Recent Advances in the BiVO₄ Photocatalyst for Sun-Driven Water Oxidation

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Abstract: The synthesis of new vicinal diamines based on aziridine and azetidine cores as well as the comparison of their catalytic activities as ligand in the Suzuki-Miyaura coupling reaction are described in this communication. The synthesis of three- and four-membered ring heterocycles substituted by a methylamine pendant arm is detailed from the parent nitrile derivatives. Complexation to palladium under various conditions has been examined affording vicinal diamines or amine-imidate complexes. The efficiency of four new catalytic systems is compared in the preparation of variously substituted biaryls. Aziridine- and azetidine-based catalytic systems allowed Suzuki-Miyaura reactions from aryl halides including chlorides with catalytic loadings until 0.001% at temperatures ranging from 100 °C to r.t. The evolution of the Pd-metallacycle ring strain moving from azetidine to aziridine in combination with a methylamine or an imidate pendant arm impacted the Suzuki-Miyaura reaction issue.

Keywords: aziridine; azetidine; vicinal diamine; imidate; ligand; Suzuki-Miyaura coupling

1. Introduction

The Suzuki-Miyaura reaction is “an easy way for C–C bonding” [1]. This statement is especially worthwhile in modern organic synthesis. Indeed, the advent of the Suzuki-Miyaura reaction represents a critical step in this field. This reaction has become for decades a major methodological tool available to chemists to build molecular architectures especially based on a biaryl scaffold. The biaryl motif can be found in numerous natural products, agrochemicals, drugs, polymers, ligands and thus triggered the attention of the scientific community for a wide range of applications [2–9]. If the formation of a biphenyl motif belongs nowadays to a textbook knowledge, the past decade has witnessed spectacular innovations and improvements such as ligandless transformations [10], supported or nanostructured catalytic systems [11–13], performing additives [14,15], neat and/or aqueous conditions [2,13,15], MW activations [10] for example.

Although the presence of a ligand is not strictly mandatory, increase of selectivity, the use of poorly reactive chlorides, room temperature conditions remains challenging and usually requires a ligand [11,13,15,16]. Additionally, preformed and geometrically constrained catalytic systems appears as crucial features beneficial to a catalytic activity enhancement [8,17]. If phosphorus-based catalytic systems dominated this area during the last decades, nitrogen-containing ligands revealed recently useful and appear as a pertinent alternative. In this context, ligands incorporating pyridyl-based scaffolds as well as combinations of pyridines linked to flexible alkylamine arms or rigid
Cycloalkylamines such as piperidines have been successfully developed in recent years [17–23]. In this communication, we describe new ligands based on strained aza-heterocycles such as aziridines and azetidines. We focused on two strategies using these small aza-heterocycles. The first one involves a combination of these small aza-heterocycles and a flexible methylamine side chain while the second requires a more rigid pendant arm based on an imidate moiety (Figure 1).

![Figure 1. Aziridine- and azetidine-based catalytic systems. Modulation of ring and side chain strain.](image)

We expect the modulation of the ring and side chain strains to impact the catalytic properties of these new ligands families. The abilities of the latter to promote couplings especially involving aromatic chlorides will be examined. In addition, room temperature conditions will further be prioritized in the context of the synthesis of variously substituted biphenyls.

2. Results and Discussion

2.1. Synthesis of Catalytic System

2.1.1. Synthesis of Ligand Precursors

Cyanoazetidine 1 and cyanoaziridine 2 have been easily obtained in two and three steps respectively starting from commercially available reactants as reported earlier [24,25]. The further step was to prepare vicinal diamines 3 and 4. Both diamines were obtained using a two-step sequence, first an addition of phenylmagnesium bromide followed by a reduction with sodium borohydride. According to recent literature [26–28] reduction afforded a 9/1 ratio of diastereomers. In the absence of X-ray data, a relative stereochemistry can only be hypothesized. In good agreement with literature data [26–28], the assumed anti selectivity, might results from a hydride attack on the less strained Re face of the imine moiety leading as depicted in Scheme 1. The proposed chelate model could result either from an intramolecular hydrogen bond between the tertiary amine and imino moieties or from the formation of a five-membered Mg-chelate after addition of the Grignard reagent. The probable major anti diastereomer was in each case isolated after silica gel chromatography purification in 56% and 69% yields respectively (Scheme 1).

![Scheme 1. Synthesis of aziridine and azetidine ligand precursors.](image)
2.1.2. Synthesis of Pd Complexes

The next step was the preparation of Pd complexes starting from both nitrile and diamine precursors.

- Synthesis of vicinal diamine-based Pd complexes

For this purpose, vicinal diamines 3 and 4 were reacted with Na₂PdCl₄ in freshly distilled MeOH for 20 h at room temperature. Expected complexes A and B were easily obtained after filtration and successive washings with cold MeOH, ether and pentane in 94% and 83% yields respectively (Scheme 2).

- Synthesis of heterocycle/amidate-based Pd complexes

Amidate-Pd complexes were prepared under similar conditions and isolated by simple filtration and washings as shown in Scheme 3. Dual complexation of the nitrile group and the heterocyclic nitrogen atom to palladium in MeOH allowed the activation of the nitrile group and the formation of the imidate fragment through nucleophilic addition of one equivalent of methanol moiety. Bidendate complexes C and D display characteristic chemical shifts in ¹H and ¹³C NMR corresponding to the presence of an imidate fragment as shown in Scheme 3. Methoxy groups appear at 3.87 and 3.65 ppm in ¹H NMR and the sp² carbon appear at 175.3 and 177.3 ppm in ¹³C NMR. Both novel complexes were obtained in 70% and 63% yields respectively (Scheme 3).
Within these series, complexes appeared more stable than the corresponding ligands. Especially the aziridine 3 displays averaged stability, we assume to arise from ring opening without careful storage under inert conditions. Complexes display high stability for months. No modification of aspect, $^1$H NMR spectra or catalytic activities was noticed.

2.2. Evaluation of Catalytic Properties

Catalytic properties of complexes A, B, C and D were next evaluated. The coupling between 4-bromonitrobenzene and 4-tolylbromonic acid was chosen as the model coupling reaction (Scheme 4). Gratifyingly, running the reaction at room temperature for 10 h, using 1% of catalytic loading and base/solvent combination (Cs$_2$CO$_3$ and DMF/H$_2$O) as already reported for benzhydrylamines [20–24], allowed us to identify 4-nitro-4’-methyl biphenyl 5 in the crude material $^1$H NMR spectra. Various conversions were observed ranging from 10% to 50% evidencing that our catalytic systems were able to trigger Suzuki-Miyaura coupling at room temperature.

![Scheme 4. Catalysts A–D applied to a model Suzuki reaction.](image)

- Optimisation of catalytic conditions

The next step was to adjust the base/solvent combination. Among several base (Na$_2$CO$_3$, NaHCO$_3$, K$_3$PO$_4$, CsF) and solvent (THF, dioxane, toluene/ethanol/H$_2$O) combination tests, Cs$_2$CO$_3$ as the base and DMF/H$_2$O (9/1) as the solvent, gave the best conversions.

All catalytic systems were further evaluated and compared each other as shown in Figure 2. In the context of the synthesis of biphenyl derivative 5, iodo-, bromo- and chloro-precursors were independently reacted with 4-tolylbromonic acid using A, B, C and D catalysts, Cs$_2$CO$_3$ as the base and DMF/H$_2$O (9/1) as the solvent at various catalytic loadings. Results obtained with 1% and 0.1% of catalyst loading at room temperature are compared in Figure 2a,b respectively and results obtained with 0.01% and 0.001% of catalyst loading at 100 °C are compared in Figure 2c,d respectively.

Figure 2a shows obtained results when using 1% of catalyst loading for 16 h at room temperature. Iodides readily react affording the expected biphenyl motif in 93% to quantitative Yields whatever the catalyst A, B, C or D. The use of bromides and chlorides allowed us to clearly differentiate the efficiency of both catalyst families. Indeed, diamine-based catalysts A and B and amine/imidate catalysts C and D behaved differently. Best results were obtained using the more strained catalysts C and D. If transformation of arylichloride using D as the catalyst led to 41% in 16 h at room temperature, an extended reaction time to 48 h at room temperature allowed us to reach 94% yield.
A similar trend was observed with 0.1% catalytic loading for 24 h at room temperature (Figure 2b). Amine/imidate complexes C and D revealed superior to diamine complexes A and B. Aryliodides were transformed up to quantitative yields at room temperature. An expected decrease of catalytic activity is observed when moving to bromides and chloride. At this loading, complex D that displays an enhanced ring strain and a more rigid side chain led to best results. Again, an extended reaction time to 48 h improved the yield of biphenyl 5% to 58% at room temperature.

At lower catalytic loadings such as 0.01% and 0.001% (Figure 2c,d) reactions were run at 100 °C. Again both complex families were compared and the amine/imidate C and D were found superior to the diamine complexes A and B. Again combination of ring and side chain enhanced strain in catalyst D revealed beneficial to catalytic activity. Indeed, the use of D at 0.01%, allowed reaching 91% yield for aryl iodides and 53% for bromides. In contrast, chlorides exhibit only poor conversion. At 0.001% at 100 °C only aryl iodides react affording the expected biphenyl motif in 38% yield. In contrast, using bromides and chlorides analogues showed no reaction.

In fact, complex D was found superior to all others at room temperature until 0.1% loading and at 100 °C at lower loadings. Better results obtained using complex D, may result from the joint presence of an enhanced ring strain and a more rigid side chain which both likely play a crucial role in the transmetalation step of the catalytic cycle and the final product releasing step.

- Application to various substrates

Complex D was next evaluated in several Suzuki-Miyaura reactions. Table 1 gathers results obtained using various combinations of electronic effects for both aryl halides and boronic acids. As shown, chlorides bearing electron withdrawing groups are transformed in fair to high yields at room temperature using catalytic loadings ranging from 1% to 0.1% (entries 1–6, 9, 12–13). Reactions using boronic acids substituted by electron withdrawing groups such as NO2-phenyl, CH3CO-phenyl or sterically hindered substituents required the use of bromides in order to obtain the desired biphenyl with fair to excellent yields (entries 10–11, 14–16). Phenyl halides substituted by electron donating
groups such as MeO-phenyl and HO-phenyl (entries 17–21) also required the use of bromides at catalytic loadings from 0.1% to 1% and/or increase of temperature from room temperature to 100 °C respectively. Finally, 2,2'-biphenyl (entries 22–24) could be obtained in high yields (89%–90%) at 100 °C using either chlorides or bromides at 0.1% and 0.01% catalytic loading.

Table 1. Synthesis of biaryls using catalyst D, Cs₂CO₃ as the base and DMF/H₂O (9/1) as the solvent.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Halide Fragment</th>
<th>Boronic Acid Fragment</th>
<th>Halide</th>
<th>Cat. Load.</th>
<th>Conditions</th>
<th>Yield (%)</th>
</tr>
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<tr>
<td>1</td>
<td>Cl</td>
<td>Cl</td>
<td>Cl</td>
<td>0.1%</td>
<td>r.t., 24 h</td>
<td>28</td>
</tr>
<tr>
<td>2</td>
<td>Cl</td>
<td>Cl</td>
<td>Cl</td>
<td>1%</td>
<td>r.t., 18 h</td>
<td>88</td>
</tr>
<tr>
<td>3</td>
<td>Cl</td>
<td>Cl</td>
<td>Cl</td>
<td>0.1%</td>
<td>r.t., 24 h</td>
<td>21</td>
</tr>
<tr>
<td>4</td>
<td>Cl</td>
<td>Cl</td>
<td>Cl</td>
<td>1%</td>
<td>r.t., 24 h</td>
<td>69 [29]</td>
</tr>
<tr>
<td>5</td>
<td>Cl</td>
<td>Cl</td>
<td>Cl</td>
<td>0.1%</td>
<td>r.t., 24 h</td>
<td>21</td>
</tr>
<tr>
<td>6</td>
<td>Cl</td>
<td>Cl</td>
<td>Cl</td>
<td>1%</td>
<td>r.t., 24 h</td>
<td>60</td>
</tr>
<tr>
<td>7</td>
<td>Br</td>
<td>Br</td>
<td>Br</td>
<td>0.01%</td>
<td>100 °C, 24 h</td>
<td>89</td>
</tr>
<tr>
<td>8</td>
<td>Br</td>
<td>Br</td>
<td>Br</td>
<td>0.1%</td>
<td>100 °C, 6 h, 93 a [30]</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Cl</td>
<td>Cl</td>
<td>Cl</td>
<td>1%</td>
<td>r.t., 24 h</td>
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<tr>
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<td>Br</td>
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<td>r.t., 24 h</td>
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<tr>
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<td>Br</td>
<td>1%</td>
<td>r.t., 24 h</td>
<td>61</td>
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<tr>
<td>12</td>
<td>Cl</td>
<td>Cl</td>
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<td>0.1%</td>
<td>r.t., 24 h</td>
<td>16</td>
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<tr>
<td>13</td>
<td>Cl</td>
<td>Cl</td>
<td>Cl</td>
<td>1%</td>
<td>r.t., 24 h</td>
<td>45</td>
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<tr>
<td>14</td>
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<td>0.1%</td>
<td>r.t., 24 h</td>
<td>58</td>
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<tr>
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<tr>
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<td>Br</td>
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<td>Br</td>
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<td>r.t., 24 h</td>
<td>81 [31]</td>
</tr>
<tr>
<td>17</td>
<td>Cl</td>
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<td>Cl</td>
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<td>100 °C, 18 h</td>
<td>32</td>
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<td>Br</td>
<td>1%</td>
<td>r.t., 24 h</td>
<td>39 [32]</td>
</tr>
<tr>
<td>19</td>
<td>Cl</td>
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<td>25</td>
</tr>
<tr>
<td>20</td>
<td>Br</td>
<td>Br</td>
<td>Br</td>
<td>1%</td>
<td>100 °C, 18 h</td>
<td>57 [33]</td>
</tr>
<tr>
<td>21</td>
<td>Br</td>
<td>Br</td>
<td>Br</td>
<td>0.1%</td>
<td>r.t., 18 h</td>
<td>45</td>
</tr>
<tr>
<td>22</td>
<td>Cl</td>
<td>Cl</td>
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<td>r.t., 24 h</td>
<td>30</td>
</tr>
<tr>
<td>23</td>
<td>Cl</td>
<td>Cl</td>
<td>Cl</td>
<td>0.1%</td>
<td>100 °C, 6 h</td>
<td>89</td>
</tr>
<tr>
<td>24</td>
<td>Br</td>
<td>Br</td>
<td>Br</td>
<td>0.01%</td>
<td>100 °C, 24 h</td>
<td>90</td>
</tr>
</tbody>
</table>

a A similar yield of 87% has been obtained using an analogue of catalyst C under similar reaction conditions [27].

3. Materials and Methods

3.1. Materials

Unless otherwise noted, all starting materials were obtained from commercial suppliers and used without purification. Petroleum ether was distilled under Argon. NMR spectra were recorded on a 300 MHz and 200 MHz Brucker spectrometers (Bruker BioSpin GmbH, Rheinstetten, Germany). Chemical shifts were reported in ppm relative to the residual solvent peak (7.27 ppm for CHCl₃) for ¹H spectra and (77.00 ppm for CDCl₃) for ¹³C spectra. High Resolution Mass spectroscopy data were recorded on an Autospec Ultima (Waters/Micromass) device (Waters, Gyancourt, France,) with a resolution of 5000 RP at 5%. Thin-layer chromatography (TLC) was carried out on aluminium sheets precoated with silica gel 60 F254. Column chromatography separations were performed using silica gel (0.040–0.060 mm). (N-benzyl)-2-cyanoazetidine 1 and (N-benzyl)-2-cyanoaziridine 2 have been prepared according to references [24,25].
3.2. Methods

3.2.1. General Procedure for Addition/Reduction Sequence

The phenylmagnesium chloride (2 mmol) was added to a solution of 2-cyanoderivative 1 or 2 (1 mmol) in dry THF (10 mL) at 0 °C under argon. After stirring for 20 min, MeOH (10 mL) and NaBH₄ (1.2 mmol) were successively added. After a further 1 h, the reaction was quenched with saturated aqueous NH₄Cl solution (5 mL), and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine, dried with magnesium sulfate and concentrated under reduced pressure. Amines 3 and 4 were purified by silica gel column chromatography using cyclohexane/Et₂O 1:1 as the eluant.

3.2.2. General Complexation Procedure

To a stirred solution of ligand 1–4 (0.25 mmol) in 5 mL of freshly distilled MeOH was added Na₂PdCl₄ (74 mg, 0.25 mmol). The mixture was stirred at room temperature for 1 to 16 h and filtered over a celite pad. The filtrate was removed by evaporation under vacuum. The residue was then purified over silica gel pad eluting first with cyclohexane/EtOAc 7:3 to remove traces of free ligand, then with EtOAc for ligands 3 and 4 and with AcOEt/MeOH 95:5 for ligands 1 and 2.

3.2.3. General Suzuki Coupling Procedure

To a stirred solution of aromatic halide (0.5 mmol), boronic acid (0.6 mmol) and Cs₂CO₃ (407 mg, 1.25 mmol) in 1 mL of DMF/H₂O (95:5) was added the palladium complex as a solid or in solution in DMF/H₂O (95:5). The mixture was stirred at room temperature or 100 °C (refer to Table 1). 10 mL of EtOAc and 10 mL of water were then added and the aqueous phase was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried (MgSO₄), filtered and concentrated under vacuum, the crude product was purified by flash chromatography on silica gel to give the biaryl product.

4. Conclusions

Two new families of ligands based on an aziridine and azetidine core have been developed. Starting from the parent aziridine- and azetidine-nitriles, vicinal diamines and amine/imidate palladium complexes were obtained respectively using a nucleophilic addition/reduction-complexation sequence or a direct complexation in methanol. Evaluation and comparison of the catalytic activities of four complexes are described. The amine/imidate family C and D was found superior to the diamine analogues family A and B. Within the amine/imidate family best results were achieved using complex D that combines both enhanced ring strain and side chain rigidity. The aziridine-imidate complex D proved to be efficient for the synthesis of various substituted biphenyls. Catalyst D allowed iodides to react at 100 °C and catalytic loadings as low as 0.001%. In addition, bromides are able to be used as partners in couplings at 100 °C and loadings of 0.01%. Finally, D catalyzes the reaction of chlorides at room temperature using catalytic loadings ranging from 1% to 0.1%.

Supplementary Materials: The following are available online at www.mdpi.com/2073-4344/7/1/27/s1, experimental procedures for the preparation of precursors, catalytic systems and Suzuki couplings as well as analytical data for new compounds.

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Author Contributions: H.B., B.L., T.B., S.P. and V.T. conceived and performed the experiments; A.G. and D.P. analyzed the data and wrote the paper.

Conflicts of Interest: The authors declare no conflict of interest.
References


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