This is an Accepted Manuscript, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this Accepted Manuscript with the edited and formatted Advance Article as soon as it is available.

You can find more information about Accepted Manuscripts in the Information for Authors.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal’s standard Terms & Conditions and the Ethical guidelines still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this Accepted Manuscript or any consequences arising from the use of any information it contains.
A polymer-supported Ir-based visible light photocatalyst was developed, and was evaluated as a heterogeneous catalyst for the aerobic phosphonylation reaction of \(N\)-aryl tetrahydroisoquinolines.
Efficient visible light-mediated cross-dehydrogenative coupling reactions of tertiary amines catalyzed by a polymer-immobilized iridium-based photocatalyst

Woo-Jin Yoo, and Shū Kobayashi*

The immobilization of an iridium-based heterogeneous photocatalyst via a radical polymerization process is described, and its catalytic activity was evaluated for the aerobic phosphorylation reaction of N-aryl tetrahydroisoquinolines under visible light irradiation.

The direct use of carbon-hydrogen (C-H) bonds in cross-coupling reactions is an exciting and challenging area of research that has the potential to streamline synthetic methods by reducing the amount of materials and energy required to make complex organic molecules.\(^1\) Despite the challenges associated with the low reactivity and selectivity in C-H bond functionalization, various successful carbon-carbon (C-C) and carbon-heteroatom (C-X) bond formation reactions have been realized with C-H bonds as reagents. The cross-dehydrogenative coupling (CDC) reaction of the α-C-H bond of nitrogen atoms represents one of the most successful examples of mild and selective C-C and C-X bond formations derived from C-H bonds.\(^5\) Although initial protocols relied heavily upon the use of stoichiometric amounts of strong oxidants,\(^3\) the rapid progress in this field has led to CDC reactions that can be performed under mild aerobic conditions.\(^4\)

The use of sunlight, as a renewable and clean source of energy to facilitate organic transformations, represents a new frontier for environmentally sustainable organic chemistry. Recently, ruthenium- and iridium-based polypyridyl complexes, well-known organometallic compounds that absorbs strongly in the visible light spectrum to produce long-lived photoexcited states, have emerged as efficient catalysts for organic transformations that are mediated by single-electron transfer (SET) processes.\(^5\) For instance, the strong oxidative potential of these photoexcited metal chromophores have been exploited to facilitate the CDC reaction of tertiary amines under ambient conditions in air.\(^8\) However, despite their emergence as efficient catalysts for a wide range of bond formation processes, the relative cost associated with ruthenium- and iridium-based photocatalysts limits their practical use. In this context, the development of easily recoverable and reusable heterogeneous visible light photocatalysts would be desirable. However, only limited examples of immobilize ruthenium- and iridium-based photocatalysts have been reported thus far.\(^7\)

In this communication, we wish to report a suspension polymerization protocol to access an immobilized iridium-based polypyridyl complex, and its evaluation, as a heterogeneous visible light photocatalyst, by examining the aerobic phosphorylation reaction of N-aryl tetrahydroisoquinoline derivatives.

Based on our interests in the CDC reaction of tertiary amines,\(^6c,8\) and Stephenson’s initial report on the use of an iridium-based photocatalyst for the oxidative aza-Henry reactions of N-aryl tetrahydroisoquinolines,\(^6a\) we targeted Ir(ppy)\(_2\)(dtbbpy)PF\(_6\) (ppy: 2-phenylpyridyl, dtbbpy: 4,4’-di-tert-butyl-2,2’-dipyridyl) for immobilization. Our strategy involved the synthesis of Ir(ppy)\(_2\)(dtbbpy)PF\(_6\) (ppy: 2-(4-vinylphenyl)pyridyl) (1), with the assumption that the introduction of the aliphatic substituent would not adversely affect the photocatalytic activity of the immobilized iridium complex (Scheme 1).

The synthesis of the photoredox active monomer 1 began with the preparation of 2-(4-vinylphenyl)pyridine via a Suzuki-Miyaura cross-coupling reaction.\(^9\) Following the literature procedure for the synthesis of Ir(ppy)\(_2\)(dtbbpy)PF\(_6\),\(^10\) the desired polypyridyl iridium complex 1 was obtained, albeit with some impurities that could not be separated. Despite this setback, the crude 1 was subjected to the heterogeneous radical polymerization process, with the understanding that the impurities would not be immobilized, with various well-established monomeric feedstocks (Scheme 2).

Our initial suspension polymerization protocol was based on our previously reported conditions,\(^11\) with a small modification with respect to the solvent choice. In general, these cationic iridium-based photocatalysts are soluble in solvents that are often miscible with water, thus unsuitable for suspension polymerization. Chlorinated solvents were found to dissolve 1 well, but inhibited...
Scheme 1 Synthesis of monomeric iridium complex 1 based on Ir(ppy)$_2$(dtbbpy)PF$_6$.

Scheme 2. Immobilization of monomer 1 via suspension polymerization.

Table 1. Evaluation of immobilized visible light photocatalysts$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Monomer</th>
<th>Amount of Monomer</th>
<th>Yield of Photocatalyst</th>
<th>Ir leaching</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3a</td>
<td>0.0590</td>
<td>74</td>
<td>1.0</td>
</tr>
<tr>
<td>2</td>
<td>3b</td>
<td>0.0586</td>
<td>83</td>
<td>2.1</td>
</tr>
<tr>
<td>3</td>
<td>3c</td>
<td>0.0523</td>
<td>90</td>
<td>0.9</td>
</tr>
<tr>
<td>4$^f$</td>
<td>3d</td>
<td>0.0255</td>
<td>92</td>
<td>0.3</td>
</tr>
</tbody>
</table>

$^a$ Reaction conditions: amine 4a (0.25 mmol), phosphite 5a (0.25 mmol), PS-Ir 3 (0.0025 mmol, 1 mol%) in MeOH (0.8 mL) at room temperature for 12 h under a balloon of dry air and 7.1 W white LED illumination.

$^b$ Ir levels were determined by inductive coupled plasma (ICP) analysis of the acid-digested PS-Ir 3.

$^c$ Yield based on 4a and determined by $^1$H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard.

$^d$ Ir levels were determined by ICP analysis of the crude reaction filtrate.

$^e$ PS-Ir 3c was subjected to the polymerization protocol with 2c.

$^f$ The reaction time was extended to 14 h.

the radical polymerization reaction. Fortuitously, benzo trifluoride (BTF), known as an excellent solvent for radical reactions,$^{12}$ was found to be the most suitable solvent for our immobilization efforts. With a polymerization protocol in hand, various monomers were utilized to immobilize 1, and these heterogeneous cross-linked copolymers 3 were evaluated as catalysts for the aerobic CDC reaction of N-phenyl tetrahydroisoquinoline (4a) with diethyl phosphate (5a) (Table 1).$^{13}$

We found that the performance of the immobilized photocatalysts was affected by the monomer choice for the visible light-mediated CDC reaction, with the acrylate-based cross-linked copolymer 3c providing the best results (entries 1-3). However, when we evaluated the effectiveness of our immobilization strategy, we found that small amounts of iridium leaching occurred. We hypothesized that an additional layer of polymer might help minimize metal leaching, and when we subjected 3c to the radical polymerization process with 2c, we found that the resulting polymer-supported iridium photocatalyst 3d was an effective photocatalyst for the aerobic phosphorylation reaction with lower levels of iridium leaching (entry 4).

Next, we examined the substrate scope of the visible light-mediated aerobic CDC reaction of N-aryl tetrahydroisoquinolines 4a-e with various phosphites 5a-d and secondary phosphate oxides 5e-j (Table 2). We initially examined various N-aryl tetrahydroisoquinolines (4a-e) and found that the substituents on the aromatic ring influenced the CDC reaction (entries 1-5). In particular, we found that the strong electron-donating methoxy group caused the oxidative coupling reaction to become sluggish, and longer reaction time and a high catalyst loading were required for complete conversion of 4c (entry 3). On the other hand, when halogen-substituted tertiary amines 4d-e were utilized as substrates, side-product formation caused decrease in the overall yields of the desired CDC adducts (entries 4-5). We then examined various aliphatic phosphites 5a-d as nucleophiles, and found that with the exception of the more bulky disopropyl phosphate (5d), the yields of the desired oxidative coupled products were excellent (entries 6-8). We also utilized our immobilized Ir photocatalyst 3d for the CDC-type reaction using secondary phosphate oxides 5e-j as P-based nucleophiles (entries 9-14). In general, the phosphate oxides were found to be excellent partners for the aerobic coupling reactions, and good to excellent yields of the expected CDC products were obtained.

Finally, we examined the viability of recovering and reusing the cross-linked co-polymer 3d for the aerobic phosphorylation reaction. It was found that the catalyst could be reused at least four times without noticeable loss of catalytic activity with minimal levels of iridium leaching (Scheme 3).

Scheme 3. Recovery and reuse of PS-Ir 3d.

In conclusion, we successfully immobilized an iridium-based polypyridyl complex, through the use of the well-established suspension polymerization method, and demonstrated its effectiveness as a visible light photocatalyst for the aerobic CDC reaction between N-aryl tetrahydroisoquinolines and various P-H...
### Table 2. Substrate scope for the aerobic oxidative coupling reaction between N-aryl tetrahydroisoquinolines 4a-e with P-H nucleophiles 5a-j. a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar</th>
<th>R</th>
<th>Product</th>
<th>Yield (%) b</th>
<th>Entry</th>
<th>Ar</th>
<th>R</th>
<th>Product</th>
<th>Yield (%) b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>OEt</td>
<td><img src="6a.png" alt="Image" /></td>
<td>87</td>
<td>8</td>
<td>Ph</td>
<td>O'Pr</td>
<td><img src="6h.png" alt="Image" /></td>
<td>67</td>
</tr>
<tr>
<td>2</td>
<td>4-Me-C_6H_4</td>
<td>OEt</td>
<td><img src="6b.png" alt="Image" /></td>
<td>97</td>
<td>9</td>
<td>Ph</td>
<td>Ph</td>
<td><img src="6i.png" alt="Image" /></td>
<td>92</td>
</tr>
<tr>
<td>3</td>
<td>4-MeO-C_6H_4</td>
<td>OEt</td>
<td><img src="6c.png" alt="Image" /></td>
<td>87</td>
<td>10</td>
<td>Ph</td>
<td>4-Me-C_6H_4</td>
<td><img src="6i.png" alt="Image" /></td>
<td>85</td>
</tr>
<tr>
<td>4</td>
<td>4-Br-C_6H_4</td>
<td>OEt</td>
<td><img src="6d.png" alt="Image" /></td>
<td>39</td>
<td>11</td>
<td>Ph</td>
<td>4-MeO-C_6H_4</td>
<td><img src="6k.png" alt="Image" /></td>
<td>89</td>
</tr>
<tr>
<td>5</td>
<td>4-Cl-C_6H_4</td>
<td>OEt</td>
<td><img src="6e.png" alt="Image" /></td>
<td>47</td>
<td>12</td>
<td>Ph</td>
<td>4-Cl-C_6H_4</td>
<td><img src="6l.png" alt="Image" /></td>
<td>87</td>
</tr>
<tr>
<td>6</td>
<td>Ph</td>
<td>OMe</td>
<td><img src="6f.png" alt="Image" /></td>
<td>95</td>
<td>13</td>
<td>Ph</td>
<td>4-CF_3-C_6H_4</td>
<td><img src="6m.png" alt="Image" /></td>
<td>61</td>
</tr>
<tr>
<td>7</td>
<td>Ph</td>
<td>O'Bu</td>
<td><img src="6g.png" alt="Image" /></td>
<td>88</td>
<td>14</td>
<td>Ph</td>
<td>c-hexyl</td>
<td><img src="6n.png" alt="Image" /></td>
<td>77</td>
</tr>
</tbody>
</table>

a Reaction conditions: amine 4 (0.50 mmol), phosphite/phosphine oxide 5 (0.50 mmol), PS-Ir 3d (0.005 mmol, 1 mol%) in MeOH (1.6 mL) at room temperature for 14 h under a balloon of dry air and 7.1 W white LED illumination.

b Yield of isolated product 6 was based on 4.

c Reaction conditions: amine 4c (0.50 mmol), phosphite 5a (0.50 mmol), PS-Ir 3d (0.010 mmol, 2 mol%) in MeOH (1.6 mL) at room temperature for 24 h under a balloon of dry air and 7.1 W white LED illumination.

nucleophiles under visible light irradiation. The synthetic utility of this heterogeneous photocatalyst was established through the recovery and reuse studies, which showed that the catalyst could be reused up to four times without loss of reactivity. We anticipate the immobilization strategy described in this report could be easily adopted to access multitudes of heterogeneous visible light photocatalysts derived from metal polypyridyl complexes.

This work was partially supported by a Grant-in-Aid for Science Research from the Japan Society for the Promotion of Science (JSPS), the Global COE Program (Chemistry Innovation through Cooperation of Science and Engineering), The University of Tokyo, the Japan Science and Technology Agency (JST), and the Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japan.
Notes and references


