Tetrahedron Letters 50 (2009) 6004–6007

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

An inexpensive cyclodiphosphazane as an efficient ligand for the palladium-catalyzed amination of aryl bromides and chlorides

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ARTICLE INFO

Article history:
Received 21 July 2009
Revised 7 August 2009
Accepted 12 August 2009
Available online 15 August 2009

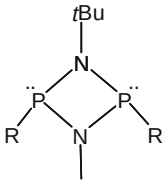
Keywords:
Aryl chlorides
C–N coupling
Amination
Palladium catalysis

ABSTRACT

An economic and novel ligand, cyclodiphosphazane $[ClPN(t\text{-}Bu)]_2$ (**1**), was introduced in the palladium-catalyzed amination of unactivated aryl halides. The catalyst allows for the amination of aryl chlorides and bromides with secondary cyclic amines and anilines in good yields.

C–N Bond formation by palladium-catalyzed cross-coupling reaction is one of the powerful techniques in synthetic organic chemistry. This method has been widely used in biological, pharmaceutical, and material sciences for various applications.[1–3] A conventional route for N-arylation of nitrogen nucleophiles with aryl halides is the Ullmann-type coupling at high temperature.[4] Activated aryl bromides and iodides can be successfully transformed to the corresponding aryl amines by employing simple copper[5] or (recently) iron salts[6] with various ligands as catalysts and also under ligand-free conditions. However, application of a similar method using unreactive aryl chlorides, especially possessing deactivated substituents on benzene ring, requires special attention because of their easy availability and cost efficiency that necessitate an exclusive catalyst design for thriving coupling reaction.[7] To achieve this goal, a number of ligands including electron-rich alkyl-substituted *tertiary* phosphines, phosphines having aryl groups at suitable positions, and various N-heterocyclic carbenes have been recently examined for palladium catalysis.[8,9] To the best of our knowledge, only two reports have appeared describing the utility of chloro (amino)phosphines as ligands in this type of coupling chemistry.[10] In this context, we felt that cyclodiphosphazane derivatives of type **1** bearing a bulky *t*-butylamino substituent that have been utilized as ligands should be quite useful.[11]

Previously, we have employed these for probing organic transformations including the Mitsunobu reaction.[12] In this Letter, we report the results of our preliminary investigations on C–N bond formation by use of the inexpensive ligand, cyclodiphosphazane **1** [R = Cl; (δ(P) 207.7], which can be readily synthesized by reacting very inexpensive reactants, PCl_3 and *t*-butylamine, in toluene.[16]



1

Our initial experiments were focused on coupling of chlorobenzene with morpholine (Table 1). In the absence of ligand **1** (R = Cl), the reaction did not proceed (entry 1). However, in the presence of ligand (12 mol %) and Pd_2dba_3 (3 mol %) at 80 °C it produced the coupled product *N*-phenyl morpholine in 25% yield. No significant improvement in the yield was observed by changing the Pd catalyst or by increasing the temperature (Table 1, entries 3–6). Interestingly, decreasing the loading of Pd_2dba_3 catalyst, cyclophosphazane ligand concentration and increasing the temperature to 120 °C resulted in 71% of the coupled product (Table 1, entry 7). As expected, decreasing the temperature to 90 °C drastically decreased the yield (Table 1, entry 8). Finally the reaction conditions were optimized by keeping the temperature constant at 120 °C and increasing the concentration of catalyst and ligand to produce the coupled product up to 94% isolated yield (Table 1, entry 10).

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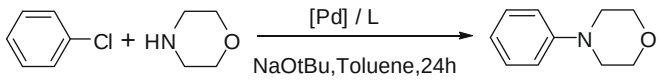
doi:10.1016/j.tetlet.2009.08.020

Table 1
Optimization of reaction conditions for the amination of chlorobenzene with morpholine[a]

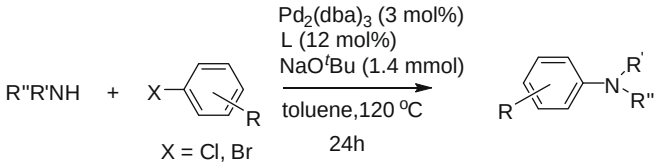


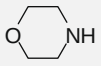
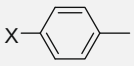
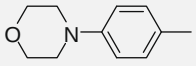
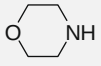
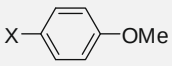
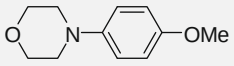
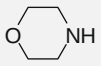
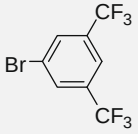
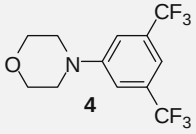
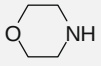
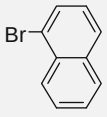
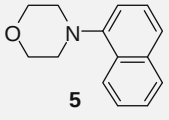
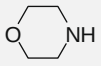
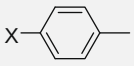
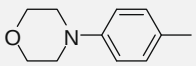
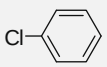
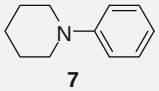
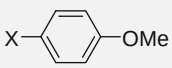
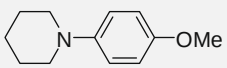
Entry	Pd source (mol %)	Ligand (L) (mol %)	T (°C)	Yield[b] (%)
1	Pd_2dba_3 (3)	—	120	nr
2	Pd_2dba_3 (3)	12	80	25
3	$Pd(dba)_2$ (5)	10	110	38
4	$Pd(dba)_2$ (6)	12	110	43[c]
5	$Pd(OAc)_2$ (6)	12	110	31
6	$[Pd(allyl)Cl]_2$ (3)	12	110	28
7	Pd_2dba_3 (2)	8	120	71
8	Pd_2dba_3 (2.5)	10	90	27
9	Pd_2dba_3 (2.5)	10	120	80
10	Pd_2dba_3 (3)	12	120	94[c]

[a] Reaction conditions: chlorobenzene (1.0 mmol), morpholine (1.2 mmol), NaO^tBu (1.4 mmol), and toluene (3 mL), 24 h (reaction times not optimized).
[b] Yields established by GC–MS with hexadecane as an internal standard.
[c] Isolated yield.

On the basis of the above optimized reaction conditions, the coupling reactions between a variety of aryl chlorides/bromides and amines were investigated. As shown in Table 2, morpholine was coupled with several deactivated aryl chlorides and bromides to produce the *N*-aryl morpholine derivatives in good yields (entries 1–5). [17] It is worth mentioning that 3,5-trifluoromethyl phenyl bromide upon coupling with morpholine under our optimized reaction conditions gave the coupled product (**4**) in 68% yield (entry 3; see Fig. 1 for X-ray structure).[13] We were able to couple the bulkier bromide (bromonaphthalene) with morpholine using our new ligand system (entry 4). Piperidine was also coupled with electron-rich chlorides and bromides to give the desired aryl amines in good yields (entries 6 and 7). Reaction of *N*-methyl aniline with aryl chlorides and bromides afforded the desired products in moderate to good yields (entries 8 and 9). *p*-anisyl chloride gave lower yields [40–50%; not given in the table] as has been observed by others.[14] Self- coupling[15] also occurs when the amine component is cyclohexylamine, as revealed by GC–MS. These are the limitations. However, substituted anilines couple with chlorobenzene and 4-chlorotoluene to give the desired prod-

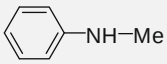
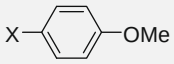
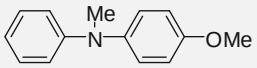
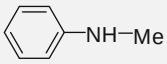
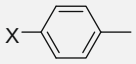
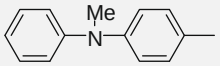
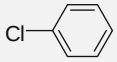
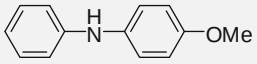
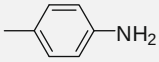
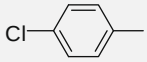
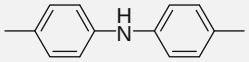
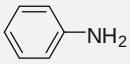
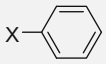
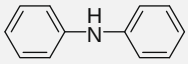
Table 2
N-Aryl-amination of aryl bromides and chlorides[a]



Entry	Amine	Ar-X	Product	Yield[b] (%)
1		 X = Cl, Br	 **2**	75 (X = Cl) 80 (X = Br)
2		 X = Cl, Br	 **3**	73 (X = Cl) 75 (X = Br)
3			 **4**	68
4			 **5**	56
5		 X = Cl, Br	 **6**	75 (X = Cl) 80 (X = Br)
6			 **7**	73[c]
7		 X = Cl, Br	 **8**	63[c] (X = Cl) 66 (X = Br)

(*continued on next page*)

Table 2 (*continued*)

Entry	Amine	Ar-X	Product	Yield[b] (%)
8		 X = Cl, Br	 **9**	55 (X = Cl) 61 (X = Br)
9		 X = Cl, Br	 **10**	62 (X = Cl) 68 (X = Br)
10			 **11**	60
11			 **12**	56
12		 X = Cl, Br	 **13**	54[d] (X = Br) 51[d] (X = Cl)

[a] Reaction conditions: aryl halide (1.0 mmol), amine (1.2 mmol), NaO^{t}Bu (1.4 mmol), Pd_2dba_3 (3.0 mol %), ligand (12 mol %), and toluene (3 mL) were heated to 120 °C with continuous stirring for 24 h under nitrogen atmosphere.
[b] Isolated yields.
[c] Reaction scaled up to 5 mmol in 8 mL toluene.
[d] GC–MS yields.

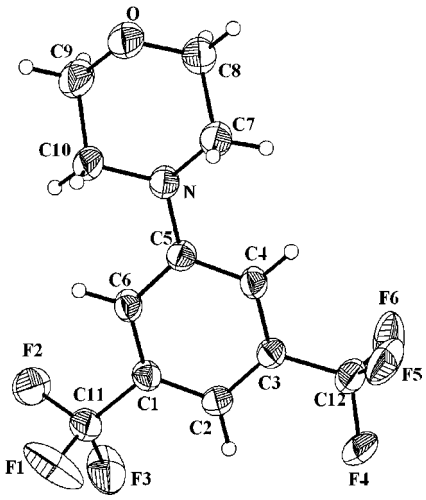


Figure 1. ORTEP diagram of the product **4** (Table 2, entry 5). The CF_3 groups show some disorder.

ucts in moderate to good yields. These results are also summarized in Table 2 (entries 10–12).

The ^{31}P NMR spectrum of the mixture of **1** (R = Cl) and Pd_2dba_3 showed a peak at δ(P) 318.9 (along with many other peaks), consistent with the formation of a Pd–cyclophosphazane complex. However, we have not succeeded in isolating this species because of the presence of other products.

In summary, we have demonstrated the use of a very inexpensive cyclodiphosphazane as a ligand in the palladium-catalyzed N-arylation of various amines with aryl halides (X = Cl, Br). The yields vary, but are in the range 51–94%. Further work in order to make the system more efficient and to broaden the scope of this catalytic system is in progress.

Acknowledgments

We thank DST (New Delhi) for financial support and for the single crystal X-ray Diffractometer facility at the University of Hyderabad, and UGC (New Delhi) for equipment under UPE and CAS programs. R.S. thanks CSIR for a fellowship.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.08.020.

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13. X-ray data were collected on a Bruker AXS SMART diffractometer using Mo Kα (λ = 0.71073 Å) radiation. The structures were solved and refined by standard methods. *Crystal data for* **4**: $C_{12}H_{11}NF_6O$, M = 299.22, monoclinic, space group $P2(1)/n$, a = 9.338, b = 7.752, c = 17.542 Å, β = 98.38°, V = 1256.3(4) Å^3, Z = 4, μ = 0.161 mm^{-1}, data/restraints/parameters: 2212/0/235, R indices ($I > 2\sigma(I)$): R_1 = 0.0843, wR_2 (all data) = 0.2530. The trifluoromethyl groups showed some disorder, but the molecule as such refined well. CCDC no. 739921.
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17. *General procedure for the amination of aryl chlorides and bromides*: All the compounds reported here are well-known. In an oven-dried Schlenk tube, 1 mL of Ligand **1** (R = Cl) (33 mg, 0.12 mmol, 12 mol %) of 0.120 M solution in toluene, Pd_2dba_3 (28 mg, 0.03 mmol, 3 mol %), and 2 mL of toluene were taken under nitrogen atmosphere and were stirred at room temperature for 30 min. To this solution, NaO^{t}Bu (135 mg, 1.4 mmol) and aryl halide (1.0 mmol) were added successively. After 15 min, amine (1.2 mmol) was added and the tube was sealed. The reaction mixture was stirred at 120 °C (oil bath) for 24 h. Subsequently, the reaction mixture was allowed to cool to room temperature and EtOAc (4 mL) was added. It was then filtered through a plug of Celite and was analyzed by GC–MS by using hexadecane as an internal standard. Further purification of the product was achieved by silica gel column chromatography [eluent: hexane/EtOAc (95:5)].