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Rhodium(I)-Catalyzed Directed Trideuteromethylation of (Hetero)arene C–H Bonds with CD_3CO_2D

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Received 00th January 20xx,
Accepted 00th January 20xx

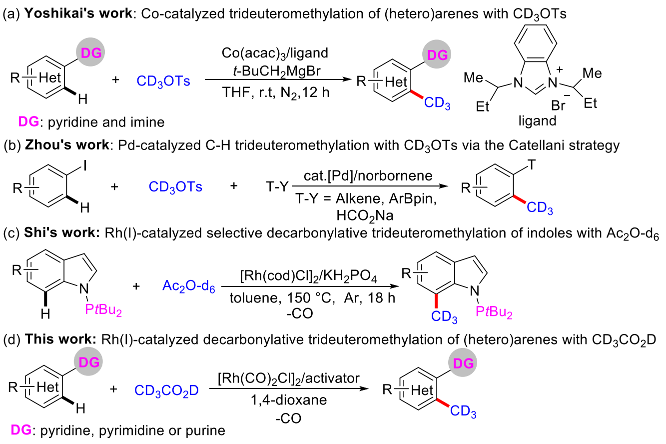
DOI: 10.1039/x0xx00000x

A Rh(I)-catalyzed trideuteromethylation of heteroarenes with inexpensive and readily available deuterated acetic acid (CD_3CO_2D) with the aid of a *N*-containing directing groups is developed. The oxidant-free reaction is applicable to a wide range of heteroarene substrates, including 2-pyridones, indoles, aryl rings, pyrroles and carbazoles. It allows installation of CD_3 groups under straightforward reaction conditions. It is expected that the salient and practical features of this trideuteriomethylation protocol will be of use to academic and industrial researchers.

Introduction

Deuterium labelled compounds continue to be of great interest in chemistry, medicine and the life sciences, because of their wide applications in exploration of reaction mechanisms,[1a] drug discovery and development,[1b] NMR[1c] and MS.[1d] Significant research effort has been dedicated to the synthesis and clinical evaluation of deuterium-labelled drug candidates.[2] In 2017 the first deuterated chiral drug (Austedo™) was approved for the treatment of chorea symptoms by the US Food and Drug Administration.[3] The majority of existing methods for the preparation of deuterium labelled compounds rely on multistep synthetic routes and catalytic H/D exchange reactions.[4] In order to meet the rising demands for deuterated compounds, more efficient and convenient deuteration methods are required.[5]

It is well-known that the installation of a methyl group into bioactive molecules can dramatically alter their biological and physical properties.[6] Given the benefits of the so-called "magic methyl" effect, the quest of efficient methylation methods has been the subject of extensive research,[7] most recently in the development of catalytic methylation of C–H bonds.[8] In contrast, the corresponding trideuteromethylation has progressed more slowly, despite the widespread use of trideuteromethylated compounds.[9] Several protocols including substitution reaction with CD_3I,[10a] transition-metal-catalyzed trideuteromethylation of *N*-heteroarenes and ketones with CD_3OD via a hydrogen borrowing approach,[10b, g, h] transition-metal catalyzed trideuteromethylation of aryl halides with CD_3I and CD_3OTs,[10c, e, f] and radical trideuteromethylation of *N*-heteroarenes and alkenes with DMSO-d_6[10d] have been developed. However, trideuteromethylation of C–H bonds under transition-metal catalysis has been less explored. In this context, the group of Yoshikai realized a cobalt-catalyzed chelation-assisted regioselective trideuteromethylation of (hetreo)arene C–H bonds with CD_3OTs (Scheme 1a).[8d] Zhou et al. achieved a Pd-catalyzed C–H deuterated methylation of iodobenzenes with CD_3OTs via the Catellani strategy (Scheme 1b).[8b] Interestingly, Shi and co-workers recently reported a Rh(I)-catalyzed C7-selective decarbonylative trideuteromethylation of indoles with Ac_2O-d_6 in the presence of a base additive (Scheme 1c).[11]



Scheme 1. Transition-metal Catalyzed C–H trideuteromethylation of heteroarenes.

Though useful, a major drawback of the chemistry was the prior preparation of Ac_2O-d_6. Clearly, the use of more readily available and inexpensive CD_3CO_2D would be more attractive and convenient. However, the only example of

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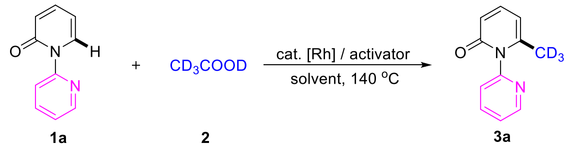
†Electronic Supplementary Information (ESI) available. CCDC 1878486 (3q) and 2102000 (7f). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/x0xx00000x

trideuteromethylation reported in the literature using CD_3CO_2D as CD_3 source was a cerium catalyst by merging electrochemistry and photocatalysis in moderate yields.[10j] The recent reports by the group of Shi and our team revealed that 2-(*m*-tolyl)pyridine, *N*-(2-pyrimidyl)-indole and 1-(2-pyridyl)-2-pyridone could undergo Rh(I)-catalyzed chelation-assisted decarbonylative C–H methylation with in situ generated Ac_2O from acetic acid and activator under base- and oxidant-free conditions.[12] Inspired by these reports, we became interested in using readily available and inexpensive CD_3CO_2D trideuteromethylation of (hetero)arene C–H bonds under Rh(I) catalysis. Herein, we describe an efficient and convenient approach for regioselective trideuteromethylation of (hetero)arene C–H bonds with CD_3CO_2D using an Rh(I) catalyst (Scheme 1d). This method features high yields, wide substrate scope, good functional group tolerance and operational simplicity.

Results and discussion

In consideration of the importance of bioactive 2-pyridones,[13] we commenced our study by surveying reaction conditions with 1-(2-pyridyl)-2-pyridone (**1a**) as the model substrate and CD_3CO_2D as the coupling partner. We started our study with the combination of $[Rh(CO)_2Cl]_2$ and Boc_2O/PivOH, which have been shown previously to be effective for the decarbonylative alkylation of 2-pyridones with different types of aliphatic acids.[12c]

Table 1 Optimization of reaction conditions.[a]

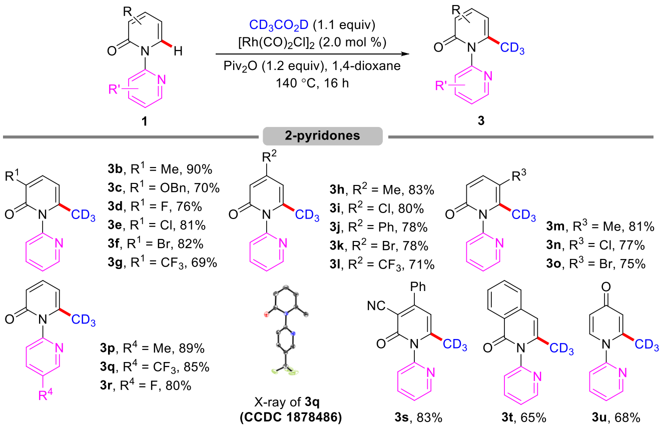


Entry	Catalyst	Activator	Yield (%)[b]
1[c]	$[Rh(CO)_2Cl]_2$	Boc_2O	84
2[c]	$[Rh(COD)Cl]_2$	Boc_2O	61
3[c]	$[Rh(COD)_2]OTf$	Boc_2O	56
4	$[Rh(CO)_2Cl]_2$	Boc_2O	21
5	$[Rh(CO)_2Cl]_2$	$(MeOCO)_2O$	13
6	$[Rh(CO)_2Cl]_2$	Piv_2O	93 (90)[d]
7	$[Rh(CO)_2Cl]_2$	PivCl	10
8	$[Rh(CO)_2Cl]_2$	Tf_2O	0

[a]Reaction Conditions: **1a** (0.1 mmol.), **2a** (0.11 mmol), [Rh] dimer (2.0 mol %), activator (1.2 equiv), additive (1.2 equiv), solvent (1.0 mL, 0.1 M), 140 ºC, 16h, under N_2. [b]Yields were determined by ^1H NMR analysis of unpurified reaction mixtures with internal standard CH_2Br_2.[c]PivOH (1.2 equiv) was employed. [d]Isolated yield. COD: cyclooctadiene.

We found that the combination of $[Rh(CO)_2Cl]_2$ (2 mol %), Boc_2O (1.2 equiv) and PivOH (1.2 equiv) worked effectively to catalyze the reaction of **1a** with CD_3CO_2D in 1,4-dioxane at 140 °C to provide the C6-trideuteromethylated product **3a** in 84% AY (Table 1, entry 1, AY = assay yield, determined by ^1H NMR integration against an internal standard). The catalytic activity decreased when $[Rh(COD)Cl]_2$ or $[Rh(COD)_2]OTf$ was employed (entries 2 and 3). Notably, solvents other than 1,4-dioxane gave either lower yields of **3a** or no reaction (for details, see SI, Table S1), indicating a dramatic solvent effect in this reaction. The reaction yield was compromised in the absence of PivOH (entry 4). Replacing Boc_2O/PivOH with other acid activators, such as $(MeOCO)_2O$, PivCl or Tf_2O, dramatically diminished the reaction efficiency (entries 5, 7 and 8). Piv_2O proved to be an effective activator, affording **3a** in 93% assay yield and 90% isolated yield (entry 6). The yield of **3a** dropped slightly to 89% when lowering the reaction temperature to 130°C (ESI, Table S1). Reducing the rhodium loading to 2 mol % led to a decrease in the assay yield of **3a** (65%, ESI, Table S1). Control experiments showed the reaction failed to proceed in the absence of $[Rh(CO)_2Cl]_2$ (ESI, Table S1). Further experiments revealed that free 2-pyridone and 2-pyridone substrates bearing other substituents on the nitrogen, such as Me, Bn, Ph, or 3-pyridyl were totally ineffective, clearly highlighting the importance of the pyridyl directing group for successful catalysis (for details see ESI, Table S2).

Table 2. Scope of 2-Pyridones.[a,b]

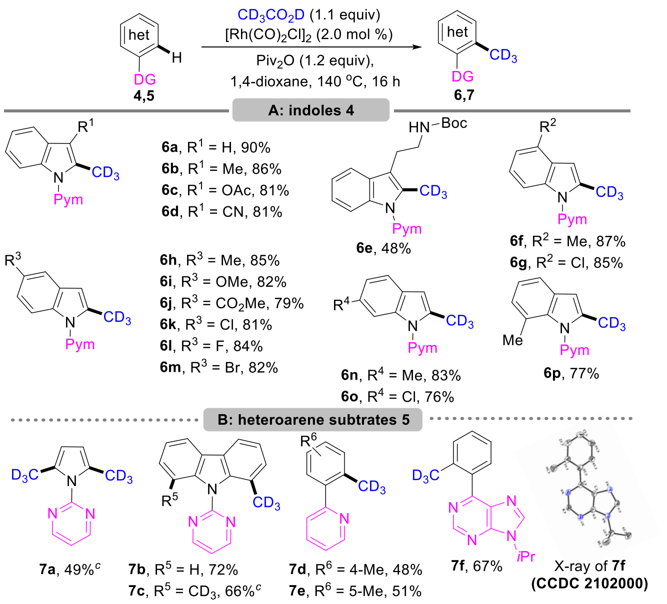


[a]General reaction conditions: **1** (0.3 mmol), CD_3CO_2D (0.33 mmol), $[Rh(CO)_2Cl]_2$ (2.0 mol %), Piv_2O (1.2 equiv), 1,4-dioxane (0.1 M), 140 ºC, 16 h, N_2. [b]Isolated yield.

Under the optimized reaction conditions, 2-pyridones were then subjected to C–H trideuteromethylation with CD_3CO_2D. 2-Pyridone (**1b–1l**) bearing substituents at C3- or C4- were readily converted into C6-trideuteromethylated products (**3b–3l**) in 69–90% yields, regardless of the nature of the substituent. The reaction is relatively insensitive to steric hinderance, as evidenced by high conversions with C5-substituted 2-pyridones (75–81% yields, **3m–3o**). The efficiency was not affected by the installation of C5-substituents on the pyridyl directing group, (**3p–3r**, 80–89% yields). The structure of **3q** was confirmed by single-crystal X-ray diffraction (CCDC 1878486). The reaction of 3,4-disubstsitued 2-pyridone **1s** proceeded readily, providing the desired product **3s** in 83% yield. Additionally, the catalytic tridueteromethylation was also applicable to isoquinolin-1(2*H*)-one (**1t**) and pyridin-4(1*H*)-one (**1u**), affording the corresponding products (**3t** and **3u**) in 65–68% yields.

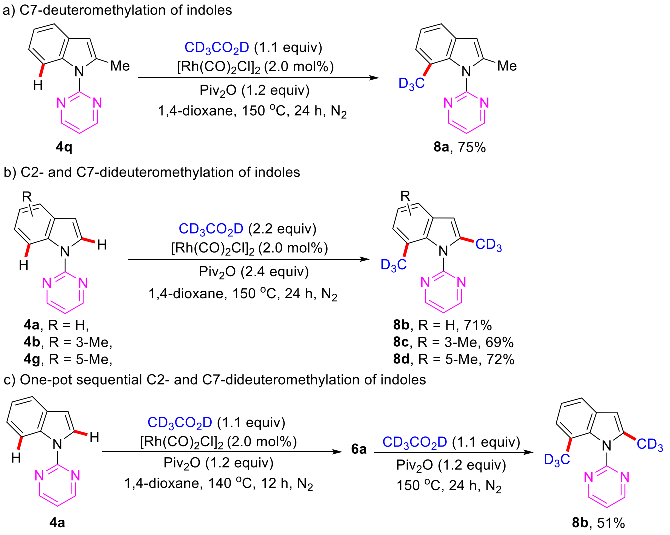
We then explored various heteroarene substrates. As shown in Table 3A, the scope of indoles was examined. Here, the pyrimidine directing group was found to give higher yields than the 2-pyridyl analogue. It was noteworthy that the sterically congested C3-substituted indoles (**4b–4d**) were smoothly converted into the corresponding C2-CD_3 products (**6b–6d**) in 81–86% yields. Of note, the reaction of tryptamine derivative **4e** gave **6e** in 48% yield. Similarly, various 4-, 5- and 6-substituted indoles (**4f–4o**) bearing electron-rich or electron-poor groups [including halogens (F, Cl, Br), methoxy and ester], afforded **6f–6o** in 76–87% yields. The C7 methyl-substituted indole **4p** gave trideuteromethylation at the 2-position (**6p**, 77% yield). Furthermore, the reaction was not restricted to indole substrates (Table 3B). Pyrrole **5a** and carbazole **5b** gave the corresponding products (**7a–7c**) in 49–72% yields. It should be noted that in the case of the pyrrole **5a**, only the formation of di-deuteromethylated **7a** was observed, but for carbazole **5b**, mono- and disubstituted products were obtained by adjusting the reaction temperature and the amounts of acid and activator. Moreover, phenylpyridine substrates **5d** and **5e** successfully engaged in the reaction to provide **7d** and **7e** in 48%–51% yields. Notably, 9-isopropyl-6-phenyl-9H-purine **5f** also participated to afford **7f** in 67% yield. The structure of **7f** was confirmed by X-ray diffraction (CCDC 2102000).

Table 3. Scope of indoles and other heteroarene substrates.[a,b]



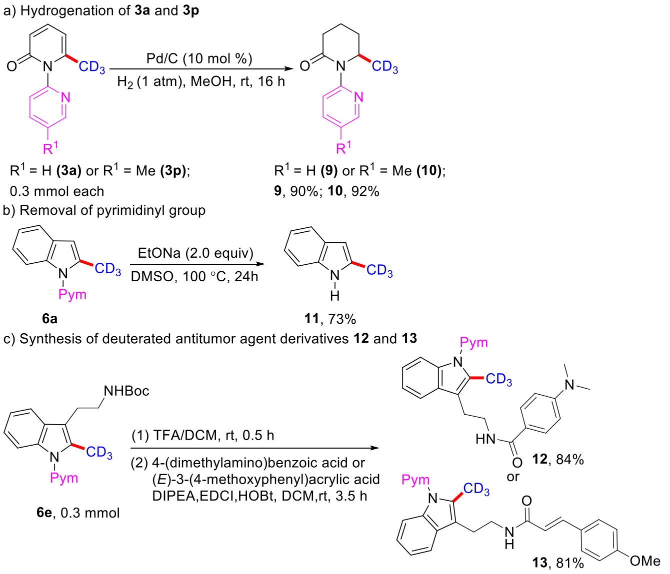
[a] General reaction conditions: **4** or **5** (0.3 mmol), CD_3CO_2D (0.33 mmol), $[Rh(CO)_2Cl]_2$ (2.0 mol %), Piv_2O (1.2 equiv), 1,4-dioxane (3 mL, 0.1 M), 140 ºC, 16 h, under N_2. [b] Isolated yield. [c] Increased reaction temperature to 150 °C, CD_3CO_2D (0.66 mmol) and Piv_2O (2.4 equiv) was employed.

With the success in C2-deuteromethylation of indoles, we then envisaged that the presence of a C2-substituent on N-(2-pyrimidyl)-indole would steer the reactivity to C7–H under similar Rh(I) catalysis. Indeed, as shown in Scheme 2a, upon slight modification of the reaction conditions, C2-substituted indole **4q** could effectively participate in the reactions to give the C7-deuteromethylated product **8a** in 75% yield. We next examined the feasibility of double trideuteromethylation of indole substrates at both the C2 and C7 positions. Fortunately, the treatment of **4a**, **4b** and **4g** with CD_3CO_2D (2.2 equiv), Piv_2O (2.4 equiv) in 1,4-dioxane at 150 °C for 24 h, provided the C2,C7-di-deuteromethylated products (**8b–8d**) in 69–72% yields (Scheme 2b). Finally, the possibility of one-pot C2,C7-sequential di-deuteromethylation was tested. As expected, the one-pot sequential bis-deuteromethylation of indole **4a** furnished the desired product **8b** in 51% yield (Scheme 2c).



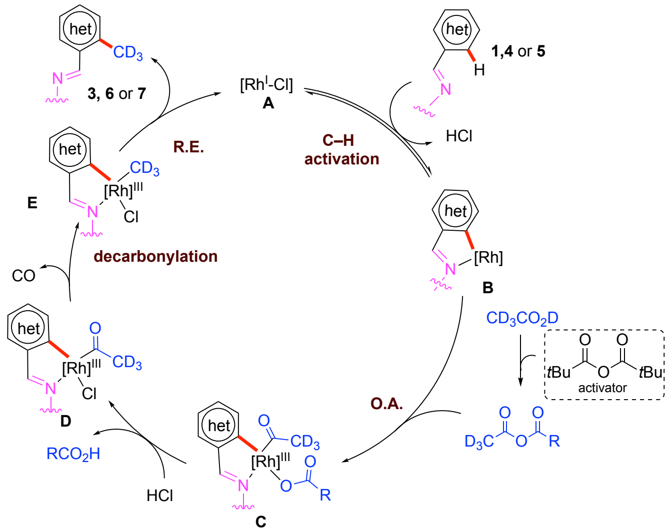
Scheme 2. Direct C7-trideuteromethylation and C2, C7-di-trideuteromethylation of indoles.

To demonstrate the synthetic utility, gram scale reactions of **1a**, **1p**, **4a** and **4e** with CD_3CO_2D were performed to deliver **3a**, **3p**, **6a** and **6e** in 40–84% yields (for details, see SI). Derivatizations of C6-deuteromethylated 2-pyridone products were then explored. It was found that **3a** and **3p** underwent hydrogenation to give **9** and **10** in 90% and 92% yields, respectively (Scheme 3a). The pyrimidinyl directing group in deuteromethylated indole products was removed by treatment with EtONa in DMSO (Scheme 3b). In this way, **6a** was easily converted into the corresponding free indole **11** in 73% yield. To further demonstrate the value of this method, we focused on the development of a unique and expeditious route to the deuterated antitumor agent derivatives.[14] As shown in Scheme 3c, from commercially available materials, we successfully prepared **12** and **13** in 84% and 81% yields, respectively.



Scheme 3. Synthetic Applications.

Preliminary experiments were performed to gain insight into the reaction mechanism. The reversibility of the C–H activation step was first investigated (for details, see SI). Treatment of **1h** with CD_3OD as a co-solvent in the absence of CD_3CO_2D and acid activator resulted in significant H/D exchange at the C–6 position of **1h**. In contrast, lower deuterium incorporation was observed at the C–3 and C–5 positions. These results suggest that the C–H activation is reversible. The parallel reactions between **1h** or $[D_1]$-**1h** with CD_3CO_2D afforded a kinetic isotope effect value of 1.9 ± 0.1 (for details, see SI)[15], implying that the C–H bond cleavage is the turnover-limiting step (TLS) in the catalytic cycle.



Scheme 4. Plausible Mechanism.

On the basis of the experimental results above, and the previous reports,[12b, c, 15-16] a plausible mechanism is proposed as described in Scheme 4. Initially, coordination of heteroarene substrates **1**, **4** or **5** to the Rh(I) species **A** followed by *N*-directing group-assisted C2–H bond activation is proposed. Next, reductive elimination of HCl is expected to afford the 5-membered rhodacycle intermediate **B** (the previous DFT calculations indicate that C-H activation is more feasible as the first step).[16a] At the same time, reaction of CD_3CO_2D with Boc_2O and pivalic acid results in in situ formation of the key mixed anhydride $CD_3COOCOR$ (R likely being *t*-Bu). Oxidative addition of the mixed anhydride at the more accessible C–O bond gives **C**. In our past computational studies on a related system the Rh(III) in **C** likely reacts with HCl to liberate the acid and form intermediate **D**.[16a] Subsequently, **D** undergoes decarbonylation to release CO and generate the CD_3–Rh(III) intermediate **E**. Finally, reductive elimination of **E** affords the desired products (**3**, **6** or **7**) with the concurrent regeneration of the Rh(I) species **A**.

Conclusions

In summary, we have developed a general and efficient method for trideuteromethylation of heteroarene substrates with inexpensive and readily available CD_3CO_2D under Rh(I) catalysis. Besides diversely substituted 2-pyridones, a variety of substituted indoles and aryl rings were tolerated, providing C2-deuteriomethylated products. Pyrrole and carbazole were also suitable substrates. This method employs a readily available and easy-to-handle catalytic system. Moreover, minor modification of the reaction conditions enabled regioselective C7-deuteriomethylation and C2,C7-dideuteriomethylation of indoles. Given the potential utility of heterocyclic compounds bearing CD_3 groups, and the straightforward method for their synthesis outlined herein, we anticipate that this trideuteromethylation will be of much use.

Author Contributions

H. Zhao performed the optimization of the reaction and analyzed the experimental results. L. Xu and H. Zhao designed the experiments. H. Zhao, L. Xu and P. J. Walsh wrote the manuscript. Q. Zeng and B. Xu performed and synthesized some of the starting materials. The research directed by H. Lei, L. Xu and P. J. Walsh.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We are grateful for financial support from Beijing University of Chinese Medicine (2022-JYB-XJSJJ023), China Scholarship Council (201806360122), H.Z. and P.J.W. thanks the US National Science Foundation (CHE-1902509).

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