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Ruthenium-catalyzed reductive deamination and tandem alkylation of aniline derivatives

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ABSTRACT

We developed two new catalytic transformations of anilines via oxidative addition of C–N bonds to ruthenium centers. One is ruthenium-catalyzed reductive deaminatoindeamination of *N*-alkylated *o*-acylanilines. The other one is catalytic coupling of *N*-alkylated *o*-acylanilines with olefins giving ortho-alkylated aromatic ketones via C–N bond cleavage. This reaction involves a ruthenium hydride species as an intermediate, formed after β-hydride elimination from the ruthenium amide species.

1. Introduction

Cleavage of unreactive sp^2 carbon–nitrogen bonds by transition metal complexes has been of great interest to many researchers because of its potential application in development of novel catalytic reactions as well as its relevance to hydrodenitrogenation processes [1]. Anilines are one of the most common types of compounds possessing such inert carbon–nitrogen bonds, but there have not been many successful examples of cleavage of aromatic carbon–nitrogen bonds in anilines by transition metal complexes [2–6]. As an early example, Fujiwara and coworkers found that oxidative arylation of olefins with anilines proceeds via cleavage of carbon–nitrogen bonds in the presence of a stoichiometric amount of palladium salts [2]. Direct observation of oxidative addition of aromatic carbon–nitrogen bonds via was achieved by Wolczanski and coworkers using tantalum complexes [3], and Boncella and coworkers also observed a cleavage of a carbon–nitrogen bond of an (*N*-silyl)arylamido molybdenum complex [4]. Catalytic conversion of inert sp^2 carbon–nitrogen bonds in anilines has rarely been achieved, and the carbon–nitrogen bonds in these compounds are usually activated by conversion to more reactive species such as diazonium salts [7], ammonium salts [8], triazenes [9], and hydrazines [10].

The first catalytic functionalization of unactivated carbon–nitrogen bonds in aniline derivatives was achieved by our group in 2007 [5]. In this reaction, coupling of *o*-acylanilines with organoboronates was catalyzed by $RuH_2(CO)(PPh_3)_3$ (**1**) under toluene refluxing conditions to transform carbon–nitrogen bonds into carbon–carbon bonds (Scheme 1). Our recent studies indicated that the reaction proceeded via oxidative addition of the carbon–nitrogen bonds, followed by transmetalation with arylboronates and reductive elimination [6].

Reductive deamination of aniline derivatives is an important process in organic synthesis, since amino groups show strong directing effects in electrophilic aromatic substitutions. However, simple catalytic deamination of unactivated anilines using transition metal complexes has not been reported [11]. In order to remove amino groups on the aromatic rings, anilines were normally converted to more reactive compounds such as diazonium salts and then reduced [12].

Here we report that catalytic reductive deamination of *o*-acylanilines was achieved by simply heating with a ruthenium catalyst. Tandem reductive deamination/alkylation of the aniline derivatives was also found to proceed using the ruthenium catalyst in the presence of olefins.

2. Results and discussion

When *N*,*N*-dimethyl-*o*-acylaniline **2a** was treated with 20 mol% of **1** in toluene at 120 °C for 24 h, the dimethylamino group of **2a** was converted to a hydrogen atom to form pivalophenone (**3a**) in

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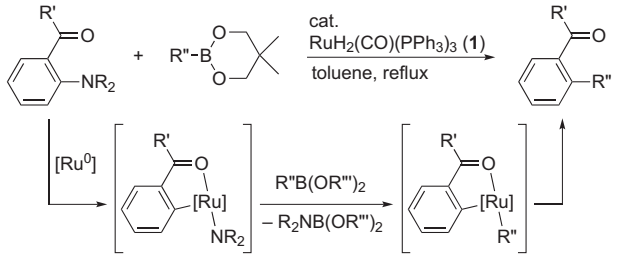


Scheme 1. Ruthenium-catalyzed coupling of *o*-acylanilines with organoboronates via carbon–nitrogen bond cleavage.

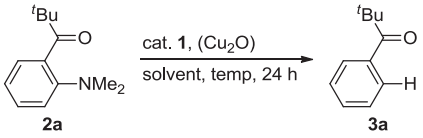
61% yield (Table 1, entry 1). Extension of the reaction time to 48 h only slightly increased the product yield to 65% (entry 2). Additives were then screened for the reaction, and cuprous oxide was found to improve the yield to 76% (entry 3). The reaction temperature was also examined, and heating in *p*-xylene at 140 °C led to significant increase of the yield to 90% (entry 4). At this temperature, addition of cuprous oxide had little effect on the yield (entry 5). Further increase of the reaction temperature to 160 °C using mesitylene as a solvent gave similar results to the reactions in *p*-xylene at 140 °C (entries 6 and 7). Lowering the catalyst loading to 10 mol% resulted in considerable decrease in the yield of **3a** (entries 8 and 9). Therefore, we chose the reaction conditions used for entry 4 for further investigation.

The ruthenium-catalyzed reductive deamination was also examined with other *o*-acylanilines (Table 2). The reaction of *N*-methyl-*o*-acylaniline **2b** gave deamination product **3a** in 68% yield (entry 1). In this case, addition of cuprous oxide did not affect the yield (entry 2), but heating at 160 °C in mesitylene increased the yield to 76% (entry 3). *N*-Isopropyl-*o*-acylaniline **2c** and pyrrolidine derivative **2d** can also be transformed into **3a** in 72% and 51% yields, respectively (entries 4 and 5). On the other hand, the reaction of *N*,*N*-dibenzyl-*o*-acylaniline **2e** resulted in the formation of **3a** in 24% yield (entry 6). The use of acetyl group as a directing group was also unsuccessful and the reaction of *N*,*N*-dimethyl-*o*-acetylaniline under the standard reaction conditions of Table 2 gave only 24% yield of acetophenone as a product.

When *p*-dimethylaminoacylaniline was reacted with catalyst **1** under the reductive deamination conditions, no formation of **3a** was observed. This result indicates that presence of an acyl group at *ortho* position to the amino group is essential to remove the amino groups.

In the presence of olefins, tandem reductive deamination/alkylation can proceed to form carbon–carbon bonds (Table 3) [13]. The reaction of **2a** with catalyst **1** in the presence of 3 equiv of trimethylvinylsilane (**4a**) gave *ortho*-alkylated pivalophenone **5a** in 73% yield along with a small amount of **3a** (entry 1). Addition of cuprous oxide resulted in decrease in the yield (entry 2). The use of 5 equiv of **4a** decreased the yield to 66% (entry 3), while reduction of the amount of **4a** to 1.5 equiv slightly increased the yield to 76% (entry 4). As one of the possibilities, we propose that the addition of olefins interferes the coordination of the aromatic ketones to the ruthenium. The yield of **5a** was not improved by performing the reaction for 48 h (entry 5). The use of 10 mol% of catalyst **1** resulted in significant lowering of the yield (entry 6). Raising of the reaction temperature to at 140 °C using *p*-xylene was effective as well for the tandem alkylation reaction, and product **5a** was obtained in 90% yield (entry 7). Lowering the catalyst loading to 10 mol% was also difficult for the reaction at 140 °C, and alkylation product **5a** was obtained in 73% yield even after 48 h (entry 8).

Table 1
Optimization of ruthenium-catalyzed deamination of *o*-acylaniline **2a**.[a]

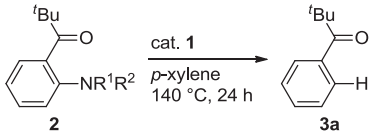


2a **3a**

Entry	Solvent	Temp (°C)	**1** (mol%)	Cu_2O	Yield (%)[b]
1	Toluene	120	20	None	61
2[c]	Toluene	120	20	None	65
3	Toluene	120	20	1 equiv	76
4	*p*-Xylene	140	20	None	90
5	*p*-Xylene	140	20	1 equiv	89
6	Mesitylene	160	20	None	93
7	Mesitylene	160	20	1 equiv	88
8	*p*-Xylene	140	10	None	61
9	*p*-Xylene	140	10	1 equiv	54

[a] Reaction conditions: **2a** (0.2 mmol), **1** (0.04 mmol), cuprous oxide (0.2 mmol, if added), solvent (0.3 mL), 24 h.
[b] GC yield.
[c] Performed for 48 h.

Table 2
Ruthenium-catalyzed deamination of *o*-acylanilines.[a]

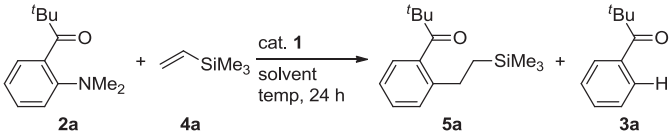


2 **3a**

Entry	**2**	R^1	R^2	Yield (%)[b]
1	**2b**	Me	H	68
2[c]	**2b**	Me	H	67
3[d]	**2b**	Me	H	76
4	**2c**	^{i}Pr	H	72
5	**2d**	$-(CH_2)_4-$		51
6	**2e**	Bn	Bn	24

[a] Reaction conditions: **2a** (0.2 mmol), **1** (0.04 mmol), *p*-xylene (0.3 mL), 140 °C, 24 h.
[b] GC yield.
[c] Performed in the presence of cuprous oxide (1 equiv).
[d] Performed in mesitylene at 160 °C.

Table 3
Optimization of ruthenium-catalyzed deamination/alkylation of *o*-acylaniline **2a**.[a]



2a **4a** **5a** **3a**

Entry	**4a** (equiv)	Solvent	Temp (°C)	Yields (%)[b]	
				5a	**3a**
1	3	Toluene	120	73	1
2[c]	3	Toluene	120	68	1
3	5	Toluene	120	66	1
4[d]	1.5	Toluene	120	76	1
5[e]	1.5	Toluene	120	74	2
6	1.5	Toluene	120	44	Trace
7	1.5	*p*-Xylene	140	90	1
8[d,e]	1.5	*p*-Xylene	140	73	Trace

[a] Reaction conditions: **2a** (0.2 mmol), **4a**, **1** (0.04 mmol), solvent (0.3 mL), 24 h.
[b] GC yield.
[c] Performed in the presence of cuprous oxide (1 equiv).
[d] Performed for 48 h.
[e] Performed with 10 mol% of **1**.