Cross-Coupling

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Nickel-Catalyzed Methylation of Aryl Halides with Deuterated Methyl Iodide

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Abstract: *A nickel-catalyzed methylation of aryl halides with cheap and readily available CH_3I or CD_3I is described. The reaction is applicable to a wide range of substrates and allows installation of a CD_3 group under mild reaction conditions without deuterium scrambling to other carbon atoms. Initial mechanistic studies on the stoichiometric and catalytic reactions of the isolated [(dppp)Ni(C_6H_4-4-CO_2Et)Br] [dppp = 1,3-bis(diphenylphosphanyl)propane] suggest that a Ni^0/Ni^{II} catalytic cycle is favored.*

The magic methyl effect has been well-documented during the past decade.[1,2] In medicinal chemistry, methylation is one of the most widely used strategies to modify bioactive compounds during lead optimization.[3] The installation of a methyl group to a drug candidate can dramatically improve its biological activities, presumably because of its stereoelectronic effects on both pharmacodynamic (PD) and pharmacokinetic (PK) profiling. For example, introduction of a methyl group to compound **A** showed a 208-fold increase in potency as an inhibitor of p38α MAP3 kinase (Figure 1).[4] Furthermore, introduction of deuterated methyl group in medicinal chemistry has been intensively attempted during the optimization of drug candidates. Several deuterated compounds such as SD-560,[5a] CTP-354,[5b] and CTP-499[5c] are now in clinical trials. It is believed that an efficient strategy for introduction of a CD_3 group by methylation is important, both for method development and intellectual property protection.[6]

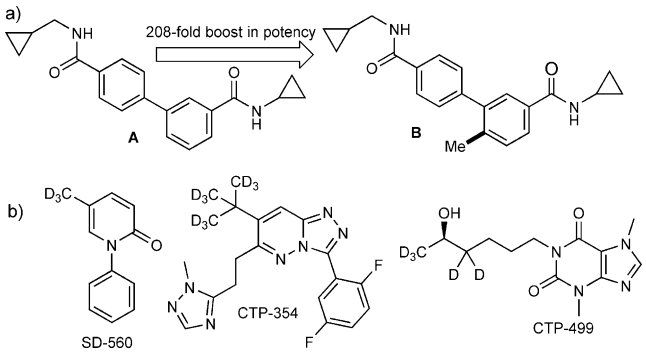

Figure 1. a) An example of the methyl effect. b) Examples of deuterated compounds in clinical trials.

The most classic methylation methods involve a lithium–halide exchange of aryl halides following by trapping of a methyl electrophile. Such methods are only useful when other electrophilic groups are absent. In addition, the use of reactive organolithium reagents is neither environmentally friendly nor operationally safe. Not surprisingly, the C–C cross-coupling reactions mediated by transition-metal complexes have emerged as a powerful tool for the installation of methyl groups to arenes. In general, the direct methylation of either a C–H or C–X bond involves the use of either methyl organometallic reagents (magnesium,[7] tin,[8] boron,[9] zinc,[10] aluminum[11]) or electrophiles.[12] While powerful, the existing methods have some common limitations, including: a) use of noble metals; b) harsh reaction conditions (high temperature, strong base and oxidants); c) limited substrate scope and the requirement for a directing group. These limitations become more pronounced when installation of a CD_3 group is desired since CD_3 organometallic reagents are very limited, and only a few are commercially available [e.g., $CD_3B(OH)_2$], albeit prohibitively expensive. To the best of our knowledge, a catalytic method which is capable of installing CD_3 on aryl halides has not been reported thus far.

To address this unmet synthetic need, we envisioned that a transition metal catalyzed C–C bond formation between readily available methyl iodide and aryl halides might provide a practical solution. Of note, such a reductive coupling between two different electrophiles is a considerable challenge because of the complication of competitive homocouplings, hydride functionalization, and catalyst deactivation.[13] Recently, Weix and co-workers reported some elegant work on a nickel-based catalyst system for reductive couplings between aryl and alkyl halides with high selectivities for cross-coupling products over that of homocoupling.[14] However, no coupling reaction with methyl halides was demonstrated for the system. This deficit could be attributed to the difficulty of either generating free methyl radicals or its subsequent involvement in C–C bond formation by nickel-mediated reductive elimination, which was implied by a proposed free-radical-chain mechanism.[15] Herein, we report a nickel(0)-catalyzed methylation of aryl halides and it features an earth-abundant nickel catalyst, an easily available methyl source, mild reaction conditions, excellent functional-group tolerance, simple reaction procedure, and scalability. More importantly, this method was successfully extended to the reaction of CD_3I, with no deuterium incorporation onto the aryl ring.

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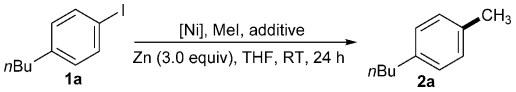
We started our investigations with a model reaction using 4-butyl-iodobenzene (**1a**) and CH_3I. When the reaction was conducted with several bidentate nitrogen-containing ligands, which were commonly employed in nickel-catalyzed cross-coupling reactions,[16] no desired product was obtained (see entries 1–4 of Table S1 in the Supporting Information). We suspected that nitrogen-containing ligands might be involved in N-methylation side reactions and not suitable for methyl iodide substrate. Thus, we switched our focus on phosphorus ligands. To our delight, the desired methylation product **2a** was obtained in 7% yield by using dppp as a ligand (Table 1,

Table 1: Optimization of reaction conditions.[a]



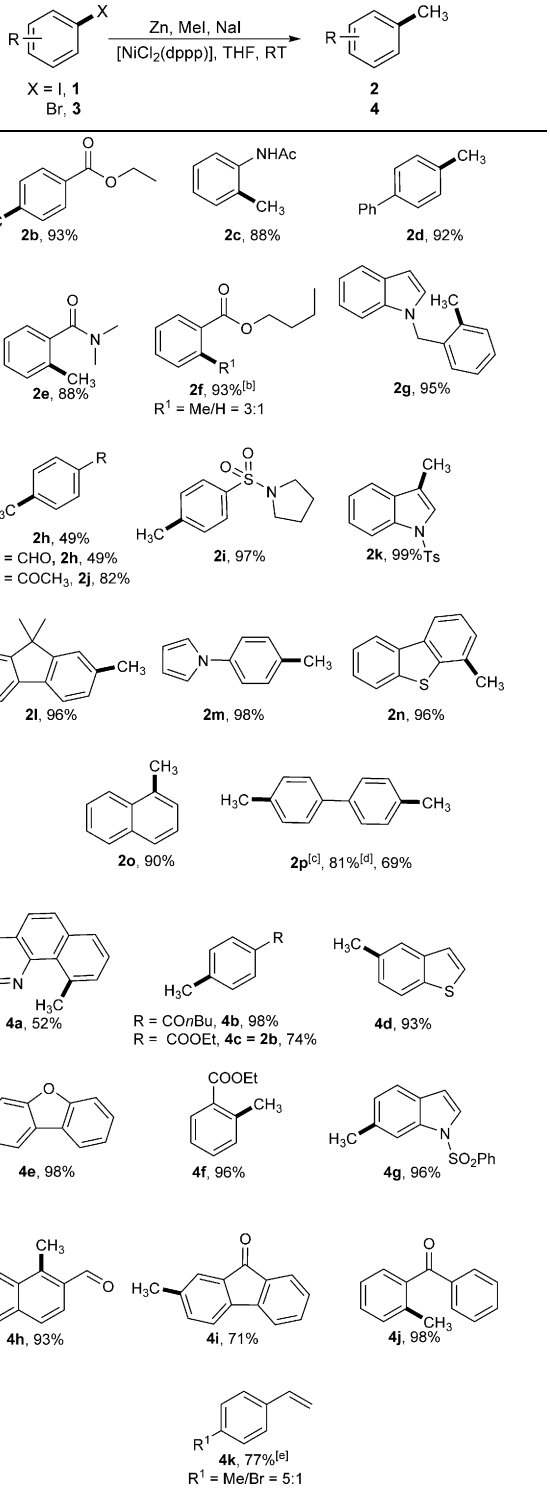
Entry	Ni (mol%)	MeI (equiv)	Additive (equiv)	Yield [%][b]
1	$[NiCl_2(dppp)]$ (5)	2.0	–	7
2	$[NiCl_2(dppp)]$ (5)	2.0	NaI (1.0)	17
3	$[NiCl_2(dppp)]$ (10)	2.0	NaI (1.0)	48
4	$[NiCl_2(dppe)]$ (10)	2.0	NaI (1.0)	19
5	$[NiCl_2(dppf)]$ (10)	2.0	NaI (1.0)	13
6	$[NiCl_2(PPh_3)_2]$ (10)	2.0	NaI (1.0)	15
7	$[NiCl_2(PCy_3)_2]$ (10)	2.0	NaI (1.0)	11
8	$[NiCl_2(dppp)]$ (10)	3.5	NaI (1.5)	74

[a] Reaction conditions (unless otherwise specified): **1a** (0.25 mmol, 1.0 equiv), CH_3I, cat. [Ni], Zn (3.0 equiv), additive, THF (0.1 M) for 24 h. [b] Yield was determined by GC using *n*-dodecane as the internal standard.

entry 1). Simply by adding NaI, which might be relevant to the generation of more reactive organozinc species and facilitate the transmetalation step based on previous work,[17] **2a** was acquired in 17% yield (entry 2). An increase of the loading of $[NiCl_2(dppp)]$ from 5 to 10 mol% further improved the yield of **2a** to 48% (entry 3). Then a variety of $NiCl_2$ precursors with coordinated monodentate or bidentate phosphine ligands were examined (entries 4–7). $[NiCl_2(dppp)]$ was found to be the best. Reactions attempted with different additional salts indicated that the efficiency of this cross-coupling was heavily affected by halide salts (see Table S2), and was consistent with findings reported by Organ and co-workers.[17b,c] A further optimization of the amount of MeI and NaI afforded the coupled product in 74% yield (Table 1, entry 8). In comparison, under the nickel-catalyzed alkylation reaction conditions reported by Weix and co-workers, only trace amounts of the desired product were achieved.[18]

With the optimized reaction conditions in hand, we began to explore the scope with respect to the aryl iodides (Table 2). A variety of aryl iodides underwent methylation with methyl iodide to furnish the desired products. In principle, electron-withdrawing, electron-donating, and electron-neutral substituents were all well-tolerated under the standard reaction conditions. Different functional groups, including amide, ester, ketone, formyl, and sulfonamide groups, were compatible with the reaction conditions to provide the corresponding methylation products in good to excellent yields (**2b–j**).

Table 2: Methylation of aryl iodides and aryl bromides.[a]



[a] Reaction conditions (unless otherwise specified): **1** or **3** (0.5 mmol, 1.0 equiv), CH_3I (3.5 equiv), $[NiCl_2(dppp)]$ (10 mol%), Zn (3.0 equiv), NaI (1.5 equiv), THF (5ml) for 24 h. Yield is that of isolated product. [b] **2f** was isolated as a mixture. The ratio was determined by ^1H NMR spectroscopy. [c] **1p** was 4-bromo-4′-iodo-1,1′-biphenyl. [d] CH_3I (7.0 equiv), Zn (6.0 equiv), NaI (3.0 equiv). [e] The yield was determined by ^1H NMR spectroscopy using the 1,3,5-trimethoxybenzene as an internal standard. dppe = 1,2-bis(diphenylphosphanyl)ethane, dppf = 1,1′-bis(diphenylphosphanyl)ferrocene, dppp = 1,3-bis(diphenylphosphanyl)propane.

Notably, the acidic NH in **1c** was well tolerated in the reaction. Substituents at the *ortho*- and *para*-position did not have much effect on the yields, except for one example wherein the side product derived from protonation was obtained (**2f**). Notably, phenyl iodide bearing a formyl group at the *para*-position could also undergo this transformation. However, since the aldehyde product **2h** was volatile, the yield was decreased to 49%. In addition, this methylation process enabled heteroaryl iodides to serve as cross-coupling partners (**2k**, **2m**, and **2n**). Interestingly, when we used 4-bromo-4′-iodo-1,1′-biphenyl as the coupling substrate, the methylated product **2p** was obtained. Our results also show that the yields of the dimethylation product were influenced by the amount of Zn, CH_3I, and NaI. Notably, the method could be easily extended to alkyl halides other than CH_3I, especially benzyl bromides.[19]

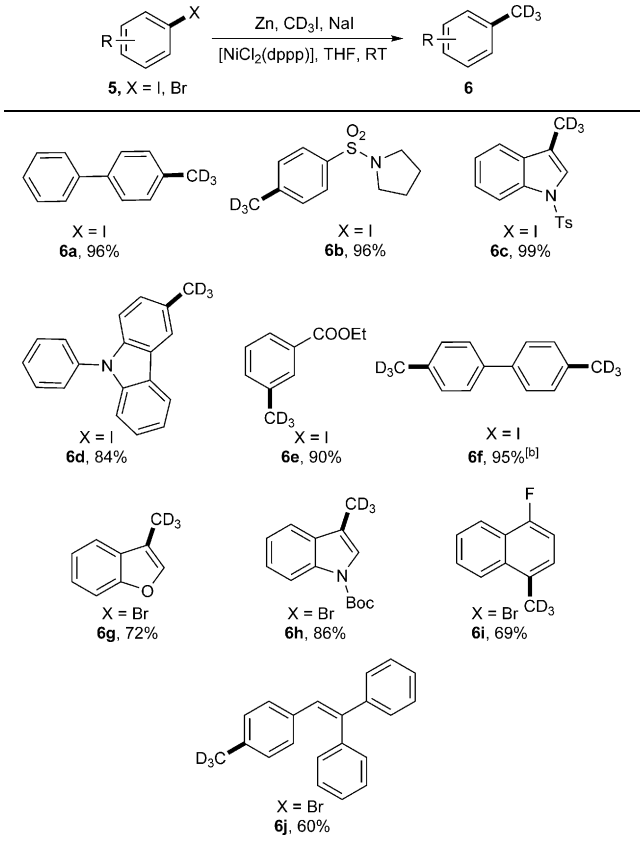
Next, we investigated this methylation process using aryl bromides as the cross-coupling partners (Table 2). As expected, the reactions with aryl bromides in the presence of a variety of functional groups proceeded smoothly. In addition, heterocyclic bromides are compatible with this transformation, thus providing the corresponding products in moderate to excellent yields (**4a**–**k**).

Finally, we examined whether this approach could be applied to introduce CD_3 (Table 3), as it would provide a useful method for the synthesis of CD_3-functionalized arenes. It was found that the cross-coupling of CD_3I with aryl iodides/bromides afforded the coupled products in good to excellent yields. The deuterated dimethylation product **6f** was obtained in 95% yield. Gratifyingly, the substrate bearing a vinyl group was also tolerated under such reaction conditions (**6j**). In all cases, no deuterium was observed to be incorporated into the other parts of the products, thus showing that C–H activation has not occurred. We further showcased the utility of our method in the synthesis of SD-560, a potentially new drug for idiopathic pulmonary fibrosis (Scheme 1). We successfully prepared SD-560 in gram quantities in just two steps with greater than 69% overall yield, compared to the existing method which resulted in less than 5% overall yield after seven steps.[20] Given the availability and cost of CD_3I, we expect our method to find further application in deuterated functional molecules.

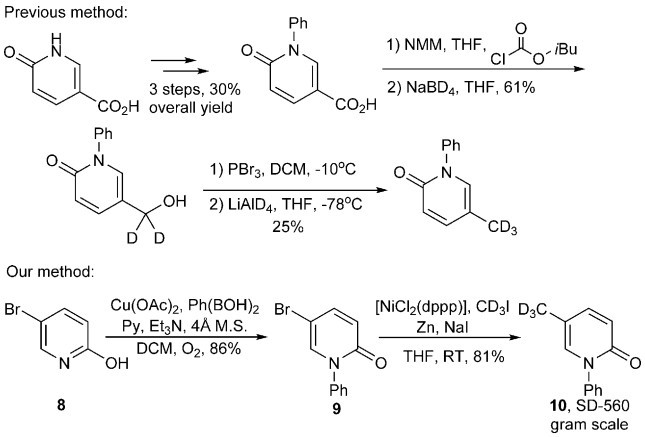
To shed light on mechanism, we isolated the possible intermediate **11** (Scheme 2; see Scheme S1). A stoichiometric reaction between **11** and $ZnMe_2$ was conducted, and then monitored by GC-MS. We found this reaction was complete in only 10 minutes (Scheme 2a). In addition, when **11** was used as a catalyst in place of $[NiCl_2(dppp)]$, the methylated product was obtained in 84% yield (Scheme 2b). Both results suggest that **11** is probably the key intermediate in the catalytic cycle.

Thus, we proposed here that this methylation could proceed through two different pathways, as shown in Scheme 3. Pathway A involves a free-radical-chain process before the product is formed, while pathway B involves a transmetallation process before reductive elimination could occur. We reasoned that if the methyl radical could be formed dominantly, this transformation would proceed by the former mechanism. Otherwise, pathway B would be favored.

Table 3: Deuterated methylation of aryl halides.[a]

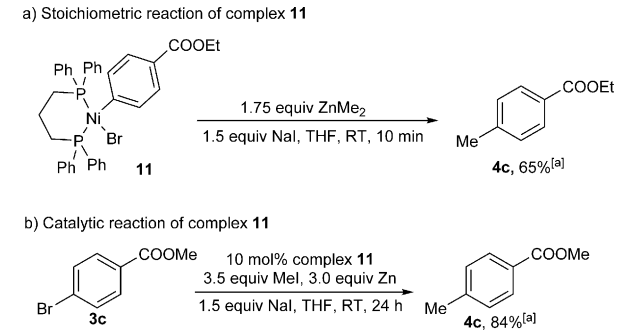


[a] Reaction conditions (unless otherwise specified): **5** (0.5 mmol, 1.0 equiv), CD_3I (3.5 equiv), $[NiCl_2(dppp)]$ (10 mol%), Zn (3.0 equiv), NaI (1.5 equiv), THF (5ml) for 24 h. Yield is that of isolated product. [b] CD_3I (7.0 equiv), Zn (6.0 equiv), NaI (3.0 equiv).

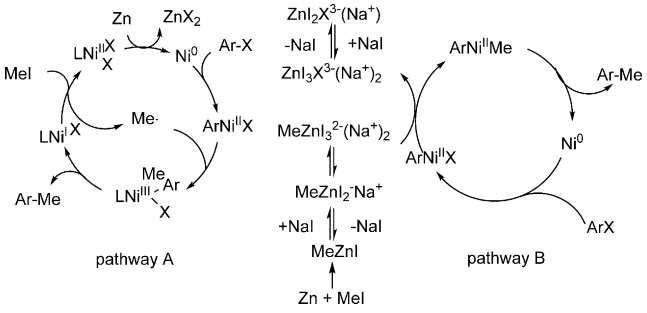


Scheme 1. Application in the synthesis of a biologically active molecule.

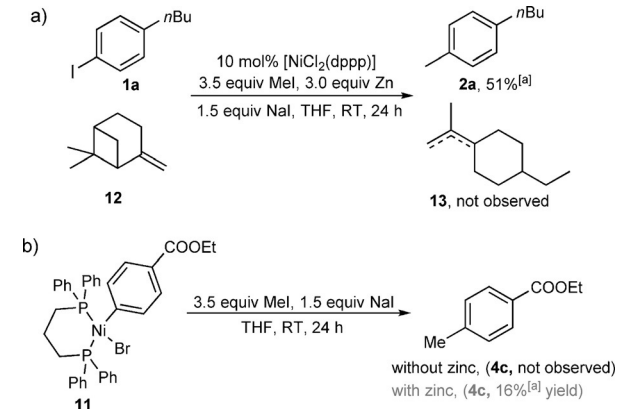
To distinguish between these two mechanisms, several control experiments were carried out. Reactions conducted in the presence of a radical trap, β-pinene (**12**), did not afford ring-opened diene **13**, and indicated this reaction might not generate a methyl radical[21] (Scheme 4a). This finding was inconsistent with the mechanism proposed by Weix and co-workers[15] (Scheme 3, Pathway A). Then [(dppp)Ni(C_6H_4-4-



Scheme 2. Reactivities of the possible intermediate **11**. [a] Yield of isolated product. THF = tetrahydrofuran.



Scheme 3. Possible mechanism.



Scheme 4. Mechanistic studies in details. [a] Determined by GC-MS.

CO_2Et)Br] was subjected to the standard reaction conditions but without Zn^0, and no desired product was observed (Scheme 4b), thus excluding zinc as the reducing agent. However, with the addition of Zn^0, the methylated product **4c** was obtained in 16% yield (Scheme 4b). We reasoned the low yield might result from unmatched rates of oxidative addition and transmetallation. When we added TEMPO to the standard reaction conditions (see Scheme S2e), the methylation reaction was suppressed, and was presumably relevant to nickel- and zinc-involved oxidative addition processes. It is well known that both nickel- and zinc-involved oxidative additions are related to the process of radical generation.[22] Consistent with this hypothesis, stoichiometric reaction of **11** and $ZnMe_2$, even with the addition of TEMPO, afforded **4c** in 76% yield (see Scheme S2c), while no product was formed when using **3c** as the coupling partner (see Scheme S2d). These results implied that oxidative addition of **3c** to form **11** proceeded through a radical pathway.[23] A similar result was observed when we investigated the formation of organozinc species with the addition of TEMPO (see Scheme S2g). A plausible mechanism involving a Ni^0/Ni^{II} catalytic cycle is proposed (Scheme 3, Pathway B), that is, Pathway B is the favored pathway. This mechanism is seemingly similar to the palladium-catalyzed aqueous Lipshutz–Negishi cross-coupling of alkyl halides with aryl electrophiles.[13d] However, under Lipshutz's standard reaction conditions, no methylation product was formed with the substrate **3e**, whereas **4e** was obtained in 98% yield using our method. It is important to note that previous mechanistic studies by the groups of Fu,[23a] Vicic,[23b] Weix,[15] and others[24a,b] all suggest a Ni^I/Ni^{III} catalytic cycle is involved in such transformations. However, we found that a nickel-catalyzed cross-coupling between aryl electrophiles and alkyl electrophiles could also favor a Ni^0/Ni^{II} catalytic cycle.[24c]

In summary, we have developed an efficient methylation method of aryl halides using CH_3I under mild reaction conditions. In addition, this method is especially appealing in the syntheses of CD_3-containing compounds by using readily available, cheap, and stable CD_3I as the CD_3 source. Studies on the stoichiometric and catalytic reactions of the isolated [(dppp)Ni(C_6H_4-4-CO_2Et)Br] suggest that a Ni^0/Ni^{II} catalytic cycle is favored. Additional mechanistic studies to further illuminate the detailed reaction mechanism are underway.

Acknowledgments

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Keywords: arenes · cross-coupling · deuterium · methylation · nickel

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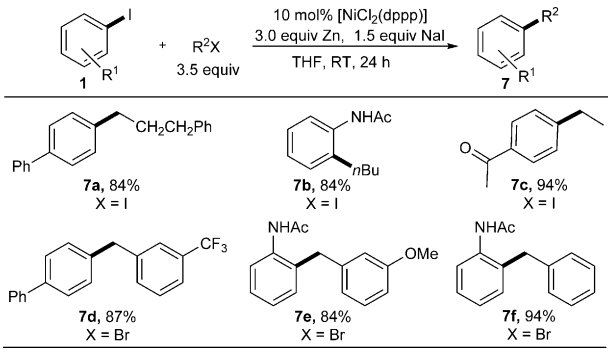

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