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Nickel and Nucleophilic Cobalt-Catalyzed Trideuteriomethylation of Aryl Halides Using Trideuteriomethyl *p*-Toluenesulfonate

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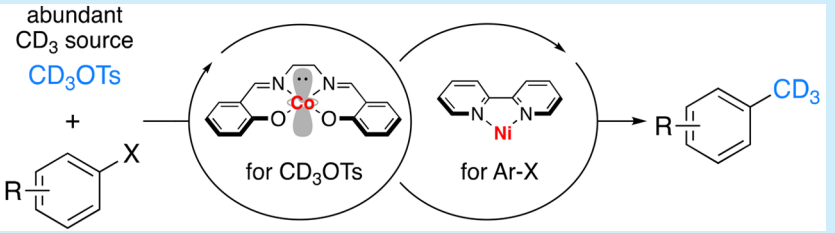
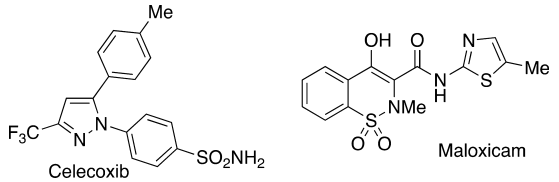
Supporting Information



ABSTRACT: Herein, a novel approach for the trideuteriomethylation of aryl halides using nickel and nucleophilic cobalt catalysts and the readily available trideuteriomethyl *p*-toluenesulfonate (CD_3OTs) is described. This method provides access to a wide range of CD_3-containing arenes. Moreover, a transmethylation step is revealed as crucial in the nickel/cobalt catalytic mechanism.

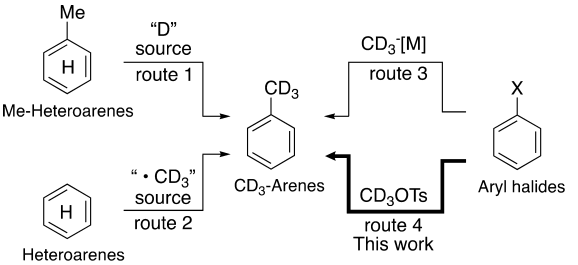
Methylation is one of the most widely recognized strategies for the structural modification of bioactive compounds. The introduction of a methyl group, which is the smallest organic substituent, into organic skeletons can induce their metabolic stabilization.[1] Thus, for example, in the selective cyclooxygenase-2 (COX-2) inhibitors celecoxib **1** and meloxicam **2**,[2] the methyl group protects the aromatic ring against metabolic oxidation,[3] which would otherwise lead to the corresponding alcohol and carboxylic acid through oxidation of the benzylic C−H bonds. This oxidation is known to cause a decrease in the metabolic stability.[4] In contrast, fluorinated substituents such as F and CF_3, which are considered to be bioisosteric to the methyl group, are also used in medicinal chemistry to improve the stability of compounds. In the context of metabolic stability, while a rapid metabolism has the obvious disadvantage of providing a short duration of bioactivity, a long half-life may lead to drug accumulation in tissues, with concomitant side effects.[1a] Therefore, the development of alternative protocols that ensure an adequate metabolic stability has been desired in the field of drug discovery.



Deuterium-labeled compounds have attracted much attention for the preparation of new chemical entities and the development of improved drugs.[5] Thus, as the carbon−deuterium (C−D) bonds are stronger than the more common carbon−hydrogen (C−H) bonds,[6] the replacement of a hydrogen atom by a deuterium atom at metabolically labile positions can significantly improve the metabolic stability of the compounds. Indeed, some trideuteriomethyl (CD_3)-containing medicines have proved to be of vital importance owing to their enhanced biological potency, thereby reducing the formation of toxic metabolites.[7]

While significant advances have been made in the development of protocols for the installation of a methyl group into aromatic rings, analogous methods for the introduction of a CD_3 group remain scarce (Scheme 1). Hydrogen−deuterium exchange in methylated arenes is one of the ideal approaches (Scheme 1, route 1).[8] However, owing to the difficult site-selective labeling at the methyl group connected to multifunctionalized arenes, this method is restricted to acidic methyl C−H bonds coupled with heteroarenes.[8j,l,m] Also limited to heteroarenes is the Minisci-type radical addition depicted in

Scheme 1. Synthetic Routes for Trideuteriomethylated Arenes



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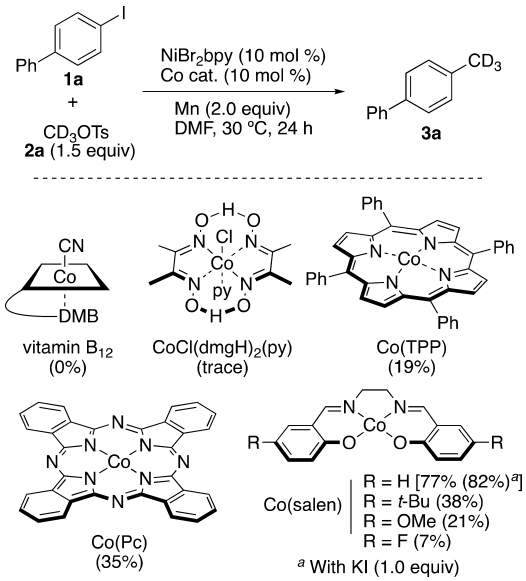
Scheme 1 (route 2).[9] Conversely, methylated arenes are conventionally prepared via transition metal-catalyzed cross-coupling between aryl halides and methyl metal reagents (Scheme 1, route 3), such as Me-[Mg],[10a−c] -[Li],[10d] -[B],[10e] -[Zn],[10f,g] or -[Al];[10h] however, their applications to trideuteriomethylation are restricted to a few examples[10d,11] due to the low availability and high cost of CD_3 metal sources.

Considering such economical and synthetic aspects, Liao recently developed a Barbier-type Negishi cross-coupling of aryl halides with CD_3−[Zn] reagents generated in situ from CD_3I and zinc powder.[12] Recently, a nickel and vitamin B_{12}-catalyzed Csp^2−Csp^3 reductive cross-coupling between aryl halides and alkyl sulfonates has been disclosed by Weix[13] and our group.[14] In the transformation, alkyl sulfonates are converted to alkyl radicals via the homolytic reductive cleavage of the corresponding alkyl−[Co(III)] intermediate, which stems from the substitution of the alkyl sulfonates with a nucleophilic cobalt complex. Herein, we wish to describe an efficient and mild trideuteriomethylation of aryl halides using nickel and nucleophilic cobalt catalysts (Scheme 1, route 4), wherein the choice of the nucleophilic cobalt species was key to the success of the reaction. This method demonstrated high catalytic performance and broad substrate scope, offering a new synthetic approach for a diverse set of CD_3-arenes obtained from CD_3OTs to act as an abundant CD_3 source.

As the origin of our investigation, we explored suitable reaction conditions, especially cobalt catalysts, for the trideuteriomethylation of 4-phenyl-1-iodobenzene (**1a**) with CD_3OTs (**2a**) as a model substrate combination (Scheme 2).

Scheme 2. Effect of Cobalts in the Ni/Co-Catalyzed Trideuteriomethylation of 4-Phenyl Iodobenzene (1a) with CD_3OTs 2a



When **1a** was treated with **2a** (1.5 equiv) in the presence of $NiBr_2$bpy (10 mol %), vitamin B_{12} (10 mol %), and Mn powder (2.0 equiv) at 30 °C for 24 h, surprisingly, no formation of the desired product **3a** was observed. Notably, although **2a** was wholly consumed, most of the iodide **1a** remained unchanged after the reaction. In addition, the use of cobaloxim $CoCl(dmgH)_2(py)$ instead of vitamin B_{12} provided similar results. Generally, the axial ligand is known to affect the nucleophilicity of square-planar [Co(I)] complexes. Thus, the axial coordination raises the energy of the filling d_{z2} orbital of [Co(I)], and the cobalt center becomes a strong nucleophile.[15] Furthermore, the stability of the generated alkyl−[Co(III)] species toward the homolytic reductive cleavage could also be influenced by the ligand.[15b] In this regard, we speculated that the low productivity might be attributed to the rapid formation and cleavage of the D_3C−[Co(III)] bond. Therefore, we set out to explore other square-planar cobalt catalysts without axial ligands. Consequently, we found to our delight that simple and commercially available [Co(II)] complexes improved the product yield. Among them, Co(salen) (R = H) was the most effective, affording **3a** in 77% yield. A slight improvement of the yield up to 82% was further achieved by adding 1 equiv of KI. None or a negligible amount of the desired product **3a** was detected in control experiments in the absence of the nickel and cobalt catalysts. Additionally, we have confirmed that no hydrogen−deuterium exchange reaction of C−H bonds, which substrates have in advance, did not occur at all.

With the optimized reaction conditions in hand, we next explored the scope of aryl halides in the Ni/Co-catalyzed trideuteriomethylation, as summarized in Scheme 3. We observed that aryl halides possessing electron-donating and -withdrawing substituents at the para or ortho positions were well tolerated, affording the CD_3-containing products in good yields. Furthermore, we found that the trideuteriomethylation of **1e** successfully proceeded on a gram scale (1.01 g, **3e**). However, when the strongly electron-deficient aryl iodides corresponding to **1g** and **1j** were used, their homocoupling products were exclusively formed, presumably due to their high reactivity toward the oxidative addition. In contrast, the trideuteriomethylated products **3g** and **3j**, which are key precursors for the synthesis of deuterium-labeled drugs such as celecoxib[16] and orphenadrine,[17] respectively, were obtained by replacing the aryl iodides with the corresponding bromides or chlorides. Furthermore, the transformation was also applicable to heteroaryl halides. Thus, CD_3-containing indole **3n** and quinoline **3o** were obtained in good yields. Moreover, the method was active not only for CD_3-installation but also for methylation, affording the corresponding methylated products **4**−**7** in satisfactory yields.

The relevance of the slow generation of MeI from MeOTs upon addition of iodide in the nickel-catalyzed reductive cross-coupling was previously discussed by Gong.[18] We decided to investigate the reaction of CD_3OTs with metal salts such as the KI additive or the generated MnI_2 in our reaction. Although the accurate role of the KI additive is not clear at present,[19] ^2H NMR monitoring of the reaction of CD_3OTs with KI (or MnI_2) indicated that CD_3I was quickly generated, and the halogen−pseudohalogen exchange concluded within only 30 min (see the Supporting Information). Therefore, the formation of CD_3I would occur in the presence of KI as the initial step. However, the results shown in Scheme 1 imply that the reaction strongly depended on the presence and nature of the cobalt catalysts rather than on the addition of KI. Additionally, the methylation of aryl triflate **1p** with CD_3OTs afforded the corresponding trideuteriomethylated product **3p** (67% yield), even in the presence of 20 mol % of Et_4NI (Scheme 4, eq 1), wherein only a catalytic amount of CD_3I should have been formed. Furthermore, we observed that the single nickel catalyst produced a negligible amount of product **4** (4%) in the reaction of aryl iodide **1e** with **2b** (Scheme 4, eq 2), whereas the nickel/cobalt combination

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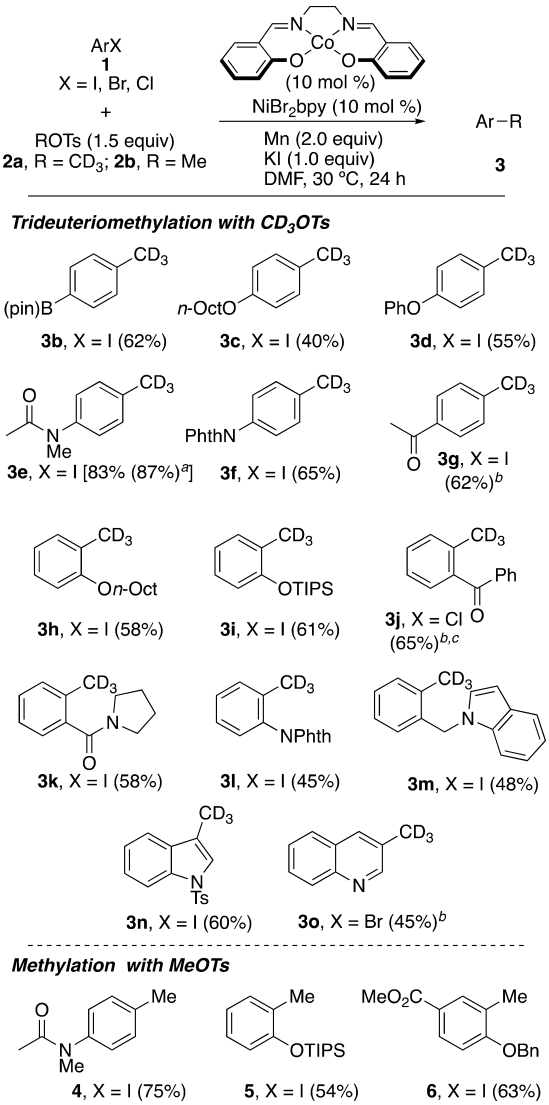
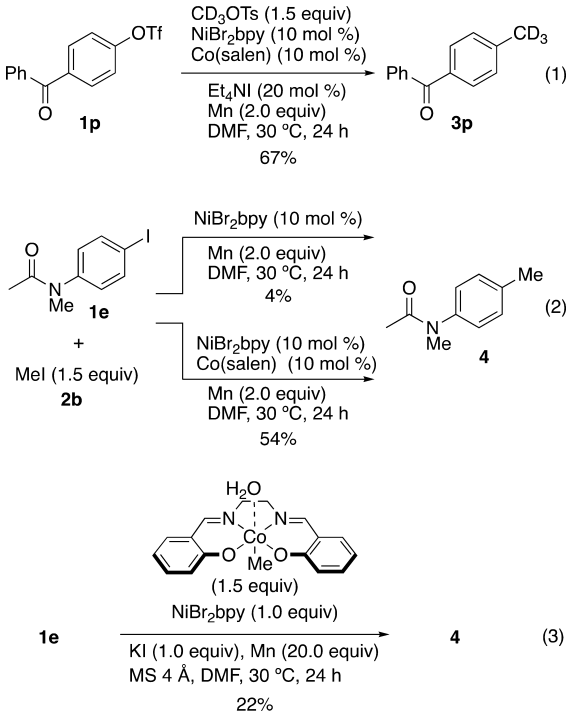
Scheme 3. Ni/Co(salen)-Catalyzed Trifluoromethylation and Methylation of Aryl Halides[a]

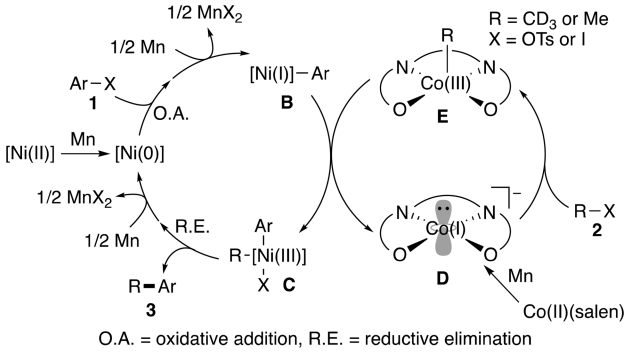


[a](a) 7.0 mmol of **1e** was used; reaction time 30 h. (b)Et_4NI (20 mol %) was used instead of KI (1.0 equiv). (c) $NiCl_2$(6,6′-Me_2bpy) was used instead of $NiBr_2$bpy.

Scheme 4. Methylation of the Aryl Iodide 1e with MeI Both in the Presence and Absence of Co(salen)



Scheme 5. Plausible Reaction Mechanism



afforded 54% of **4**. These results add support to the important role of the nucleophilic cobalt in the present cross-coupling reaction.

On the basis of these experimental results, we envisaged the catalytic cycle illustrated in Scheme 5 for the Ni/Co(salen)-catalyzed trideuteriomethylation and methylation of aryl halides. First, two active catalysts, [Ni(0)] and [Co(I)] **D**, would be initially generated from the reaction of [Ni(II)] and [Co(II)] with the Mn reductant. The oxidative addition of aryl halides **1** to [Ni(0)] and its subsequent reduction would provide Ar−[Ni(I)] intermediate **B**. On the other hand, the substitution of methyl electrophiles R−X **2** with the in situ generated nucleophilic [Co(I)] **D** would afford R−[Co(III)] **E**. Transmethylation between **B** and **E** through a single electron transfer (SET) process would produce the high-valent Ar−[Ni(III)X]−R nickel(III) species **C** and regenerate the nucleophilic [Co(I)] **D**. The reductive elimination of **C** would result in the formation of methylated arenes **3** and [Ni(I)]−X, which would then be reduced by Mn to regenerate the [Ni(0)] species.

A related transmethylation of Me−[Co(III)] with [Ni(I)] had been previously demonstrated,[20] wherein the nickel acts as one electron reductant for Me−[Co(III)] to form Me−[Co(II)], and a homolytic cleavage follows, providing Me−[Ni(II)] species via a radical mechanism. Inspired by this study, we conducted the stoichiometric reaction of aryl iodide **1e** with Me−Co(III)(salen)(H_2O) in the presence of $NiBr_2$bpy and Mn reductant, which afforded the methylated product **4** in 22% yield (Scheme 4, eq 3). However, no product was obtained when using a catalytic amount of nickel (10 mol %). On the basis of these results, the controllable transmetalation between the Me-Co(salen) and nickel species seems to be key to the present efficient methylation, most likely due to the weakening of the Co−C bond prompted by the axial ligand.[15b]

In conclusion, we have developed a nickel and nucleophilic cobalt-catalyzed reductive cross-coupling between aryl halides and CD_3OTs, affording a diverse set of CD_3-arenes. The

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choice of the cobalt catalyst was found to be crucial to the reaction efficiency, with Co(salen) exhibiting the highest performance. Although the accurate role of the cobalt is still to be clarified, some mechanistic investigations revealed that the present reaction involved a transmethylation between organonickel and methyl cobalt intermediates. Further studies on the mechanism and synthetic applications of the Ni/Co catalytic system are currently ongoing in our group.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01863.

Experimental procedure and spectroscopic data (PDF)

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Notes

The authors declare no competing financial interest.

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