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Simple pyridylmethylamines: efficient and robust *N,N*-ligands for Suzuki–Miyaura coupling reactions

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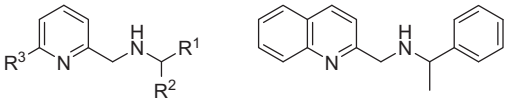
ABSTRACT

A series of pyridylmethylamines have been synthesized in one step from commercially available starting material and identified as effective ligands for Pd-catalyzed carbon–carbon bond formation through Suzuki–Miyaura coupling reaction. The *N,N*-pyridylmethylamine-Pd catalytic systems appeared as an interesting and robust compromise between catalytic efficiency, substrate compatibility, and practical aspects.

Transition metal-catalyzed reactions provide some of the most attractive methodologies for the creation of carbon–carbon bonds. Among them, the Suzuki–Miyaura reaction[1] became over only two decades one of the most popular, powerful, and useful tools in organic synthesis for the preparation of biaryls.[2] This has been driven by the increasing interest of the scientific, academic, and industrial community. Indeed, numerous pharmaceutical drugs, agrochemicals, materials, optical devices, or products of industrial significance that include the biaryl core have been recently patented and commercialized.[3] In order to overcome the remaining historical drawbacks of phosphorus-based catalytic systems, chemists tried to outdo each other in ingenuity. Indeed, phosphine-free,[4] or ligand-free Pd-catalysts,[5] hydrosoluble PEG-based ligands,[6] the use of aqueous[4,7,9] or alternative solvents,[8] heterogenization of homogeneous catalysts,[9] as well as stabilization of Pd nanoparticles[10] are among the most significant contributions to this area. An additional emerging trend relies on the determination of robust compromises between catalytic efficiency, substrate compatibility, and practical aspects that allow to overcome most of the strong limitations to convenient or industrial process applicability.[3,11] Within this context catalysts that would overcome concerns such as (i) time-consuming multistep access to ligands, (ii) poor functional group tolerance and thermal stability, (iii) sensitivity to air and moisture, and (iv) lack of ligand modulation and reactivity in electronically demanding reactions are thus higly desirable.

We recently reported efficient *N,N*-pyridylamine- and *N,N*-pyridylpiperidine-Pd catalytic combinations for Suzuki–Miyaura couplings.[12] Although, such ligands revealed useful in a large panel of transformations with low catalytic loadings, benefits arising from this efficiency were somewhat hampered by the multistep sequences required to their preparation. Thus, we turned our attention toward new series of *N,N*-type ligands accessible through a convenient one-step process, starting from commercially available starting material and detailed herein their application in some demanding coupling reactions.

Pyridylmethylamine-based *N,N*-bidendate ligands were prepared in one step through reductive amination from pyridine- or



1 : R^1 = *i*Pr; R^2 = H; R^3 = H
2 : R^1 = Et; R^2 = H; R^3 = H
3 : R^1 = Cy; R^2 = H; R^3 = H
4 : R^1 = Ph; R^2 = H; R^3 = H
5 : R^1 = Ph; R^2 = Me; R^3 = H
6 : R^1 = Ph; R^2 = Ph; R^3 = H
7 : R^1 = Ph; R^2 = Me; R^3 = Me

8

Figure 1. *N,N*-Bidendate pyridylmethylamine ligands **1**–**8**.

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quinoline-2-carboxaldehydes and the appropriate commercially available amines. Introduction of alkyl, benzyl, and dibenzyl groups into the pendant methylamine as well as the use of 6-methylpyridine or quinoline instead of pyridine accounts for the modulation at the pyridylmethylamine core (Fig. 1).

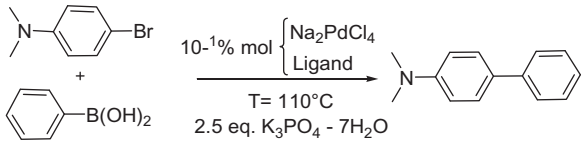
We next started to examine the catalytic efficiency of the pyridylmethylamine-based ligand series in Suzuki–Miyaura reactions. Recent examples of ligand-free reactions show that the presence of ligands is not strictly required in combinations involving bromides or iodides especially when substituted by electron-withdrawing groups and boronic acids substituted by electron-donating moieties or in increasing the steric crowding around the neo-formed C–C bond.[5] In contrast to these examples, ligands play a major role for electronically or sterically demanding reactions. Thus we started to compare the catalytic combination in the synthesis of 4-dimethylamino-1,1′-biphenyl (Scheme 1, Table 1). As expected the use of neither $Pd(OAc)_2$ nor Na_2PdCl_4 without ligand afforded the biphenyl core. Table 1 gathers results obtained by using 1.1 equiv of boronic acid and compares conversion of boronic acid after 1 and 3 h reaction course.

In most cases, reactions were conducted in DMF/H_2O as the solvent indicating a good compatibility of the catalytic combination under aqueous conditions. Switching to toluene and dioxane did not increase conversions after 3 h (entries 6, 7). Similarly, K_3PO_4 revealed superior to other classical bases such as carbonates. In contrast, reducing the reaction temperature or the catalytic loading proved detrimental to the overall reactivity in this context. Best combination was obtained using ligand **5**. The latter represents the optimal compromise between reaction rate, substrate conversion, and reduced amount or absence of boronic acid homocoupling byproduct. Indeed, moving toward less sterically strained ligands such as **1**–**4** afforded lower rates in 1 h but conversions as high as ligand **5** (entries 1–4). In contrast, most congested ligands in this series, namely **6**, **7,** and **8**, in which the pendant methyl arm is substituted with a bisbenzylic subunit or the pyridine replaced by a 6-methylpyridine or a quinoline heterocycle, respectively, afforded both lower rates and conversions (entries 8–10).

Pertinence of the structural simplicity of ligands in this series can be easily understood by comparing the above obtained results with the overall efficiency of more elaborated *N*,*N*-pyridinyl-based ligands.

Indeed, as shown in Table 2, the use of ligand **9**[12] in the preparation of model compound 4-dimethylamino-1,1′-biphenyl afforded 56 and 75% conversion after 1 and 3 h of reaction course, respectively. The embedding of the methylamine arm into a piperidinyl structure may be responsible for the increase of steric strain around the Pd center and account for the higher efficiency observed. Although slightly superior to ligand **1**, the preparation of ligand **9** required a five-step sequence that strongly hampers its use and allows a clear discrimination between both ligands. In addition, a simple structural modulation from **1** (R^1 = *i*Pr) to **5** (R^1 = Ph) gave similar catalytic efficiency (61 and 75% after 1 and 3 h, respectively) and thus represented an appealing alternative by integrating the ease of ligand synthesis into the global catalytic compromise.

Several examples of biaryls prepared using **5** as the ligands are shown in Table 3. Under the aforementioned conditions (DMF/H_2O: 95:5, 10^{-1}% cat., 1/1 ligand/Pd ratio, 16 h, 110 °C) bromides and chlorides couple with various boronic acids substituted by nitro, cyano, fluoro, and acetyl groups affording high to quantitative yields of the targeted biaryls. As shown in Table 3, ligand **5** revealed efficient for most of the demanding reactions involving



Scheme 1. Synthesis of 4-dimethylamino-1,1′-biphenyl.

Table 1
Ligand comparison in the synthesis of 4-dimethylamino-1,1′-biphenyl

Entry	Ligand	Solvent	Reaction time (% conversion)	
			1h	3h
1	**1**	DMF/H_2O (95:5)	23	59
2	**2**	DMF/H_2O (95:5)	51	69
3	**3**	DMF/H_2O (95:5)	41	72
4	**4**	DMF/H_2O (95:5)	44	73
5	**5**	DMF/H_2O (95:5)	61	75
6	**5**	Toluene	50	74
7	**5**	Dioxane	49	63
8	**6**	DMF/H_2O (95:5)	49	56
9	**7**	DMF/H_2O (95:5)	39	43
10	**8**	DMF/H_2O (95:5)	46	55

Table 2
Impact of structural modulation on the overall catalytic compromise

Entry	Ligand	Conversion (%)		Synthesis (step)
		1h	3h	
1	**1**	23	59	1
2	**9**	56	72	5
3	**5**	61	75	1

Table 3
Example of various biaryls prepared using ligand **5**

Entry	Boronic acid	Aromatic halide	Yield (%)
1	O_2N, $B(OH)_2$	N, Br	92
2	F_3C, $B(OH)_2$	Br	68
3	$B(OH)_2$, CN	Br, OMe	Quant.
4	O, $B(OH)_2$	Cl	65
5	$B(OH)_2$, NO_2	Br, OMe	—
6	F, $B(OH)_2$, F	HO, HO, O, Br	92

deactivated haloaromatics. Indeed, reactions using *p*-dimethylamino-, *o*-methoxy-bromobenzene, and 2-methyl-1-bromonaphthalene were successfully achieved in high yields (entries 1, 2, 3). More interestingly, this catalytic system allowed not only the use of *p*-chlorotoluene (entry 4) but also the combination of both deactivated haloaromatics and boronic acids. In this context, *p*-trifluoromethyl, *m*-nitro, *m*-acetyl, and *p*,*o*-difluoro phenyl boronic acids reacted under the above-mentioned conditions to afford the expected birayls in high yields (entries 1, 2, 4, 6). Attempts to prepare 2,2′-disubtituted-1,1′-biphenyls are shown in entries 3 and 5. If *o*-cyano phenylboronic acid readily reacted with *o*-methoxy-bromobenzene to afford the corresponding biphenyl in quantitative yield, no conversion could be observed using the more bulky *o*-nitro analog.

In conclusion, a new series of pyridylmethylamine-based *N*,*N*-bidendate ligands have been prepared in one step from commercially available starting material. Within this series, such ligands represent an efficient and robust catalytic compromise that takes into account ease of preparation, low catalyst loadings, as well as catalytic efficiency in some sterically and electronically demanding reactions.

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