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A convenient method for the Ru(0)-catalyzed regioselective deuteration of *N*-alkyl-substituted anilines

Miao Zhan [a], Hongxia Jiang [a], Xuehai Pang [b], Tao Zhang [a], Ruixue Xu [a], Lifeng Zhao [a], Yu Liu [a], Yu Gong [b], Yuanwei Chen [a,b,*]

[a] *State Key Laboratory of Biotherapy, West China Hospital, West China Medical School, Sichuan University, Chengdu 610041, China*
[b] *Hinova Pharmaceuticals Inc, Suite 801, Building C1, #88 South KeYuan Road, Chengdu Tianfu Life Science Park, Chengdu 610041, China*

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ABSTRACT

A highly effective and operationally practical method for the regioselective deuteration of *N*-alkyl-substituted anilines employing $Ru_3(CO)_{12}$ ($\leqslant$1 mol %) as catalyst and D_2O as deuterium source was described. A variety of *N*-alkyl-substituted anilines were efficiently deuterated (up to 98%) at the *ortho* and/or *para* position with respect to the nitrogen at neutral conditions. Under the present conditions, deuterated anilines can be easily obtained with simple extraction and evaporation. Substituents with aromatic methoxy groups would not influence the selectivity compared to previous method.

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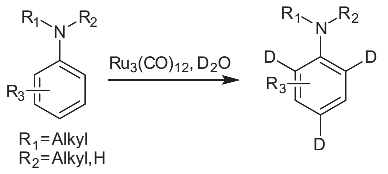
Deuterium-labeled compounds have been widely used in different branches of science including investigation of reaction mechanisms and kinetics, analysis of drug metabolism, structural elucidation of biological macromolecules, quantitative analysis of environmental pollutants and residual pesticides, optical materials, and so forth.[1] Recently, deuterated drugs have drawn great interests among pharmaceutical community.[2] Consequently, extensive researches have concentrated on the development of diverse and selective synthetic methodologies for the preparation of deuterium labeled compounds.[3]

Recently, there were many researches which focused on the deuteration of amines employing transition metals.[4] Moreover, for the preparation of deuterium labeled anilines, a number of H–D exchange procedures were reported, for instance, the H–D exchange reactions catalyzed by transition metals (Pt/C–D_2O–H_2,[5a] Pd/C–Pt/C–D_2O–H_2,[5b] $NaBD_4$–Rh/Pt/Pd,[5c] Ir,[6] and Rh[7]) or microwave enhanced metal- and acid-catalyzed[8] exchange reactions. However, these methods often suffer from low deuterium-exchange efficiency,[6,7b] high catalyst loadings and/or expensively or difficultly accessible catalysts and deuterium sources.[6,7] It is worth mentioning that Mark Lautens's group reported that anilines were efficiently deuterated at the *ortho* and/or *para* position with respect to the nitrogen in the presence of concd HCl (1 equiv) in D_2O under microwave irradiation at 180 °C.[8c] While, to achieve high levels of deuterium incorporation, the method required a large amount of D_2O (250 equiv) due to that the concd HCl would bring H_2O into the system and also basic workup was needed.

Recently, Gröll et al., reported the capability of $Ru_3(CO)_{12}$ to selectively catalyze H–D exchange of nitrogen-containing heterocycles with ^{t}BuOD as deuterium source.[4c] Also, Chatani et al., have reported that the treatment of 2-(1-pyrrolidinyl)pyridine with $Ru_3(CO)_{12}$–CO system in 2-propanol-d_8 at 140 °C showed deuterium incorporation at all positions.[9] The studies above implied that $Ru_3(CO)_{12}$ could be applied to aniline deuteration. The aim of this investigation is to study on the regioselective deuteration of *N*-alkyl-substituted anilines under neutral conditions (Scheme 1).

Initially, $Ru_3(CO)_{12}$ (1 mol %) as catalyst and D_2O (75 equiv) as deuterium source were used for the deuteration of *N*,*N*-dimethylaniline. The reaction mixture was heated to 100 °C overnight, and deuterium incorporation reached to 94% at the *ortho* and *para* positions (Table 1, entry 1). Delightfully, further reduction of the



Scheme 1. $Ru_3(CO)_{12}$ catalyzed deuteration of *N*-alkyl-substituted anilines.

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* Corresponding author. Tel.: +86 18602831330; fax: +86 02885058465.
E-mail address: ywchen@scu.edu.cn (Y. Chen).

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Table 1
Optimization of deuteration conditions on *N*,*N*-dimethylaniline

Entry	Catalyst	Amount (mol %)	*T* (°C)	D content[a] (%)
1	$Ru_3(CO)_{12}$	1	100	94
2	$Ru_3(CO)_{12}$	0.5	100	94
3	$Ru_3(CO)_{12}$	0.25	100	95
4	$Ru_3(CO)_{12}$	0.1	100	91
5	$Ru_3(CO)_{12}$	0.25	100	94[b]
6	$Ru_3(CO)_{12}$	0.25	100	98[c]
7	$Ru_3(CO)_{12}$	0.25	100	96[d]
8	None	0	100	0
9	$Ru_3(CO)_{12}$	0.25	80	68
10	$Fe_3(CO)_{12}$	1	100	77
11	10% Pd/C	10[e]	100	87
12	10% Ph/C	10[e]	100	32
13	20% Ru/C	5[e]	100	54
14	HCl	100	100	38

[a] Unless otherwise mentioned, the reaction was conducted with 1 mmol of *N*,*N*-dimethylaniline in 1.5 mL D_2O at 100 °C overnight. The D content was calculated on the basis of ^1H NMR spectrum.

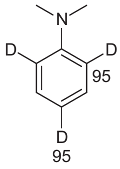
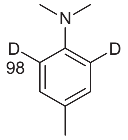
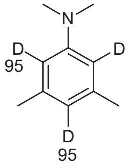
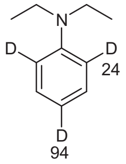
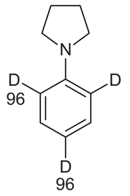
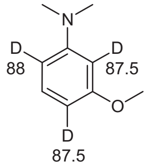
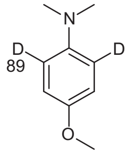
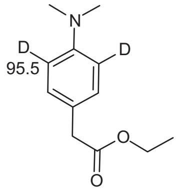
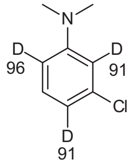
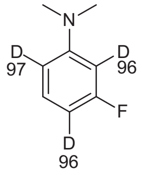
[b] 6 h.

[c] After repeating the labeling procedure once with fresh $Ru_3(CO)_{12}$ and D_2O.

[d] Toluene as co-solvent.

[e] Wt %.

Table 2
Deuteration of various anilines catalyzed by $Ru_3(CO)_{12}$ in D_2O[a]

Entry	D content (%)	Yield[b] (%)
1		95
2		93
3		93
4		96
5[c]		92
6		91
7[d]		90
8[d]		93
9		91
10		94

(*continued on next page*)

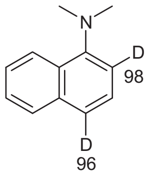
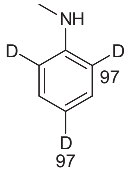
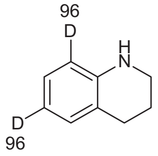
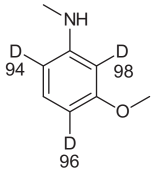
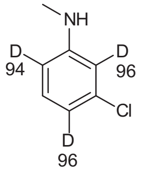
catalyst amount to 0.25 mol % resulted in high deuterium content (Table 1, entry 3). Moreover, 0.1 mol % of $Ru_3(CO)_{12}$ still allowed high deuteration degree (91%, Table 1, entry 4). Reducing the reaction time to 6 h also led to 94% of deuterium incorporation when 0.25 mol % of the catalyst was used (Table 1, entry 5). Additionally, nearly complete deuteration (98%, Table 1, entry 6) could be achieved by repeating the labeling procedure once. Toluene as co-solvent maintained the efficiency of the deuteration process (Table 1, entry 7). As expected, H–D exchange of *N*,*N*-dimethylaniline was not observed without catalyst (Table 1, entry 8). Decreasing the temperature led to a lower deuteration degree (Table 1, entry 9). However, other zero-valent catalysts gave lower deuterium efficiency (Table 1, entries 10–13). Stoichiometric amounts of 37% concd HCl, which was used for the regioselective deuteration of anilines under microwave irradiation,[8] allow only 38% of deuterium incorporation at 100 °C (Table 1, entry 14). Therefore, the optimized conditions were obtained by using 0.25 mol % of $Ru_3(CO)_{12}$ in D_2O (75 equiv) and heating to 100 °C for 12 h.

A variety of substituted anilines were subjected to the optimized conditions to evaluate the scope of the reaction (Table 2). Spectrographically pure labeled anilines were obtained through simple extraction and evaporation, and no further purification process was required. Tertiary anilines with the electron-donating group were efficiently deuterated (Table 2, entries 1–3 and 6–8). However, when steric hindered substituent is on the aniline nitrogen, the degree of deuterium incorporation is diminished *ortho* to the nitrogen (Table 2, entry 4). An attempt to deuterate the 1-phenylpyrrolidine was less satisfactory at this condition because of steric hindrance, however 96% of deuterium incorporation was achieved by further optimizing the temperature from 100 °C to 120 °C (Table 2, entry 5). The presence of phenols slightly reduced the degrees of deuterium incorporation.[10]

However, substrates with the electron-withdrawing group (Br, CN, carbonyl, ester, and NO_2) could not be labeled even at 140 °C probably due to low activity of the substrates and/or the weak interaction between anilines and the catalyst. To our delight, anilines with weak electron-withdrawing group in *meta*-position were efficiently deuterated (Table 2, entries 9 and 10).

In the case of secondary anilines, elevated temperature and high loading of the catalyst (1 mol %) were needed to achieve high degree of deuterium incorporation and the substituent effects were similar to those of tertiary anilines (Table 2, entries 12–15).

Table 2 (*continued*)

Entry	D content (%)	Yield[b] (%)
11[e]		96
12[c]		94
13[c]		99
14[c]		91
15[c]		90

[a] Unless otherwise noted, the reaction was conducted with 1 mmol of the substrate and 0.25 mol % of $Ru_3(CO)_{12}$ in 1.5 mL D_2O at 100 °C overnight. The D content was calculated on the basis of ^1H NMR spectrum.

[b] Isolated yield.

[c] 1 mol % of $Ru_3(CO)_{12}$ was used at 120 °C.

[d] Toluene as co-solvent.

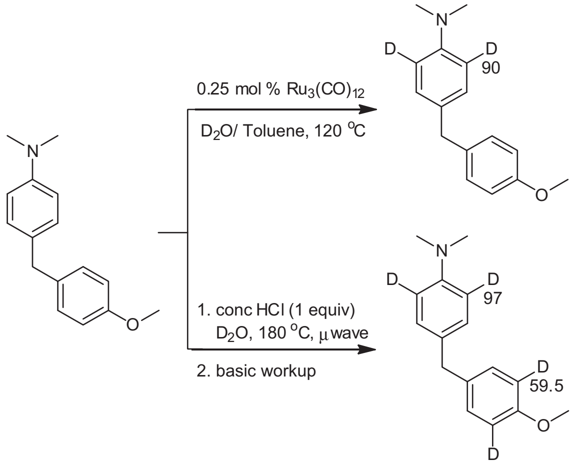
[e] 140 °C.

Unfortunately, deuteration of primary anilines failed, maybe due to the catalyst poisoning.

Compared to established methods, it showed special selectivity to substrates with aromatic methoxy groups as depicted in Scheme 2. As reported, microwave mediated H-D exchange of anilines often suffers from selectivity problems.[8]

To gather further insight into our novel $Ru_3(CO)_{12}$-catalyzed deuteration of *N*-alkyl-substituted anilines, radical scavenger, such as 1,1-diphenylethylene[11] (1 equiv), was employed in the reaction. The deuteration of *N*,*N*-dimethylaniline was immune to the radical scavenger, which could indicate that the exchange reaction did not involve in radical intermediates. In addition, toluene as co-solvent did not affect the deuterium efficiency (96%, Table 1, entry 6), which indicated that the catalyst may bond to the nitrogen of the aniline rather than the aromatic ring to some extent. To review the existing method for the labeling of anilines, the use of a variety of Brønsted and Lewis acids in D_2O under microwave irradiation afforded considerable amounts of deuteration (15–58%),[8c] which was proposed to occur via electrophilic aromatic substitution upon deuterium ions and so was our method.

In summary, the method for Ru(0)-catalyzed regioselective deuteration of *N*-alkyl-substituted anilines was developed under neutral conditions with conventional heating. Only simple extraction and evaporation were needed to obtain spectrographically pure labeled anilines. This exchange method also showed high selectivity to substrates with aromatic methoxy groups when compared to the existing methods. It is envisaged that this methodology can also be extended to the tritium-labeling of pharmaceutically interesting molecules for medicinal applications.



Scheme 2. $Ru_3(CO)_{12}$ catalyzed deuteration of *N*-alkyl-substituted anilines.

Representative procedure for deuteration reactions

N,*N*-Dimethylaniline (2 mmol) and $Ru_3(CO)_{12}$ (3.2 mg, 0.005 mmol) in D_2O (3 mL) were stirred at 100 °C in a sealed tube under a N_2 atmosphere for 12 h. After the mixture was cooled to room temperature, water (10 ml) was added, and then extracted with diethyl ether (2×10 mL). The organic layer was washed with brine (5 mL), dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated to afford *N*,*N*-dimethylaniline-*d*$_3$. The total incorporation yield was determined by ^1H NMR spectroscopy relative to the intensity of a nonexchangeable proton in the molecule and confirmed by ^2H NMR and mass spectrometry.

Supplementary data

Supplementary data (general procedures and ^1H, ^2H and ^{13}C NMR spectra of all compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.07.071.

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