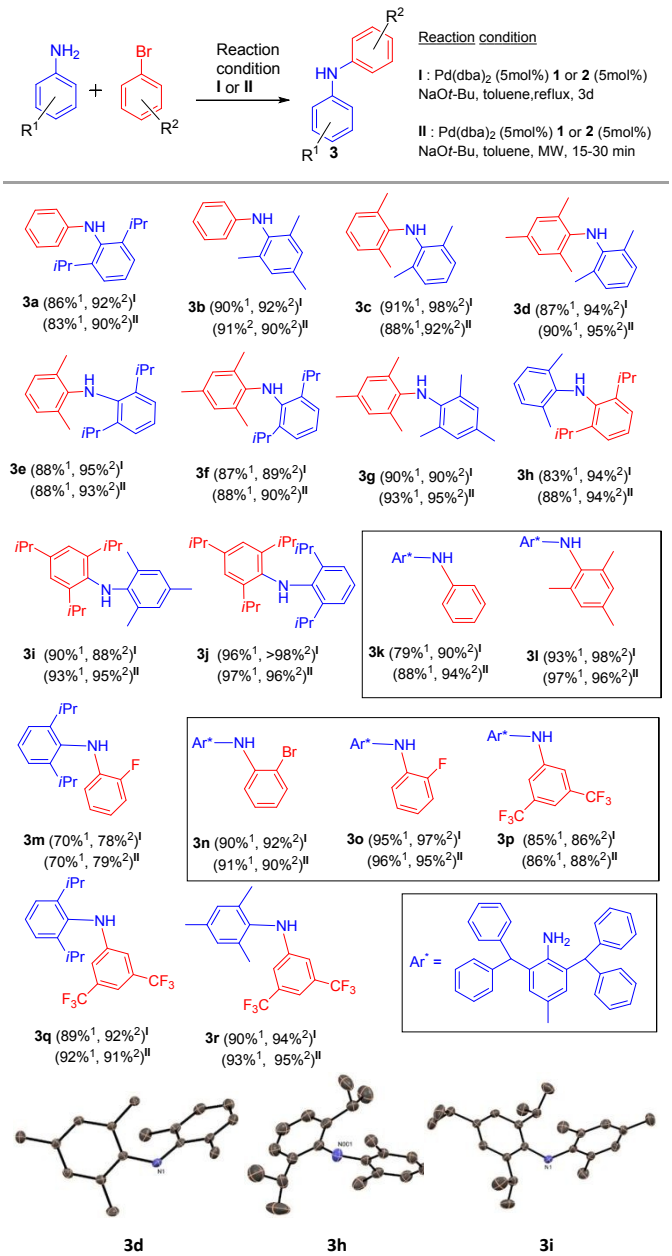
Entry	Ligand	Conversion Yield (%)[a]	Entry	Ligand	Conversion Yield (%)[a]
1	A[b,17]	100 (96)[e]	12	*t*-Bu_2PMe[c,26]	83
2	B[b,17]	24	13	P (*o*-tol)$_3$[c,26]	29
3	C[b,17]	100 (98)[e]	14	BINAP[c,17]	0
4	D[b,17]	72	15	Xanthphos[c,17]	46
5	E[b,17]	61	16	PCy_3[c,26]	100
6	F[b,17]	24	17	Johnphos[c,17]	0
7	G[b,17]	70	18	SPhos[c,17]	18
8	H[c,26]	36	19	XPhos[c,17]	5
9	I[c,26]	0	20	I.HBF_4[d,23]	(75)
10	J[c,26]	4	21	**1**	100 (96[I]/97[II])[e]
11	K[c,26]	100	22	**2**	100 (>98[I]/96[II])[e]

[a]Determined by GC and HPLC analysis, [b]Conditions: aryl bromide (1.0 equiv.), amine (1.2 equiv.), $Pd_2(dba)_3$ (0.05 mol%)/Ligand (0.3 mol%) 1:3, NaO-*t*-Bu (1.5 equiv.), toluene, 110°C, 20 h. [c]Reaction conditions: 1-bromo-2,4,6-triisopropylbenzene (1.0 mmol), 2,6-diisopropylaniline (1.2 mmol), $Pd_2(dba)_3$ (0.5 mol %), Ligand (1.0 mol %), NaO*t*-Bu (1.5 mmol), toluene (2 mL), 80 °C, 1 h. [d]Aryl bromide (0.8 mmol), aniline (1.0 mmol), NaO-*t*-Bu (0.85 mmol), Pd (2 mol %), DTBNpP.HBF_4 (2 mol %), toluene (2 mL), 50°C, 3-4 hrs. I, II: Reaction condition I (Conventional heating), II (Microwave heating); [e]Isolated yield is given in bracket.

We have carried out density functional calculations at the M06/def2-TZVPP//BP86/def2-SVP level of theory[31] to explore the possible mechanism for palladium catalyzed Buchwald-Hartwig coupling reaction of p-bromo toluene with p-toluidine. The variation of reaction energetics in presence of solvent as compared to that in gaseous phase (Scheme S4) is minimal. The overall reaction of p-bromo toluene with p-toluidine in presence of sodium tert-butoxide (in presence of the solvent) is exothermic by 40.3 kcal/mol and exergonic by 37.4 kcal/mol (Scheme S1). The first step of the reaction can be considered

as the formation of tri-coordinated planar complex **Int1** by coordinating the lone pair on bromine atom of aryl bromide with the catalyst **Pd2** (Scheme S3). This step of reaction is thermodynamically favourable (ΔE = -16.7 kcal/mol and ΔG = -5.5 kcal/mol).

Table 3. Pd(dba)2/1 or 2-Catalyzed coupling of aryl Bromides with aryl amines and substrate scope.



Isolated yields using [1]: Ligand **1** and [2]: Ligand **2** (average of two runs), Reaction conditions: Aryl bromide (1 mmol), Aryl amine (1 mmol), sodium tert-butoxide (2.8 mmol) dba = dibenzylideneacetone, Palladium source (5 mol%), ligand (5 mol%), Reaction condition **I** : Conventional heating, Reaction condition **II** : Microwave heating.

The formation of **Int2** type of intermediate was further supported by NMR and mass data of the reaction of mesityl bromide, $[(Ph_2P)_2N(p\text{-}FC_6H_4)]$ ligand and $Pd(dba)_2$ (see SI for details). A peak at m/z = 784 $[M+H]^+$ was observed in the mass spectrum of the reaction mixture which could be assigned for the corresponding intermediate of **Int2** type. The reaction energy for this step is highly favourable (ΔE = -25.8 kcal/mol and ΔG = -24.3 kcal/mol) and the corresponding energy barrier is also very low ($\Delta E^{\ddagger}$= 2.2 kcal/mol and $\Delta G^{\ddagger}$ = 3.1 kcal/mol). The hydrogen bonded N-H bond length (1.07 Å) in **Int3** is elongated as compared to the non-hydrogen bonded N-H bond length (1.02 Å). This step is slightly endothermic (ΔE = 1.9 kcal/mol) and endergonic (ΔG = 15.9 kcal/mol) and involves a low activation energy barrier ($\Delta E^{\ddagger}$= 7.6 kcal/mol and $\Delta G^{\ddagger}$ = 21.9 kcal/mol). The hydrogen bonded acidic proton can be easily removed by the base NaO*t*Bu resulting Pd(II) complex **Int4**, *t*-BuOH and NaBr, which is thermodynamically favorable. Earlier studies by Norrby *et al.* predicted very low energy barrier/barrier less process for similar deprotonation step (Scheme S3).[32] The next step is the coupling between the N-atom of $NH\text{-}C_6H_4\text{-}CH_3$ group with phenylic carbon atom of $C_6H_4\text{-}CH_3$ group resulting tri-coordinated planar Pd(0) complex **Int5**. This step is thermodynamically (ΔE = -9.6 kcal/mol and ΔG = -10.5 kcal/mol) as well as kinetically favorable ($\Delta E^{\ddagger}$= 18.4 kcal/mol and $\Delta G^{\ddagger}$ = 19.1 kcal/mol) at the reaction conditions.

In summary, we have demonstrated the easily accessible, cost effective diphosphinoamine ligands, **1** and **2** in the C-N cross coupling of sterically demanding aryl bromides and aryl amines, by conventional as well as microwave-assisted organic synthesis (MAOS) technique. All the coupling products are obtained in multigram scale with good to excellent yields. This catalytic system was found very efficient for a variety of bulky substrates. In fact, this is a rare catalytic system which exploited the one of the bulkiest amine Ar^*NH_2 to show the C-N coupling of sterically demanding substrates in excellent isolated yields.

S.K. thanks BRNS and SERB (India) for financial support and also acknowledges Dr. Srinivas Hotha and G. Walke for their valuable support. N.K. thanks UGC, India for providing fellowship. P.P. thanks SERB, India for financial support. S.P. thanks NIT Calicut for providing fellowship.

Experimental Section

All manipulations were performed under a dry and oxygen-free atmosphere (N_2) using standard Schlenk techniques and a glove box. All solvents were dried over activated molecular sieves after distillation. ^1H, ^{13}C, ^{31}P, and ^{19}F solution NMR spectra were recorded on Jeol and Bruker 400 MHz instrument. Fourier-transform infrared (FT-IR) spectra were taken on a PerkinElmer spectrophotometer. Synthesis of ligand **1** and **2** is done as per the reported procedure.[27]

Typical procedure for coupling reactions:

NaO^{t}Bu (0.24 gm, 1 mmol), Pd $(dba)_2$ (29 mg, 5 mol%), PNP ligand **1** (24 mg, 5 mol%) and **2** (28 mg, 5 mol%) was taken in 100 mL schlenk flask inside the glove box. To that flask 5 mL of

toluene, aromatic amine (1 mmol) and aromatic bromide (1 mmol) was added and the reaction mixture was subjected for conventional heating (110°C for 5 d) as well as microwave heating (184°C for 15-30 min). Reaction completion monitored by TLC and NMR, and the compound was extracted in diethyl ether and organic layer was washed with distilled water. Further isolation and purification was done by using column chromatography in *n*-Hexane (100%).

Microwave method: Required amount of NaOtBu (7 eq), 5 mol% of Pd $(dba)_2$ and 5 mol% PNP ligand (**1** or **2)** was taken in microwave tube inside the glove box. 4 mL of toluene added to that tube and required amount of aromatic amine and aromatic bromide was added and subjected to microwave heating (184°C for 15-30 min) reaction. Reaction completion monitored by TLC and NMR and some of the compounds purified using column chromatography using ethyl acetate and *n*-Hexane mixture (2% EA + 98% *n*-Hexane).

Crystallographic details

Crystallography Reflections were collected on a Bruker Smart Apex Duo diffractometer at 100 K using Mo Kα radiation (λ = 0.710 73 Å) for **3d**, **3h**, and **3i**. The structures were solved by direct methods and refined by full-matrix least-squares methods against F^2 (SHELXL-2014/6). Crystallographic data (including structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre with no. 1872189-1872191. The copies of the data can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. (fax, (internat.) +44(1223)336-033; e-mail, deposit@ccdc.cam.ac.uk).

Conflicts of interest

There are no conflicts to declare.

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