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1,3-Phenylene-bis-(1*H*)-tetrazole Pincer Ligand for Palladium-Catalyzed Suzuki Cross-Coupling Reactions of Arylhalides with Arylboronic Acids

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Abstract: 1,3-Phenylene-bis-(1H)-tetrazole pincer ligand was synthesized by the reaction of 1, 3-phenylenediamine, sodium azide and triethyl orthoformate in acetic acid and successfully used in Suzuki cross coupling reactions of aryl halides with aryl boronic acids.

Key words: 1,3-phenylene-bis-(1*H*)-tetrazole pincer ligand, Suzuki cross-coupling reactions, aryl halides

The tetrazole functionality plays an important role in medicinal chemistry as a pharmacophore due to its ability to serve as a bioequivalent (bioisostere) of the carboxylic group, as well as in synthetic organic chemistry as a synthon.¹ There are few examples in which tetrazoles were used as ligands with Ni or Ru.² To our knowledge, however, reports on usage of tetrazole in palladium- or platinum-catalyzed reactions are scarce.3 Transition metal pincer complexes using phosphorus as the donor atom (PCP pincer complex) were reported in the early 1970's.⁴ Since then, many research groups have developed a variety of pincer ligands; they offer a unique and highly protective environment for the resident metal. Opportunities to fine-tune the metal properties have spawned extensive research into the use of these complexes as catalysts. These complexes are used in a variety of reactions, including the Heck reaction.⁵ Recently, new types of non-phosphine ligands, such as heterocyclic carbenes, imines, imidazoles, and 1,2,4-triazoles, have emerged as alternatives for the carbon-carbon bond forming reactions.⁶ There is a continuing need for simple and versatile synthetic ligands and catalysts for this type of reaction. In continuation of our research interest in the development of new and novel synthetic methodologies,^{7,8} here we wish to report a new and novel ligand, 1,3-phenylene-bis-(1H)tetrazole (2), which worked efficiently in Suzuki reaction. Ligand 2 was readily prepared in one step from 1,3-phenylene-diamine (1), sodium azide and triethyl orthoformate in acetic acid (Equation 1).⁹

We believe that this tetrazole ligand **2** can have ability to coordinate with palladium either through nitrogen as in the case of 1,2,3-triazole pincer ligand (NCN),¹⁰ or by C-H activation as in the case of imidazolyl pincer ligand (NHC).¹¹ Although we have not yet fully characterized





the tetrazole pincer complexes, the ligand, in combination with palladium acetate, has been shown to catalyze the coupling reactions of aryl halides with arylboronic acids efficiently. A characteristic feature of our palladacycle is the thermal stability, which makes it possible to perform the reactions even at a temperature above 100 °C, which is necessary for less reactive substrates such as aryl chlorides and aryl bromides.

A preliminary screening of this ligand **2** for Suzuki coupling of a chemically inert, cheap and readily accessible 4chlorotoluene (**3a**) with 4-methoxyphenylboronic acid (**4c**) revealed that the coupling proceeds smoothly in DMF solvent in the presence of Pd(OAc)₂ metal catalyst, *t*-BuOK as a base and tetrabutylammonium bromide (TBAB) as an additive (Equation 2).¹² In order to compare the reactivity of the ligand and to optimize the reaction conditions, we have screened various solvents (THF, toluene, etc.), bases (Cs₂CO₃, K₂CO₃, etc.), and different catalysts (PdCl₂, PtCl₂, etc.). The results are summarized in Table 1, Table 2, and Table 3, respectively.





Table 1Reaction of 4-Chlorotoluene 3a with 4-Methoxy Phenylboronicacid 4c in Various Solvents

Entry	Solvent	Temp (°C), time (h)	Yield (%, conversion)
1	THF	60, 24	Trace
2	Toluene	115, 12	18 (40)
3	CHCl ₃	60, 24	Trace
4	DMF	100, 12	88 (100)

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Table 1 Reaction of 4-Chlorotoluene 3a with 4-Methoxy Phenylboronicacid 4c in Various Solvents

Entry	Solvent	Temp (°C), time (h)	Yield (%, conversion)
5	1,4-Dioxane	100, 24	34 (56)

 Table 2
 Reaction of 4-Chlorotoluene 3a with 4-Methoxy Phenyl boronic Acid 4c with Different Bases

Entry	Base	Temp (°C), Time (h)	Yield (%, conversion)
1	Cs ₂ CO ₃	100, 12	Trace
2	K ₂ CO ₃	100, 12	9 (21)
3	K ₂ CO ₃ , TBAB	100, 12	22 (65)
4	t-BuOK	100, 12	56 (60)
5	t-BuOK, TBAB	100, 12	88 (100)
6	Sodium methoxide	100, 12	20 (53)
7	KF·2H ₂ O	100, 12	18 (40)

 Table 3
 Reaction of 4-Chlorotoluene 3a with 4-Methoxy Phenyl boronic Acid 4c with Different Catalysts

Entry	Catalyst	Temp (°C), time (h)	Yield (%, conversion)
1	Pd(OAc) ₂	100,12	88 (100)
2	PdCl ₂	100, 12	12 (15)
3	PtCl ₂	100, 12	13 (15)
4	$Pd(Ph_3P)_4$	100, 12	Trace
5	$Pd(Ph_3P)_4$	100, 12	Trace
6	(CH ₃ CN) ₂ PdCl ₂	100, 12	31 (45)
7	Pd ₂ dba ₃	100, 12	37 (40)
8	NiCl ₂	100, 12	23 (25)

From these experimental results, a combination of $Pd(OAc)_2$ and ligand 2 in DMF as solvent were found to be the most suitable conditions. We believe that ligand 2 plays an effective role in the present reaction, because Pd(II) acetate itself can not catalyze Suzuki cross-coupling reaction, when aryl chlorides are used. Although low turn-over-number (TON, about 20-100) in the present reaction is one major disadvantage, the reactivity of ligand 2 was checked with various types of arylhalides **3a**–i vs. arylboronic acids **4a**–f (Equation 3 and Table 4). 4-Chlorotoluene (3a) treated with five different arylboronic acids 4a-f from phenyl boronic acid (4a), p-tolylboronic acid (4b), p-methoxyphenylboronic acid (4c), 3,5-dimethylphenylboronic acid (4d), and 4-cyanophenyl boronic acid (4e) to a sterically hindered 2,6-dimethoxyphenyl boronic acid (4f). In all these cases except 4f, we have obtained cross-coupled biphenyl compounds 5aa-ae LETTER

pected, the reaction of 4-cholorotoluene (3a) with 2,6dimethoxy phenylboronic acid (4f) afforded only 10% yield. The similar reactivity was observed with 4-chloroanisole (3b) with five different arylboronic acids 4a-f.



Table 4	Reactions of	f Arylhalides 3a –	i with Arylboronic	Acids 4a-
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Aryl halides	R ¹ B- (OH) ₂	Base	Temp (°C), time (h)	Yield (%) ^a
3a	4a	t-BuOK, TBAB	100, 12	77
	4c		100, 12	88
	4d		100, 12	79
	4e		100, 12	72
	4f		100, 48	10
3b	4a	t-BuOK, TBAB	100, 12	81
	4b		100, 12	83
	4d		100, 12	76
	4e		100, 12	78
	4f		100, 18	18
3c ^a	4b	K ₂ CO ₃ , TBAB	100, 10	81
	4c	K ₂ CO ₃ , TBAB	100, 10	82
3d ^a	4b	K ₂ CO ₃ , TBAB	100,10	65
3e ^a	4b	K ₂ CO ₃ , TBAB	100, 10	69
3f ^a	4b	K ₂ CO ₃ , TBAB	100, 10	62
3g ^a	4b	K ₂ CO ₃ , TBAB	100, 10	58
3h ^a	4a	K ₂ CO ₃ , TBAB	100, 12	86
	4b		100, 12	81
	4d		100, 12	88
	4e		100, 12	84
	4f		100, 12	59
3i ^b	4a	Cs ₂ CO ₃	80, 8	90
	4c		80, 8	95
	4d		80, 8	89
	4e		80, 8	83
	4f		80, 10	85
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^a 3 mol% catalyst was used.

^b 1 mol% catalyst was used.

3a-i		4a–f
X = Cl	$R^{1} = 4-CH_{3} (3a)$ $R^{1} = 4-OCH_{3} (3b)$	$R^2 = H (\mathbf{4a})$
	$ \begin{array}{l} {R^1} = {\rm{4-NO}_2}\left({{\rm{3c}}} \right) \\ {R^1} = {\rm{2-NO}_2}\left({{\rm{3d}}} \right) \end{array} $	$R^2 = 4\text{-}CH_3 (\mathbf{4b})$
	$R^{1} = 4$ -CHO (3e) $R^{1} = 4$ -COCH ₃ (3f)	$R^2 = 4\text{-OCH}_3 (\mathbf{4c})$
	$\mathbf{R}^1 = 3\text{-}\mathbf{NO}_2\text{-}\mathbf{pyridyl} (\mathbf{3g})$	$R^2 = 3,5-(CH_3)_2$ (4d)
X = Br	$R^{1} = 4\text{-OCH}_{3}(\mathbf{3h})$	$R^2 = 4$ -CN (4e)
X = I	$R^{1} = 4-CH_{3} (3i)$	$R^2 = 2,6-(OCH_3)_2$ (4f)

Next, we took more reactive aryl halides like 4-nitrochlorobenzene (3c), 2-nitrochloro benzene (3d), 4-chlorobenzaldehyde (3e), 4-chloro-acetophenone (3f) and 2chloro-3-nitro pyridine (3g) in the presence of K_2CO_3 as a base and TBAB. The reactions underwent very smoothly even in 3 mol% usage of ligand 2 and Pd(OAc)₂ and gave the corresponding coupling products 5 in very good yields. In order to extend the scope of the present ligand 2, we tested an aryl bromide and an aryl iodide. 4-Bromoanisole (3h) as a representative aryl bromide was treated with aryl boronic acids 4a-e. Here we have taken a mixture of ligand (3 mol%), Pd(OAc)₂ (3 mol%), potassium carbonate (2 equiv), TBAB, and heated for 10-12 hours in DMF. All arylboronic acids 4a-f including sterically hindered arylboronic acid 4f gave the coupling products in excellent yields. The same methodology was also successfully applied to 4-iodotoluene (3i) with only 1 mol% of the catalyst. In summary, we have synthesized the new ligand 1,3-phenylene-bis-(1H)-tetrazole ligand (2) and have shown to be an effective catalyst for the Suzuki cross-coupling reactions of various aryl chlorides, bromides and iodides in combination with Pd(OAc)₂. We believe that tetrazole-related ligands can offer promising features for a number of other important palladium-catalyzed reactions.

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- (12) General Procedure: Palldium acetate (5 mol%), ligand 2 (5 mol%), and appropriate base (2 equiv) and additive TBAB (10 mol%) were taken in DMF (10 mL) and the mixture was stirred at r.t. for 1 h. Appropriate aryl halides 3a-i (0.1 mol) and arylboronic acids 4a-f (0.11 mmol, 1.1 equiv) were added followed by additional portion of DMF (1.0 mL). The mixture was then stirred at 80–120 °C. The reaction was monitored by TLC. The reaction mixture was cooled, diluted with 20 mL of H₂O and extracted with Et₂O (2 × 20mL). The combined organic portion was washed with brine solution, dried over anhyd MgSO₄, and finally filtered. Evaporatation of the volatiles under reduced pressure to get the corresponding biphenyl products *5*.