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# Selective Alkylation of (Hetero)Aromatic Amines with Alcohols Catalyzed by a Ruthenium Pincer Complex

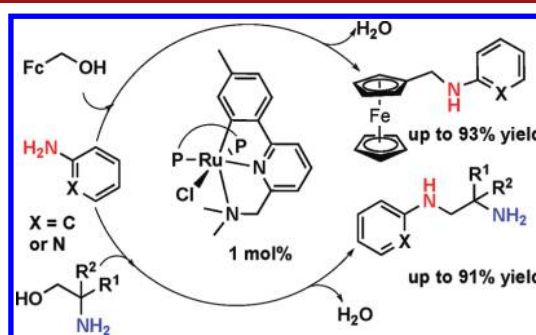
Santosh Agrawal, Maud Lenormand, and Belén Martín-Matute\*

Department of Organic Chemistry, The Arrhenius Laboratory, Stockholm University,  
SE 106 91 Stockholm, Sweden

belen@organ.su.se

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## ABSTRACT



A readily available pincer ruthenium(II) complex catalyzes the selective monoalkylation of (hetero)aromatic amines with a wide range of primary alcohols (including pyridine-, furan-, and thiophene-substituted alcohols) with high efficiency when used in low catalyst loadings (1 mol %). Tertiary amine formation *via* polyalkylation does not occur, making this ruthenium system an excellent catalyst for the synthesis of *sec*-amines.

Aromatic amines are important building blocks used in the synthesis of a wide range of pharmaceuticals, agrochemicals and bioactive molecules.<sup>1</sup> They also play an important role in organometallic and coordination chemistry.<sup>2</sup> The alkylation of amines with alcohols to give higher order amines and water as sole byproduct is a very attractive and environmentally friendly alternative to other methods, such as alkylation of amines by alkyl halides under basic conditions,<sup>3</sup> hydroamination of alkenes<sup>4</sup> or reductive

amination of carbonyl compounds.<sup>5</sup> The principle governing the use of alcohols as alkylating reagents involves their oxidation by a transition metal complex; after *in situ*

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reaction with an amine, the imine formed is reduced by the transition metal hydride formed in the first step, yielding a higher order amine.<sup>6</sup> Since the early 80s, transition metal complexes,<sup>7–18</sup> in particular iridium and ruthenium, have been shown to be active for this transformation. We have recently used this method to synthesize nitrogen-containing pseudodisaccharides.<sup>16</sup> In general, iridium<sup>8e,13,14,18</sup> complexes are more reactive than ruthenium-based catalysts, making possible the use of iridium loadings as low as 0.1 mol %.<sup>18e</sup> Recently, Williams, Beller and co-workers<sup>8f</sup> were able to obtain good yields in the *N*-alkylation of indoles by using 0.2–0.5 mol % of the dimeric Shvo's ruthenium catalyst (0.4–1 mol % Ru) at 110 °C. Also, Madsen and co-workers reported an elegant synthesis of substituted indoles using readily available RuCl<sub>3</sub> (1 mol %) at 170 °C.<sup>15b</sup> Williams also reported that small loadings of [Ru(*p*-cymene)Cl<sub>2</sub>]<sub>2</sub> (1 mol % Ru) afford excellent results in the *N*-alkylation of *sec*-amines, forming *tert*-amines.<sup>8c</sup>

Baratta and co-workers have communicated that Ru(II)-CNN (C = carbon; N = nitrogen) pincer complex **1** affords impressive TONs ( $1.7 \times 10^5$ ) in the reduction of ketones under hydrogen transfer conditions.<sup>19</sup> However,

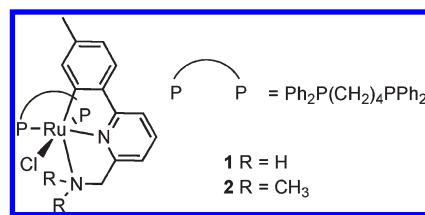


Figure 1. CNN-Ruthenium complexes **1** and **2**.

neither **1** nor the methylated derivative complex **2** have been used in the reduction of imines. Here, we communicate that the readily available Ru(II)-CNN pincer complex **2** (Figure 1) is, however, an excellent catalyst for the alkylation of amines by alcohols, which is thought to proceed by reduction of imine intermediates. Ruthenium complex **2** catalyzes the alkylation of anilines and heteroaromatic amines by alcohols (including pyridine-, furan-, and thiophene-substituted alcohols) with high efficiency, using low catalyst loadings (1 mol %). A large substrate scope is demonstrated, and products derived from polyalkylation are not detected, making this ruthenium system an excellent catalyst for the synthesis of *sec*-amines.

Aniline (**3a**) and benzyl alcohol (**4**) were chosen as model substrates. In the presence of K<sub>2</sub>CO<sub>3</sub> (30 mol %), neither **1** nor **2** (2.5 mol %) afforded the desired product in good yield. However, when KO*t*-Bu was used instead of K<sub>2</sub>CO<sub>3</sub>, complex **2** catalyzed the formation of amine **5** in excellent yield, while only moderate yields were obtained with **1**. This is in high contrast with the results obtained by Baratta and co-workers, who found complex **1** to be significantly more reactive than **2** in the reduction of ketones under hydrogen transfer conditions.<sup>19</sup> Further optimization allowed us to use catalyst loadings as low as 1 mol % when combined with stoichiometric amounts of KO*t*-Bu (Scheme 1a, and Table S1, Supporting Information). Similarly, 2-amino pyridine **6a** gave the corresponding alkylated amine (**7**) in quantitative yield (91% isolated, Scheme 1b). In all cases, higher yields were obtained when MS 4 Å were added to the reaction mixture.

Having established the optimal reaction conditions we turned our attention to the use of a ferrocenyl-substituted alcohol (**8**) as alkylating reagent. Quantitative yields of the corresponding *sec*-amines were obtained from a range of substituted anilines (**3a–f**) as well as heteroaromatic amines (**6a–c**) with different electronic properties (Scheme 2). The secondary amines obtained (**9a–f**, **10a–c**) were isolated in good to excellent yields.

The catalyst system [Ru **2** (1 mol %)/KO*t*-Bu] is highly selective and yielded monoalkylated products exclusively, even when excess of alcohol was used (see Supporting Information). Hence, it was of interest to explore whether diamines could be *N,N'*-dialkylated (i.e., introduction of one substituent on each nitrogen). Few reports on the synthesis of such types of compounds are available in the literature,<sup>20</sup> and most of them yield a mixture of products

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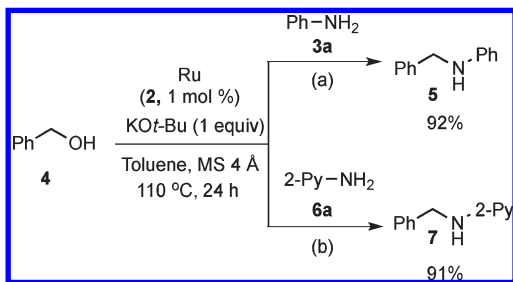
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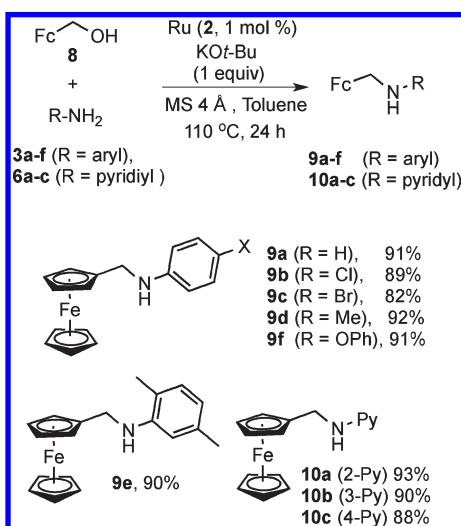
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**Scheme 1.** Ru (**2**) Catalyzed Alkylation of **3a** and **6a** by Alcohol **4**<sup>a</sup>



<sup>a</sup> Isolated yields.

**Scheme 2.** *N*-Alkylation of Anilines and Heteroaromatic Amines<sup>a</sup>



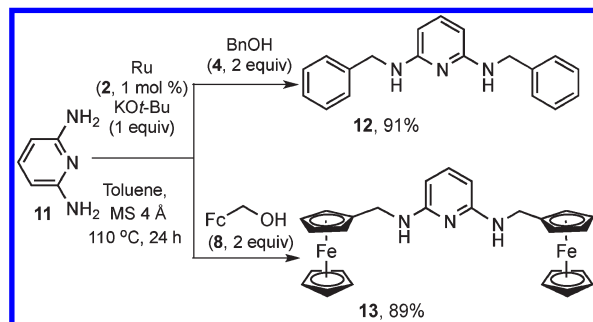
<sup>a</sup> Isolated yields.

due to mono, di, tri and tetra-alkylation. When 2,6-diamino pyridine **11** was treated with either alcohol **4** or **8** (2 equiv) in the presence of complex **2** (1 mol %) and KOt-Bu (1 equiv), *N,N'*-dialkylation took place exclusively, affording diamines **12** and **13**, respectively, in excellent yields (Scheme 3). Interestingly, although two C–N bonds are formed, the catalyst loading could be kept as low as 1 mol %.

The use of heteroaromatic alcohols as latent electrophiles is also a challenging goal. Kempe and co-workers<sup>18a</sup> have reported that their iridium-based catalyst afforded from moderate to low yields of higher order amines when using alcohols such as furfuryl alcohol (**14**) or 2-thiophenemethanol (**15**). Ruthenium complex **2** is highly active when heteroaromatic alcohols are used as alkylating reagents. Table 1 shows the results obtained in the *N*-alkylation of aniline **3a** and heteroaromatic amine **6a** by heteroaromatic

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**Scheme 3.** Selective Mono *N,N'*-Dialkylation of **11**<sup>a</sup>



<sup>a</sup> Isolated yields.

**Table 1.** *N*-Alkylation of **3a** and **6a** by Heteroaromatic Alcohols **14–16**<sup>a</sup>

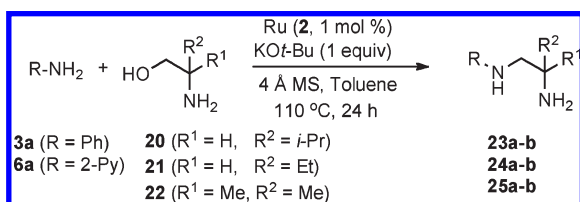
entry	amine/alcohol	product	yield (%) <sup>b</sup>
1	<b>3a</b> / <b>14</b>	<b>17a</b>	86
2	<b>3a</b> / <b>15</b>	<b>18a</b>	83
3	<b>3a</b> / <b>16</b>	<b>19a</b>	74
4	<b>6a</b> / <b>14</b>	<b>17b</b>	81
5	<b>6a</b> / <b>15</b>	<b>18b</b>	81
6	<b>6a</b> / <b>16</b>	<b>19b</b>	71

<sup>a</sup> All reactions were carried out using Ru (**2**, 4 mg, 1 mol %), amine (0.5 mmol), alcohol (0.5 mmol), MS 4 Å, KOt-Bu (0.5 M in THF, 1 mL, 0.5 mmol) in dry toluene (0.5 mL), 24 h, 110 °C. <sup>b</sup> Isolated yield.

alcohols [i.e., furfuryl alcohol (**14**), 2-thiophenemethanol (**15**) and 2-pyridinemethanol (**16**)] using 1 mol % of Ru complex **2**. The *sec*-amines obtained were isolated in good yields (71–86%).

We also tested the alkylation of amines such as benzylamine and hexylamine under the optimized reaction conditions. However, these substrates afforded the products in trace amounts. Neither the use of amines that cannot be oxidized to imines (e.g., 1-*tert*-octylamine) gave the desired product (see Supporting Information, Table S2). On the other hand, the lack of reactivity of aliphatic amines under the reaction conditions opens the possibility of using aliphatic amino alcohols<sup>18c</sup> (**20–22**) as alkylating reagents.

**Table 2.** *N*-Alkylation of **3a** and **6a** by Heteroaromatic Alcohols **14–16**<sup>a</sup>



entry	amine/alcohol	product	yield (%) <sup>b</sup>
1	<b>3a</b> / <b>20</b>		91
2	<b>3a</b> / <b>21</b>		83
3	<b>3a</b> / <b>22</b>		80
4	<b>6a</b> / <b>20</b>		74
5	<b>6a</b> / <b>21</b>		78
6	<b>6a</b> / <b>22</b>		79

<sup>a</sup> All reactions were carried out using Ru (**2**, 4 mg, 1 mol %), amine (0.5 mmol), amino alcohol (0.5 mmol), MS 4 Å, KO*t*-Bu (0.5 M in THF, 1 mL, 0.5 mmol) in dry toluene (0.5 mL) for 24 h at 110 °C. <sup>b</sup> Isolated yield.

Indeed, reaction of aniline **3a** with amino alcohol **20** afforded *N*-arylated diamine **23a**, which was isolated in

excellent yield (Table 2, entry 1). Branched amino alcohols **21** and **22** also afforded excellent yields (entries 2–3). The reaction was also successful for the *N*-alkylation of heteroaromatic amine **6a** with amino alcohols **20–22** (Table 2, entries 4–6).

In conclusion, ruthenium **2** is able to achieve excellent results, and can be compared with those obtained with the highly reactive iridium catalysts under homogeneous conditions in the alkylation of amines with alcohols. (Hetero)aromatic amines could be alkylated with alcohols, such as ferrocenyl methanol, heteroaromatic alcohols and amino alcohols. Furthermore, selective *N,N'*-dialkylation occurred when aromatic diamines were subjected to the reaction conditions. In this way, structural variants of *N*-substituted aminoferrocenes, *N,N'*-dialkylamines and *N*-arylated diamines can be synthesized selectively in excellent yields. We are currently investigating the mechanism and our results will be communicated in due course.

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**Supporting Information Available.** Detailed experimental procedures and spectral data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.