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Ruthenium-catalysed *N*-alkylation of anilines with primary carbohydrate alcohols *via* borrowing hydrogen strategy†

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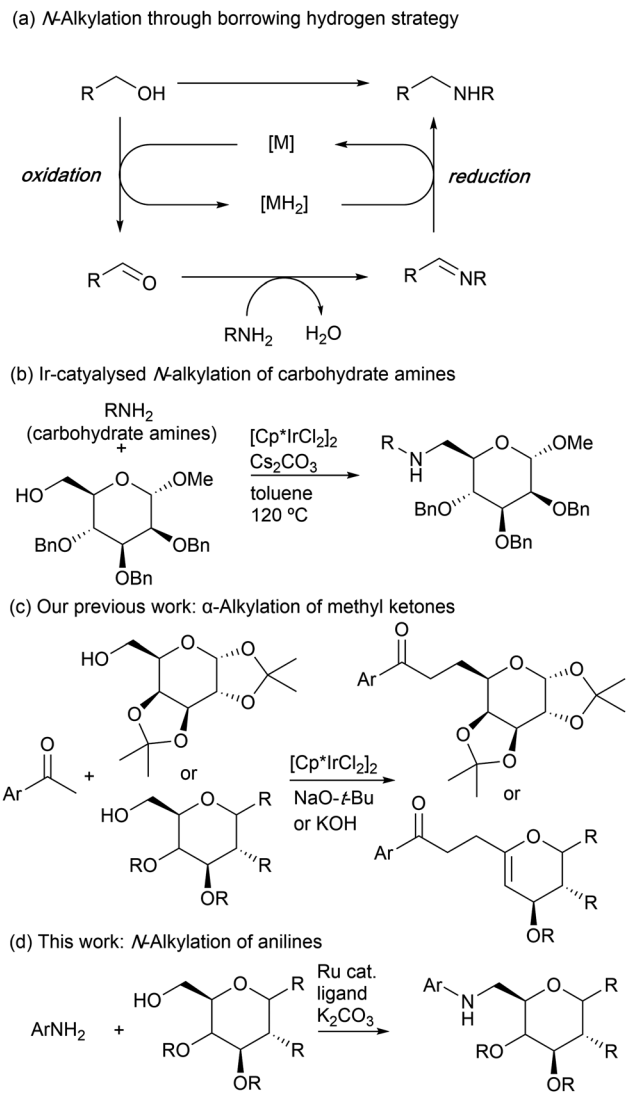
Ruthenium-catalysed *N*-alkylation of anilines with sugar derivatives proceeded *via* the borrowing hydrogen strategy. Primary carbohydrate alcohols were successfully applied to *N*-alkylation of aniline derivatives to give the corresponding aminosugars in high yields.

Transition-metal-catalysed *N*-alkylation of amines *via* the borrowing hydrogen strategy is a desirable process for the formation of carbon–nitrogen bonds, enabling alcohols to be employed directly as alkylating agents (Scheme 1a).[1] A variety of catalytic systems based on the late-transition metals have been developed for the *N*-alkylation of amines by using simple alcohols.[2–5] Biomass-derived alcohols, such as ethylene glycol, 1,3-propanediol, isohexides, and so on, have also been recognized as important reaction partners in the borrowing hydrogen strategy.[6] However, carbohydrate alcohols have been scarcely used for the direct *N*-alkylation reaction. In this respect, in 2011, Cumpstey and Martín-Matute reported the first example of *N*-alkylation of alkylamines derived from sugars with primary carbohydrate alcohols catalysed by an Ir(III) complex, where amine-linked pseudodisaccharides are successfully synthesized in a single step through borrowing hydrogen strategy (Scheme 1b).[7] In this context, we recently reported α-alkylation of methyl ketones with primary carbohydrate alcohols as alkylating agents (Scheme 1c).[8] The reaction is efficiently catalysed by an Ir(III) complex in the presence of a strong base. During our studies on the catalytic functionalization of sugar derivatives,[8,9] it was found that a ruthenium complex was effective in catalyzing the borrowing hydrogen reaction between anilines and sugars (Scheme 1d). Here we describe that a ruthenium/dppf type ligand complex efficiently



Scheme 1 Borrowing hydrogen reactions.

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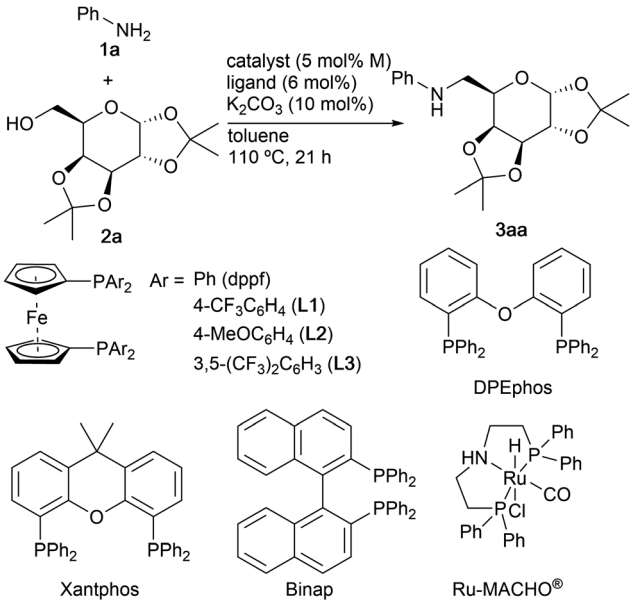
Table 1 Ruthenium-catalysed *N*-alkylation of aniline **1a** with galactopyranose **2a**[a]



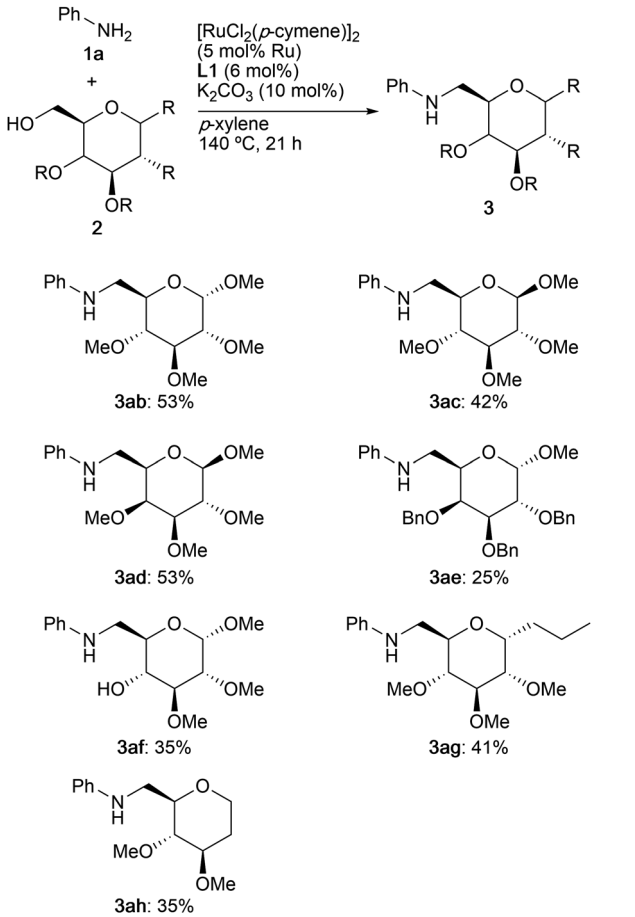
Entry	Catalyst	Ligand	Yield[b] (%)
1	$[RuCl_2(p\text{-cymene})]_2$	dppf	31
2	$[RuCl_2(p\text{-cymene})]_2$	—	0
3[c]	$[RuCl_2(p\text{-cymene})]_2$	dppf	0
4	$[RuCl_2(p\text{-cymene})]_2$	**L1**	69
5	$[RuCl_2(p\text{-cymene})]_2$	**L2**	6
6	$[RuCl_2(p\text{-cymene})]_2$	**L3**	0
7	$[RuCl_2(p\text{-cymene})]_2$	DPEphos	15
8	$[RuCl_2(p\text{-cymene})]_2$	Xantphos	6
9	$[RuCl_2(p\text{-cymene})]_2$	Binap	0
10[d]	$[RuCl_2(p\text{-cymene})]_2$	**L1**	76
11[de]	$[RuCl_2(p\text{-cymene})]_2$	**L1**	45
12[df]	$[RuCl_2(p\text{-cymene})]_2$	**L1**	53
13[dg]	$[RuCl_2(p\text{-cymene})]_2$	**L1**	87 (82)[h]
14	$[RuCl_2(benzene)]_2$	**L1**	7
15[cd]	$Ru_3(CO)_{12}$	—	0
16[d]	$Ru_3(CO)_{12}$	—	0
17[d]	Ru-MACHO®	—	0

[a] Reaction conditions: **1a** (0.24 mmol), **2a** (0.20 mmol), $[RuCl_2(p\text{-cymene})]_2$ (0.0050 mmol, 5 mol% of Ru), and base (10 mol%) in toluene (0.30 mL) at 110 °C for 21 h. [b] Determined by ^1H NMR. [c] Without K_2CO_3. [d] Performed with **1a** (0.20 mmol) and **2a** (0.24 mmol). [e] With Na_2CO_3 instead of K_2CO_3. [f] With Cs_2CO_3 instead of K_2CO_3. [g] At 140 °C in *p*-xylene. [h] Isolated yield.

catalyses *N*-alkylation of anilines with primary carbohydrate alcohols, providing a new method for the synthesis of aminosugar derivatives.[10] Aminosugars possess potential properties that take part in a variety of biological functions, and therefore, the development of the synthesis of the aminosugars is important for the understanding of their functions.[11]

Our initial studies focused on the *N*-alkylation of aniline (**1a**) with 1,2 : 3,4-di-*O*-isopropylidene-α-D-galactopyranose (**2a**) in the presence of ruthenium complexes directed toward the catalytic synthesis of aminosugar **3aa** (Table 1).[12] Treatment of **1a** (1.2 equiv.) with **2a** (1.0 equiv.) in the presence of $[RuCl_2(p\text{-cymene})]_2$ (5 mol% of Ru), dppf (6 mol%), and K_2CO_3 (10 mol%) in toluene, which is one of the reaction conditions reported by Williams and co-workers,[2c] at 110 °C for 21 h gave alkylated product **3aa** in 31% yield (entry 1). The ligand and base were necessary to obtain **3aa** (entries 2 and 3). The aryl groups on dppf ligands significantly influenced the reactivity. The use of ligand **L1** substituted with *p*-(trifluoromethyl)phenyl groups improved the yield of **3aa** up to 69% (entry 4). In contrast, methoxy-substituted **L2** diminished the yield (entry 5), and ligand **L3** inhibited the reaction, probably due to the bulkiness (entry 6). DPEphos, Xantphos, or Binap were not effective in catalyzing the present reaction (entries 7–9). The use of a slight excess (1.2 equiv.) of alcohol **2a** toward aniline (**1a**) improved the yield up to 76% (entry 10). Na_2CO_3 and Cs_2CO_3 were less effective than K_2CO_3, thus giving **3aa** in 45 and 53% yields, respectively (entries 11 and 12). The reaction in *p*-xylene at 140 °C gave **3aa** in 87% yield (entry 13). The catalytic activity of $[RuCl_2(benzene)]_2$ was quite low (entry 14). $Ru_3(CO)_{12}$[2d] and Ru-MACHO®[2j] did not work as catalysts (entries 15–17).

Scheme 2 summarizes the results obtained for the reaction of several primary carbohydrate alcohols. The reactions of *O*-methylated α-glucose **2b**, β-glucose **2c**, and β-galactose **2d** with aniline (**1a**) gave the corresponding sugars **3ab**–**3ad** in 42–53%

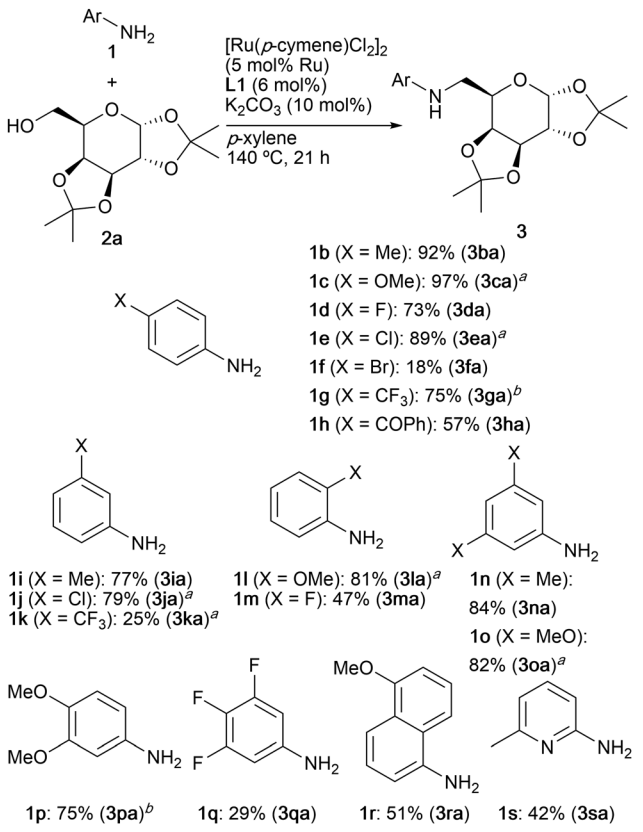


Scheme 2 Scope of carbohydrate alcohols. Reaction conditions: **1a** (0.10 mmol), **2** (0.12 mmol), $[RuCl_2(p\text{-cymene})]_2$ (0.0025 mmol, 5 mol% of Ru), **L1** (6 mol%) and K_2CO_3 (10 mol%) in *p*-xylene (0.15 mL) at 140 °C for 21 h.

yields. Alcohol **2e** having benzyl ether moieties and **2f** with a free hydroxy group reacted with **1a** to give *N*-alkylated products **3ae** and **3af** in 25% and 35% yields, respectively. The reaction of *C*-glycoside **2g** and deoxyglucose **2h** also proceeded to give the corresponding aminosugars **3ag** and **3ah**.

A variety of aniline derivatives **1** participated in the reaction with carbohydrate alcohol **2a** as summarized in Scheme 3. *N*-Alkylation of anilines having electron-donating and -withdrawing substituents (**2a**–**2m**) at the *o*-, *m*-, and *p*-positions proceeded to give the corresponding aminosugars in 18–97% yields, where anilines substituted with electron-withdrawing groups displayed the low reactivity. In particular, the loss of the catalytic activity was observed in reaction of *p*-bromoaniline (**1f**). Dimethyl (**1n**) and dimethoxyanilines (**1o** and **1p**) reacted with **2a** to give aminosugars **3na**, **3oa**, and **3pa**, respectively, in high yields. Modest yields were observed for 3,4,5-trifluoroaniline (**1q**), 5-methoxy-1-naphthylamine (**1r**), and 6-methyl-2-aminopyridine (**1s**). In sharp contrast, *N*-methylaniline or aliphatic amines such as *n*-butylamine and piperidine were not alkylated under the present reaction conditions.

In summary, we have developed ruthenium-catalysed *N*-alkylation of anilines with primary carbohydrate alcohols. A variety of aniline derivatives were applied to the reaction to give the corresponding aminosugars in high yields. Several *O*-protected sugar derivatives could be used as alkylating agents for *N*-alkylation of aniline derivatives.



Scheme 3 Scope of anilines **1**. Reaction conditions: **1** (0.10 mmol), **2a** (0.12 mmol), $[RuCl_2(p\text{-cymene})]_2$ (0.0025 mmol, 5 mol% of Ru), ligand (6 mol%), and K_2CO_3 (10 mol%) in *p*-xylene (0.15 mL) at 140 °C for 21 h. [a]0.20 mmol scale reaction. [b]For 48 h.

Conflicts of interest

There are no conflicts to declare.

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