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Bisamides as ligands in Suzuki coupling reactions catalyzed by palladium

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ABSTRACT

This protocol uses palladium chloride and bisamides as ligands for Suzuki cross-coupling reactions, in mild (25° for 2 h) aerobic conditions. This study was efficient for arylboronic acids and/or aryl bromides with activating or deactivating substituents in the ring with high yields (81–95%).

Introduction

Cross-coupling reactions are one of the most efficient methods for the construction of molecules C_{aryl}–C_{aryl} bonds with widespread use in organic synthesis.[1–4] There was substantial growth in terms of publications and patents with the Suzuki–Miyaura cross-coupling, Heck, Sonogashira, and Negishi coupling reactions in the last decade.[5] Due to these important reactions, Richard Heck, Ei-ichi Negishi, and Akira Suzuki were awarded the Nobel Prize in Chemistry in 2010. Furthermore, these reactions have been extensively used in the synthesis of pharmaceuticals,[6,7] liquid crystal compounds,[8] natural products, industrial intermediates, and molecular materials.[9,10,3] Phosphine ligands and derivatives have been most commonly employed in reactions,[11–13] though most of these phosphines are sensitive to air and moisture, besides being expensive and toxic. Needless to say, it places significant limits on their synthetic applications.[14] Therefore, new ligands have been studied for the Suzuki reaction such as N-heterocyclic carbenes,[15,16] imine[17] diamino,[18,19] iminophosphine,[20] aryloximes,[21–23] guanidenes,[24–26] ligandless [27–30] and few examples with bisamides.[10] In this Letter, we have reported a simple system—composed by palladium chloride and bisamide as ligands—which is able to perform the Suzuki cross-coupling reaction with both arylboronic acids and/or aryl bromides with activating or deactivating substituents in the ring, in aerobic and mild conditions.

Results and discussion

Different types of ligands have been used over the past few years; however, there are few examples using bisamide compounds as ligands. In this Letter, we aimed at reporting that a simple system, such as palladium chloride and bisamide as ligands, is able to perform the Suzuki cross-coupling of arylbromides in mild conditions and with low loadings of catalyst.

Firstly, we synthesized two different bisamides, compounds **1a**[31] and **1b**, both derived from etylenediamine (Scheme 1).

These bisamides, which provided yields above 70%, were not applied to cross-coupling. After being synthesized and characterized, these bisamides were used as ligands in Suzuki reactions. Firstly, a set of experiments was carried out with 4-bromotoluene and phenylboronic acid in order to establish the best conditions for cross-coupling. Bases (K_3PO_4, K_2CO_3) were evaluated in the solvent (THF, dioxane, acetonitrile, MeOH, and toluene). For both auxiliary ligands **1a** and **1b**, the best base was K_2CO_3 and the best solvent was MeOH.

For both auxiliary ligands, catalytic precursor $Pd(OAc)_2$ and $PdCl_2$ (Table 1) were tested. Although two catalyst precursors provided the expected coupling product, palladium chloride showed better results in reactions.

Low conversion were obtained in the absence of bisamide ligand (Table 1, entries 3 and 6). Both ligands were found to be efficient. However, $PdCl_2$ was more efficient, principally for ligand **1b**. It may have occurred because, in $PdCl_2$, the metal is more available to undergo oxidative addition.

Temperatures ranging from 25 to 130 °C were screened in this system (Table 2). Table 2 also compares the efficiency of both catalytic bisamide ligands and ethylenediamine, precursor of the

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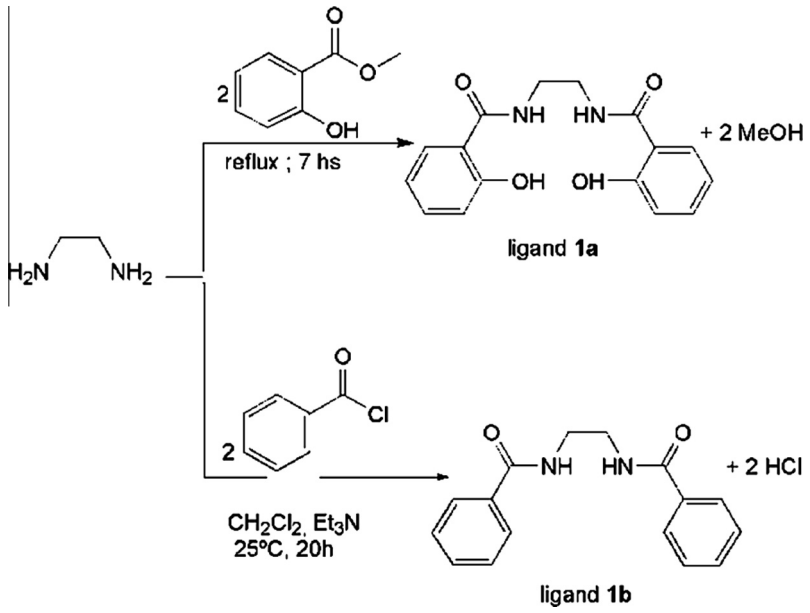


Scheme 1. Synthesis of symmetrical bisamides.

Table 1
Effect of the bisamide ligand and the palladium on Suzuki–Miyaura reaction of 4-bromotoluene with phenylboronic acid

Entry	Ligand	[Pd]	Conv (%)	Yield[a] (%)
1	**1a**	$Pd(OAc)_2$	98	92
2	**1b**	$Pd(OAc)_2$	89	81
3	—	$Pd(OAc)_2$	39	32
4	**1a**	$PdCl_2$	99	98
5	**1b**	$PdCl_2$	99	97
6	—	$PdCl_2$	48	43

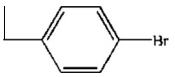
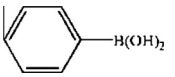
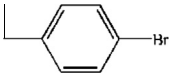
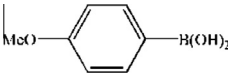
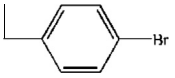
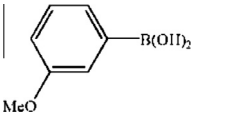
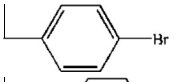
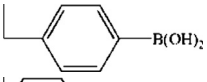
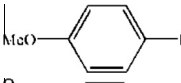
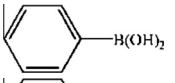
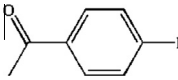
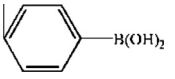
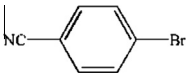
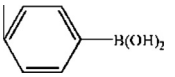
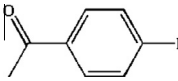
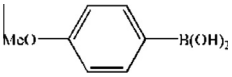
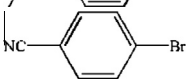
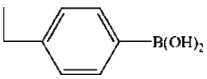
Conditions: 4-bromotoluene (0.5 mmol), phenylboronic acid (0.75 mmol), K_2CO_3 (1 mmol), [Pd] (0.01 mmol), ligand (0.015 mmol), toluene (6 mL), 130 °C,16 h.
[a] Yields determined by GC.

Table 2
Influence of temperature on Suzuki–Miyaura reactions

Entry	Ligand	Temp (°C)	Conv (%)	Yield[a] (%)
7	**1a**	130	100	98
8	**1b**	130	99	97
9	en[b]	130	56	47
10	**1a**	80	99	96
11	**1b**	80	98	95
12	en	80	45	38
13	**1a**	50	100	98
14	**1b**	50	98	97
15	en	50	30	18
16	**1a**	25	98	97
17	**1b**	25	98	97
18	en	25	34	13
19	**1a**	25[c]	98	97
20	**1b**	25[c]	98	97

Conditions: 4-bromotoluene (0.5 mmol), phenylboronic acid (0.75 mmol), K_2CO_3 (1 mmol), $PdCl_2$ (0.01 mmol), ligand (0.015 mmol), MeOH (6 mL),6 h.
[a] Yields determined by GC.
[b] en = ethylenediamine.
[c] Reactions carried out in 2 h. TON: mol of substrate converted/mol of catalyst.

Table 3
Reaction of substituted aryl halides and phenylboronic acids using **1a** as ligand

Entry	Aryl halides	Phenylboronic acid	Isolated yield (%)
21			92
22			89
23			85
24			90
25			90
26			98
27			94
28			95
29			90

Conditions: arylhalides (1.0 mmol), arylboronic acid (1.5 mmol), K_2CO_3 (2 mmol), $PdCl_2$ (0.02 mmol), ligand (0.03 mmol), MeOH (6 mL), 25 °C, 2 h.

compounds that were synthesized. Results indicate that the bisamides were more efficient than ethylenediamine. Furthermore, the reaction showed excellent results at room temperature (Table 2, entries 19 and 20) show high TON 4900.

Encouraged by these results, we applied the optimized conditions to other aryl halides and arilboronic acids (Table 3). The catalytic system proved to be very versatile and can use aryl bromides with activating or deactivating substituents in the ring and aryl boronic acids with activating or deactivating substituents.

Conclusions

We have found that a simple catalyst precursor prepared in situ from palladium chloride and bisamide with ligand can be used for the Suzuki cross-coupling reaction, in which both aryl boronic acid and aryl bromide can have substituent activators or deactivators in the ring. The reaction can be carried out at low catalyst loading (2 mol %) with new ligand (bisamides) in mild conditions (25° for 2 h), providing biphenyl derivatives in high yields (81–98%). This protocol is inexpensive and uses bisamides, compounds that are not commonly applied to cross-coupling reactions, as ligands.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.06.110.

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