

# In-Water Dehydrative Alkylation of Ammonia and Amines with Alcohols by a Polymeric Bimetallic Catalyst

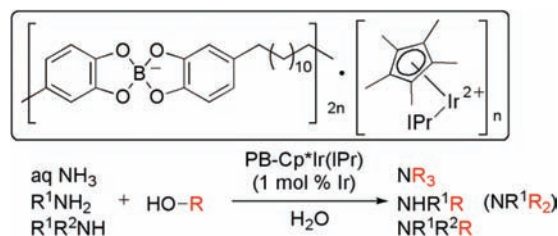
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## ABSTRACT



An in-water dehydrative alkylation with a novel heterobimetallic polymeric catalyst is described. Thus, a boron–iridium heterobimetallic polymeric catalyst was prepared by ionic convolution of a poly(catechol borate) and an iridium complex. The alkylation of ammonia and amines with alcohols, alkylating agents, was performed with 1 mol % Ir of the heterogeneous catalyst in water without the use of organic solvents under aerobic conditions to give the corresponding alkylated amines.

An in-water dehydration reaction is a paradox under equilibrium conditions, also known as “water paradox”.<sup>1</sup> But enzymes in living things promote such reactions with extremely high efficiency. For example, nucleic acids (DNA and RNA) are prepared from mononucleotides by forming phosphate ester bonds. Proteins are synthesized from amino acids by an amidation. *N*-methyltransferases are enzymes for methylation of terminal amines to form *N*-methylated amines.<sup>2</sup> Consequently, development

of enzyme-mimic catalysts for the in-water dehydration reaction system has attracted interest.<sup>3</sup> The esterification of carboxylic acids with alcohols<sup>4</sup> and the dehydrative Mannich-type reaction<sup>5</sup> are typical examples. Also, an in-water hydrogen-transfer dehydrative *N*-alkylation of amines with alcohols is a fundamental and straightforward method for the synthesis of *N*-alkylated amines as well as nitrogen-containing bioactive compounds, drug molecules, and agrochemicals.<sup>6,7</sup> In this reaction, alcohols are used as alkylating agents in place of harmful and toxic alkyl halides. Several researchers have carried out pioneering studies on the

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*N*-alkylation of amines with alcohols using a homogeneous catalyst of Ir, Ru, Rh, and Pt;<sup>8,9</sup> Madsen, Milstein, Williams, Fujita, and Yamaguchi independently developed the in-water alkylation reactions of amines with alcohols by using homogeneous catalysts.<sup>10</sup> In the development stage of this reaction, construction of an aqueous and heterogeneous<sup>11</sup> fusion system, a reaction that would satisfy green chemistry requirements, still remains a major challenge.

We previously developed a new method for the preparation of highly active and reusable polymer-supported catalysts.<sup>12</sup> In this method, a soluble linear polymer having multiple ligand groups is convoluted with neutral metals or anionic metal salts via coordinate or ionic complexation to

obtain an insoluble polymer/metal composite in a single step. We paid attention to a dicationic iridium complex and a catechol borate polymer as a heterobimetallic multifunctional catalyst;<sup>13,14</sup> An iridium species should work not only as a cross-linker of borate polymers but also as a catalytic species. A catechol borate polymer should be a main-chain polymer backbone as well as a Brønsted base. Herein, we report the preparation of a novel convoluted polymeric heterobimetallic catalyst for the in-water hydrogen-transfer dehydrative *N*-alkylation of amines with alcohols. In this catalytic system, aqueous ammonia, as well as amines, was efficiently alkylated in water under aerobic conditions.

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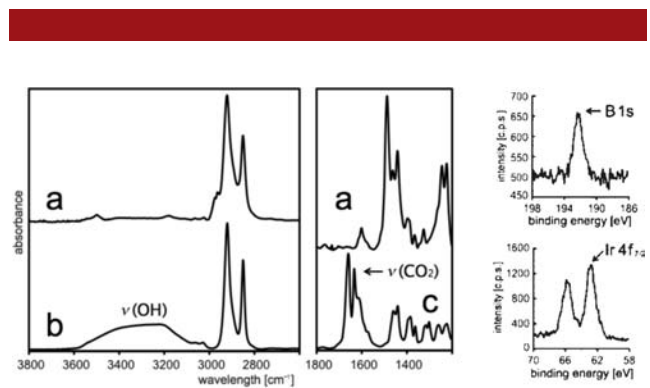
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**Figure 1.** ATR-IR spectra of **3** (line a), **1** (line b), and **2** (line c) (left), and XPS spectra of **3** (B 1s and Ir 4f<sub>7/2</sub>) (right).

A linear polymer of catechol borate **1** was prepared from 1,2-dimethoxybenzene **4** and dodecanediyl dichloride **5** in four steps (see Supporting Information).<sup>15</sup> The polymer **1** was a white powder that was soluble in DMSO, DMF, MeOH, MeCN, DME, THF, and acetone. The <sup>11</sup>B{<sup>1</sup>H} NMR spectrum of **1** in DMSO-*d*<sub>6</sub> showed a broad singlet peak that could be assigned to catechol borate at 14.7 ppm.<sup>16</sup> Self-assembly of the borate polymer and an iridium species was carried out by our convolution method based on Danjo and Yamaguchi's process of the self-assembled D<sub>3</sub>-symmetric tris(spiroborate) cyclophane–Ir complex.<sup>17</sup> Thus, an ionic convolution of **1** and Cp\*Ir(κ<sup>2</sup>-CO<sub>3</sub>)(IPr)<sup>18</sup> (**2**) (brownish orange) was carried out in a DME–MeCN mixture at 50 °C for 24 h to give **3** as a brown precipitate,

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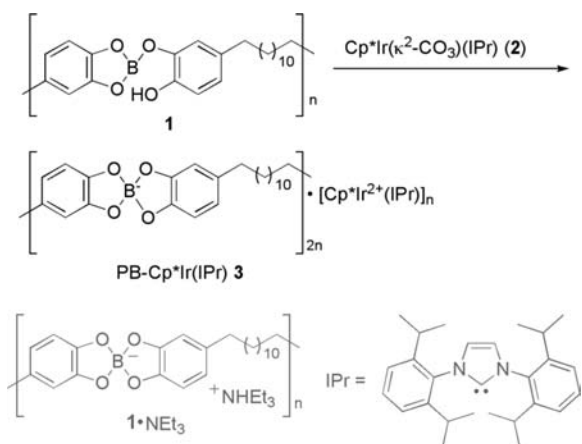
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(18) See the Supporting Information for the preparation of **2**.

which had poor solubility in H<sub>2</sub>O, MeOH, MeCN, DME, THF, Et<sub>2</sub>O, acetone, toluene, and hexane. In the ATR-IR spectrum of **3**, the absorption peaks corresponding to the hydroxy group in **1** and the carbonate group in **2** disappeared, indicating the formation of **3** (Figure 1). The XPS spectrum of **3** showed five characteristic peaks attributed to C, B, O, N, and Ir (Figures 1 and S1, Supporting Information). The B 1s binding energy in the case of **3** was 192.2 eV, which was close to that of the tetravalent ate **1**•Et<sub>3</sub>N complex (192.4 eV)<sup>19</sup> and was lower than that of the trivalent **1** (193.0 eV), indicating the formation of a tetravalent borate anion species. The Ir 4f<sub>7/2</sub> binding energy in **3** was 62.7 eV that could be assigned as an Ir(2+) species. ICP-AES analysis of **3** revealed that the loading ratio of Ir was 12.06 wt %. These results clearly indicated that the precipitate **3** comprised anionic spiroborate polymer species and dicationic Cp\*Ir<sup>2+</sup>(IPr) (IPr) species, as shown in Scheme 1. This result was also supported by elementary analysis.

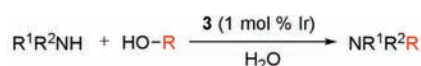
**Scheme 1.** Preparation of Ionically Convolved Poly-(spiroborate)iridium Catalyst PB-Cp\*Ir(IPr) **3**



After the successful preparation of the convoluted polymeric heterobimetallic catalyst **3**, we carried out the in-water hydrogen-transfer dehydrative alkylation of a variety of amines by using alcohols as the alkylating reagents. The reaction was carried out in water without employing additional bases, and the corresponding *N*-alkylated amines were obtained. The representative results are summarized in Table 1. Thus, the reaction of aniline (**9a**) with benzyl alcohol (**10a**) proceeded smoothly in the presence of **3** (1 mol % Ir) in water (100 °C, 24 h) to afford *N*-benzylaniline (**11a**) in 85% yield (entry 1). It is noteworthy that the reaction was carried out under aerobic conditions. The reaction of electron-rich (entries 2 and 3) and electron-poor (entries 4 and 5) anilines **9b–e** with **10a** was carried out under similar conditions to afford the corresponding *N*-alkylated anilines **11b–e** in 63–93% yield. Alkylation of 1-naphthylamine (**9f**) with **10a** afforded *N*-benzylated amine **11f** in 89% yield (entry 6). The catalyst was recovered by decantation, and ICP-AES

(19) See the Supporting Information for the preparation of **1**•NEt<sub>3</sub>.

**Table 1.** In-Water Dehydrative *N*-Alkylation of Amines with Alcohols Promoted by **3**<sup>a</sup>



**9a/11a:** R<sup>1</sup> = Ph, R<sup>2</sup> = H, R = CH<sub>2</sub>Ph  
**9b/11b:** R<sup>1</sup> = 2-MeC<sub>6</sub>H<sub>4</sub>, R<sup>2</sup> = H, R = CH<sub>2</sub>Ph  
**9c/11c:** R<sup>1</sup> = 4-MeOC<sub>6</sub>H<sub>4</sub>, R<sup>2</sup> = H, R = CH<sub>2</sub>Ph  
**9d/11d:** R<sup>1</sup> = 4-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>, R<sup>2</sup> = H, R = CH<sub>2</sub>Ph  
**9e/11e:** R<sup>1</sup> = 3-ClC<sub>6</sub>H<sub>4</sub>, R<sup>2</sup> = H, R = CH<sub>2</sub>Ph  
**9f/11f:** R<sup>1</sup> = 1-naphthyl, R<sup>2</sup> = H, R = CH<sub>2</sub>Ph  
**9a/11g:** R<sup>1</sup> = Ph, R<sup>2</sup> = H, R = CH<sub>2</sub>C<sub>6</sub>H<sub>4</sub>-2-Me  
**9a/11h:** R<sup>1</sup> = Ph, R<sup>2</sup> = H, R = CH<sub>2</sub>C<sub>6</sub>H<sub>4</sub>-4-OMe  
**9a/11i:** R<sup>1</sup> = Ph, R<sup>2</sup> = H, R = CH<sub>2</sub>C<sub>6</sub>H<sub>3</sub>-3,5-(OMe)<sub>2</sub>  
**9a/11j:** R<sup>1</sup> = Ph, R<sup>2</sup> = H, R = CH<sub>2</sub>C<sub>6</sub>H<sub>4</sub>-4-Cl  
**9f/11k:** R<sup>1</sup> = 1-naphthyl, R<sup>2</sup> = H, R = *n*-C<sub>8</sub>H<sub>17</sub>  
**9g/11l:** R<sup>1</sup> = PhCH<sub>2</sub>, R<sup>2</sup> = H/PhCH<sub>2</sub>, R = CH<sub>2</sub>Ph  
**9h/11l:** R<sup>1</sup> = PhCH<sub>2</sub>, R<sup>2</sup> = PhCH<sub>2</sub>, R = CH<sub>2</sub>Ph  
**9i/11m:** morpholine/*N*-benzyl morpholine  
**9j/11n:** 4-piperidinemethanol/*N*-benzyl 4-piperidinemethanol

entry	amine <b>9</b>	<b>10</b> (R)	product <b>11</b>	yield [%] <sup>b</sup>
1	PhNH <sub>2</sub> ( <b>9a</b> )	<b>10a</b> (PhCH <sub>2</sub> )	<b>11a</b>	85
2	2-MeC <sub>6</sub> H <sub>4</sub> NH <sub>2</sub> ( <b>9b</b> )	<b>10a</b>	<b>11b</b>	80
3	4-MeOC <sub>6</sub> H <sub>4</sub> NH <sub>2</sub> ( <b>9c</b> )	<b>10a</b>	<b>11c</b>	63
4	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> NH <sub>2</sub> ( <b>9d</b> )	<b>10a</b>	<b>11d</b>	92
5	3-ClC <sub>6</sub> H <sub>4</sub> NH <sub>2</sub> ( <b>9e</b> )	<b>10a</b>	<b>11e</b>	93
6	1-naphNH <sub>2</sub> ( <b>9f</b> )	<b>10a</b>	<b>11f</b>	89
7 <sup>c</sup>	<b>9f</b>	<b>10a</b>	<b>11f</b>	87
8 <sup>d</sup>	<b>9f</b>	<b>10a</b>	<b>11f</b>	87
9	<b>9a</b>	<b>10b</b> (2-MeC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> )	<b>11g</b>	79
10	<b>9a</b>	<b>10c</b> (4-MeOC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> )	<b>11h</b>	78
11	<b>9a</b>	<b>10d</b> (3,5-diMeOC <sub>6</sub> H <sub>3</sub> CH <sub>2</sub> )	<b>11i</b>	83
12	<b>9a</b>	<b>10e</b> (4-ClC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> )	<b>11j</b>	86
13	<b>9f</b>	<b>10f</b> ( <i>n</i> -C <sub>8</sub> H <sub>17</sub> )	<b>11k</b>	86
14 <sup>e,f</sup>	PhCH <sub>2</sub> NH <sub>2</sub> ( <b>9g</b> )	<b>10a</b>	<b>11l</b>	83
15 <sup>e</sup>	(PhCH <sub>2</sub> ) <sub>2</sub> NH ( <b>9h</b> )	<b>10a</b>	<b>11l</b>	83
16 <sup>e</sup>	<b>9i</b>	<b>10a</b>	<b>11m</b>	83
17 <sup>e</sup>	<b>9j</b>	<b>10a</b>	<b>11n</b>	61

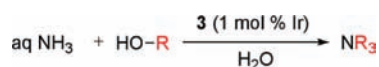
<sup>a</sup> All reactions were carried out using **9** (0.5 mmol), **10** (0.6 mmol), and **3** (1 mol % Ir) in water (0.5 mL) at 100 °C for 24 h under aerobic conditions. <sup>b</sup> Isolated yield. <sup>c</sup> Second use of **3**. <sup>d</sup> Third use of **3**. <sup>e</sup> 150 °C, microwave in pH 4 buffer aqueous solution in a sealed tube. <sup>f</sup> **10** (2.5 mmol).

analysis indicated 95% recovery of the Ir species.<sup>20</sup> The recovered catalyst was reused twice without loss of activity to afford **11f** in stable chemical yield (second use: 87%, third use: 87%; entries 7–8). Substituted benzylic alcohols were found to be suitable alkylating agents for this reaction. Thus, the reaction of **9a** with 2-methylbenzyl, 4-methoxybenzyl,

(20) In the reaction mixture, iridium species were detected (0.008%; ICP-AES analysis).

4-chloro, and 3,5-dimethoxybenzyl alcohols **10b–e** afforded the corresponding *N*-alkylated amines **11g–j** in 78–86% yield (entries 9–12). The alkylation of **9f** with a less reactive aliphatic alcohol **10f** under similar conditions also proceeded smoothly to afford an octylated amine **11k** in 86% yield (entry 13). When the reaction of an aliphatic primary amine **9g** was carried out in a pH 4 standard buffer aqueous solution under microwave conditions in a sealed tube, the alkylation proceeded to give tribenzylamine (**11l**) in 83% yield (entry 14).<sup>21</sup> The reaction of an aliphatic secondary amine **9h** also gave **11l** in 83% yield (entry 15). An alicyclic amine **9i** was also reacted under similar conditions to afford *N*-benzyl morpholine (**11m**) in 83% yield. *N*-Benzyl 4-piperidine-methanol (**11n**), a substrate for the synthesis of an Alzheimer's disease drug Aricept (donepezil hydrochloride),<sup>22</sup> was given from 4-piperidinemethanol **9j** in 61% yield (entry 17).

**Table 2.** In-Water Dehydrative *N*-Alkylation of Aqueous Ammonia Promoted by **3**<sup>a</sup>



entry	<b>10</b> (R)	product <b>11</b>	yield [%] <sup>b</sup>
1	<b>10a</b> (PhCH <sub>2</sub> )	<b>11l</b>	84
2	<b>10c</b> (4-MeOC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> )	<b>11o</b>	76
3	<b>10e</b> (4-ClC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> )	<b>11p</b>	93
4 <sup>c</sup>	<b>10g</b> (4-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> )	<b>11q</b>	95
5	<b>10h</b> (4-MeC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> )	<b>11r</b>	68

<sup>a</sup> All reactions were carried out using **9** (0.5 mmol), **10** (3.4 mmol), and **3** (1 mol % Ir) in pH 4 buffer aqueous solution (0.5 mL) at 150 °C for 24 h under microwave conditions in a sealed tube under air. <sup>b</sup> Isolated yield. <sup>c</sup> 48 h.

Furthermore, the catalyst was applied to the in-water reaction of aqueous ammonia as a substrate (Table 2).

(21) The reaction in water at 100–150 °C without the use of a microwave was sluggish.

(22) Abe, T.; Haga, T.; Negi, S.; Morita, Y.; Takayanagi, K.; Hamamura, K. *Tetrahedron* **2001**, *57*, 2701.

Aqueous ammonia is less reactive than other amines, so the in-water alkylation of ammonia with alcohols is challenging. Recently, Yamaguchi and Fujita et al. reported the reaction of aqueous ammonium with alcohols by homogeneous catalysts in water.<sup>10c</sup> Milstein et al. reported the preparation of amines from alcohols and NH<sub>3</sub> gas (7.5 atm) by a homogeneous ruthenium complex in toluene and water.<sup>10b</sup> Beller<sup>23</sup> and Vogt<sup>24</sup> reported amination of alcohols with liquid ammonia in organic solvents. We were pleased to find that the reaction of aq. NH<sub>3</sub> and benzyl alcohol (**10a**) proceeded in the presence of the heterogeneous catalyst **3** (1 mol % Ir) in a pH 4 standard buffer aqueous solution under microwave conditions to give tribenzyl amine (**11l**) in 84% yield (entry 1). The reaction with both electron-sufficient and -deficient (methoxy, chloro, trifluoromethyl, and methyl) benzylic alcohols was also carried out under the similar conditions to afford the corresponding tribenzylic amines **11o–r** in 68–95% yield (entries 2–5).

In conclusion, we have developed a convoluted polymeric novel heterobimetallic iridium boron catalyst that promoted the in-water alkylation of amines, in particular aqueous ammonia, with alcohols without the use of organic solvents under aerobic conditions to meet green chemical requirements.

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**Supporting Information Available.** Experimental details and NMR data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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