



## Iridium-catalyzed formylation of amines with paraformaldehyde

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### ARTICLE INFO

#### Article history:

Received 10 June 2010

Revised 2 August 2010

Accepted 31 August 2010

Available online 6 September 2010

### ABSTRACT

Amines have been formylated using aqueous formaldehyde or paraformaldehyde and the iridium catalyst  $[\text{Cp}^*\text{IrI}_2]_2$ . Paraformaldehyde acts as both a formylating agent and an oxidant.

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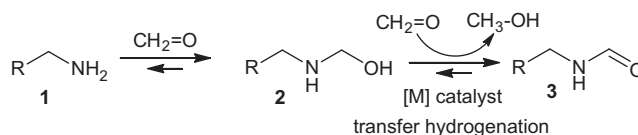
Formamides are an important class of intermediate in organic synthesis which have been widely used as amine-protecting groups<sup>1</sup> and as precursors to isocyanides,<sup>2</sup> formamides<sup>3</sup> and heterocycles.<sup>4</sup> They have found many other applications including their use as reagents in Vilsmeier formylation<sup>5</sup> and as Lewis base catalysts.<sup>6</sup> The formylation of amines is usually performed by reaction of the amine with either formic acid or its derivatives. The direct reaction of amines with formic acid can be achieved in the absence of catalyst,<sup>7</sup> although there are many catalyzed variants of the process.<sup>8</sup> Formic anhydrides,<sup>9</sup> formate salts,<sup>10</sup> formate esters<sup>11</sup> and *N,N*-dimethylformamide<sup>12</sup> have all been used for the conversion of amines into formamides.

We reasoned that an alternative approach to the formylation of amines would be achieved by using formaldehyde or its precursors with a suitable hydrogen transfer catalyst, as outlined in Scheme 1. The favourable equilibrium between amine **1** with formaldehyde to give a hydroxymethylamine **2** is well known,<sup>13</sup> although subsequent reactions including trimerization can occur. However, in the presence of a hydrogen transfer catalyst, the relatively unstable formaldehyde should readily accept hydrogen from the hydroxymethylamine which has a strong driving force to form the stable formamide **3**.

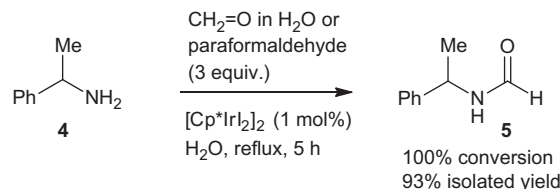
We recently reported the use of the SCRAM catalyst<sup>TM</sup>,<sup>14</sup>  $[\text{Cp}^*\text{IrI}_2]_2$ , for the alkylation of amines and sulfonamides by alcohols in an aqueous environment.<sup>15</sup> The iridium catalyst is an effective transfer hydrogenation catalyst that we have used in several other applications.<sup>16</sup> The use of heterogeneous catalysts for the *N*-formylation of amines by methanol in the presence of a suitable oxidant has been reported.<sup>17</sup> In addition, there have been several more general approaches to amide formation by oxidative coupling of amines with alcohols.<sup>18</sup> Beller and co-workers reported the rho-

dium-catalyzed conversion of aldehydes and amine into amides along with the reductive amination product.<sup>19</sup> The amidation of aldehydes with amines has been reported with various lanthanide catalysts.<sup>20</sup>

As a test reaction we chose the formylation of 1-phenethylamine (**4**) to give the formamide **5**. Water was found to be the ideal solvent, with no product formation observed when the reaction was attempted in THF or toluene. Initial studies revealed that the use of a formaldehyde solution in water (37 wt %) or paraformaldehyde gave essentially indistinguishable results, and we chose to use paraformaldehyde in further investigations. Thus, treatment of amine **4** with paraformaldehyde (calculated as 3 equiv of the monomer) led to complete conversion into formamide **5** after heating in water for five hours in the presence of 1 mol %  $[\text{Cp}^*\text{IrI}_2]_2$  (Scheme 2). When the reaction was performed using enantiomerically pure (*S*)-1-phenethylamine, the product was obtained in 75%



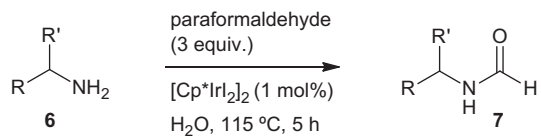
Scheme 1. Formylation of amines with formaldehyde.



Scheme 2. Formylation of 1-phenethylamine (**4**).

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**Table 1**  
Formylation of primary amines<sup>a</sup>


Entry	Formamide product	Yield <sup>b</sup> (%)
1		90
2		89
3		93
4		82 <sup>c</sup>
5		77

<sup>a</sup> Reaction conditions; 1 mol % [Cp\*IrI<sub>2</sub>]<sub>2</sub>, amine **1** (1 mmol), paraformaldehyde (3 equiv) water (2 mL), reflux, 10 h.

<sup>b</sup> Isolated yield after purification.

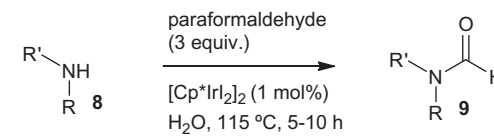
<sup>c</sup> Reaction was run for 10 h.

ee, retaining most of the original stereochemistry. This result suggests that the reversible oxidation of the amine to imine is suppressed using water as the solvent, since the same catalyst is known to effect reversible oxidation in organic solvents.<sup>14,15</sup>

Having established conditions for the complete conversion of amine **4** into formamide **5**, we investigated the use of alternative primary amines in this reaction, as detailed in Table 1. All the reactions proceeded with complete conversion as judged from the <sup>1</sup>H NMR spectra, and good isolated yields were obtained after extraction of the product into ethyl acetate and purification by column chromatography.<sup>21</sup> The benzylamine in entry 4 required a longer reaction time in order to achieve complete conversion, and aniline, *p*-toluenesulfonamide and amides were not formylated under these conditions. Nevertheless, we were pleased to find that the iridium catalyst was able to withstand the hostile conditions of formaldehyde in water for the formylation of simple amines.

We also investigated the formylation of secondary amines, and again found that the corresponding formamides were generally formed in good yields. Even *N*-benzylisopropylamine (Table 2, entry 3) was found to be reactive, despite the steric bulk of this substrate. Additionally, it was interesting to note that indoline (Table 2, entry 7) underwent formylation even though primary anilines were unsuccessful and the acyclic secondary aniline (Table 2, entry 8) gave a significantly lower yield. Tribenzylamine was recovered unreacted when exposed to these reaction conditions.

We briefly investigated the use of other aldehydes and found that enolizable aldehydes led to a complex mixture consistent with aldol/Mannich reaction products. In the case of benzaldehyde, the reaction with primary amines led to the formation of the corre-

**Table 2**  
Formylation of secondary amines<sup>a</sup>


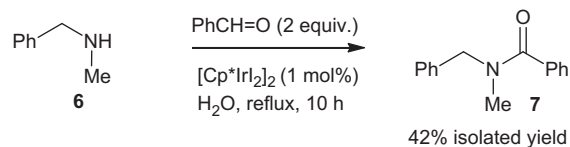
Entry	Formamide product	Yield (%) <sup>b</sup>
1		73 <sup>c</sup>
2		95 <sup>c</sup>
3		78 <sup>c</sup>
4		41 <sup>d</sup>
5		65 <sup>d</sup>
6		41 <sup>d</sup>
7		91 <sup>d</sup>
8		46 <sup>d</sup>

<sup>a</sup> Reaction conditions; 1 mol % [Cp\*IrI<sub>2</sub>]<sub>2</sub>, amine **1** (1 mmol), water (2 mL), reflux, 10 h.

<sup>b</sup> Isolated yield after purification.

<sup>c</sup> Reaction was run for 5 h.

<sup>d</sup> Reaction was run for 10 h.

**Scheme 3.** Attempted reaction of a secondary amine with benzaldehyde.

sponding imines and further oxidation to benzamides was not observed. However, the reaction of benzaldehyde with *N*-benzylmethylamine (**6**) did lead to the formation of some tertiary benzamide product **7** (Scheme 3), although the reaction was much

slower than when using formaldehyde and the crude reaction mixture contained unidentified impurities. These findings are consistent with the lower reactivity of benzaldehyde towards reduction and the relative ease of elimination of water to form an imine.

In summary, formaldehyde and paraformaldehyde have been used as formylating agents for a range of amines using an iridium catalyst in water.

### Acknowledgements

We thank the EPSRC and GlaxoSmithKline for funding.

### Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.tetlet.2010.08.106](https://doi.org/10.1016/j.tetlet.2010.08.106).

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- Typical procedure for the formylation of 1-phenylethylamine (4) with paraformaldehyde.* To a nitrogen-purged carousel tube was added [Cp\*Ir]<sub>2</sub> (0.01 mmol, 11.6 mg), 1-phenylethylamine (1 mmol, 127 μL), paraformaldehyde (3 mmol, 90 mg) and deionised H<sub>2</sub>O (2 mL). The reaction was heated to reflux (external temperature 115 °C) for 5 h, then cooled down to room temperature. The crude mixture was extracted three times with EtOAc (3 × 5 mL), dried over MgSO<sub>4</sub>, concentrated in vacuo and then purified by flash chromatography eluting with hexane then (DCM/ MeOH; 98:2) to give a colourless oil (139 mg, 93%).