Methylation of Arenols through Ni-catalyzed C-O Activation with Methyl Magnesium Bromide

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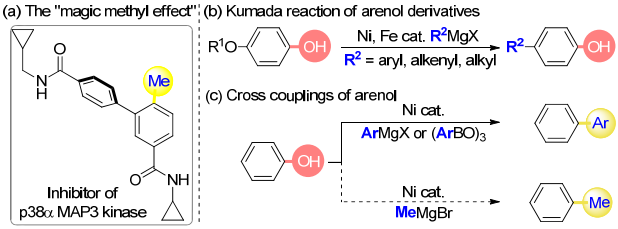
Abstract: Direct alkylation of arenols with alkyl organometallic reagents has never been approached. Herein we reported the first successful example of nickel-catalyzed methylation of arenols with methyl Grignard reagents to construct C(sp^2)-C(sp^3) bond under mild conditions. The transformation was compatible with broad substrate scope of 2-naphthol derivatives. Benzyl alcohol and biphenols were also suitable substrates for this methylation.

Methylation is an essential and ubiquitous reaction that plays an important role in biochemistry.[1] The stereo- and electronic effects make methyl group significant for the molecular recognition in bio-interaction since such a recognition results in diversified biological effects, such as the augment of solubility, the increase of lipophilicity and the change of the interaction modes between small molecules and their receptors.[1b] 6/20 of natural amino acids bear methyl groups and the methylation of cysteine residue of protein can alter the ubiquitin-chain binding and change the signaling pathway.[2] The methylation is also a common strategy to modify the structure of drugs and intrinsically affects their bio-efficacy[1b] since methylation can adjust three dimensional conformations of molecules, thus making them match the active sites of their receptors more efficiently.[1b] This modification can also decrease the conformational reordering energy. For instance, the *ortho*-methylation of the inhibitor of p38a MAP3 kinase twisted the dihedral angle of biaryl bond from 50° to 65°. The locked conformation of this drug candidate became closer to the ideal dihedral angle (85°). Therefore, the IC_{50} value of this methylated analogue was 208-fold decreased (**Scheme 1a**).

This phenomenon was the so-called “magic methyl effect”.[1] Indeed, methylation became a hot topic in both academy and industry to respond to the call for direct methylation of different types of molecules.[1a]

The conventional methylation on the carbon atom starts from methyl halides and organometallic nucleophiles.[3] Since 1970s, the powerful transition-metal-catalyzed cross coupling of electrophiles with methyl metallic nucleophiles is the other promising pathway.[4] Compared to aryl halides, the abundant, cheap, eco-friendly and readily available arenols and their derivatives are highly valuable alternative of halo-based electrophiles. Recently, much progress has been made in the methylation of arenol derivatives.[5] Obviously, for the ecological and economic advantages, direct methylation of arenols is more attractive. However, there are several remaining challenges that hampered the developments in this field if the reaction starts from arenols: (1) the high bond dissociation energy (BDE) of phenolic C-O bond; (2) the further increased BDE due to the p-π conjugative effect between the phenolic anion and aryl ring under basic conditions; (3) the poison of transition metal catalyst arising from the coordination of phenolic anion to the transition metals; (4) the poor leaving ability of phenolic hydroxyl group. Thus, compared to the arenol derivatives,[6] the direct cross couplings of arenols are rare[7] and the formed C-C bonds are only limited to the C(sp^2)-C(sp^2) bonds up to date [5a, 7a-c] (**Scheme 1**).



Scheme 1. (a) The “magic methyl effect” on the lead compound in drug discovery. (b) Kumada reaction of arenol derivatives with Grignard reagents. (c) The desirable coupling of arenols with different organometallic reagents.

In 1979, Wenkert and co-workers[5a] first reported the Kumada reaction of C-O bonds of anisole and vinyl methyl ether derivatives. In their studies, they first observed that 2-naphthol showed a very low reactivity with PhMgBr. In 2004, Dankwardt[8] pioneered the cross coupling of anisoles with aryl Grignard reagents by the utilization of bulky and electron-rich phosphine ligand in nonpolar solvents. In 2015, Chatani group made significant contributions in the cross couplings of anisoles with alkyl[5l] and alkynyl[9] Grignard reagents in the presence of bulky and electron-rich NHC ligand. In those studies, phenolic group possessed a credible stability and was compatible under different conditions,[10] showing the challenges on the cleavage of

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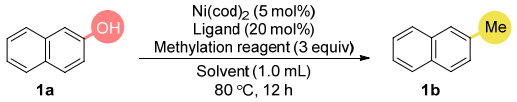
aryl C-O bond of phenolic salts. In 2010, our group[7b] carried out the first successful example of cross coupling between arenols and aryl Grignard reagents. It is important to note that no methylated product was observed although 5.0 equivalent of MeMgBr was used as a base over 2.0 equivalent of PhMgBr as a coupling partner under the reaction conditions. This result further demonstrated high challenges in the methylation of phenolic C-O bond. With our continuous efforts, we herein reported the first successful example of nickel-catalyzed cross coupling of arenols with MeMgBr to construct the $C(sp^2)$-$C(sp^3)$ bond under mild conditions.

Table 1. Optimization of reaction conditions.



1a **1b**

Entry	Ligand	Methylation reagent	Solvent	Yield[a]
1[b]	Sphos	MeLi *etc*	toluene	< 5
2	Sphos	MeMgBr	toluene	9
3	Sphos	MeMgBr	THF	< 5
4	Sphos	MeMgBr	hexane	16
5	bipy	MeMgBr	toluene	< 5
6	Xphos	MeMgBr	toluene	< 5
7	CyJohnPhos	MeMgBr	toluene	17
8	Mephos	MeMgBr	toluene	14
9	Davephos	MeMgBr	toluene	12
10	PCy_3	MeMgBr	toluene	78
11	dcype	MeMgBr	toluene	< 5
12	^{t}BuDavePhos	MeMgBr	toluene	< 5
13	I^{t}Bu	MeMgBr	toluene	91
14	CMphos	MeMgBr	toluene	86
15	CMphos	MeMgCl	toluene	25
16	CMphos	MeMgI	toluene	41
17	CMphos	MeMgBr	toluene	72[c]

[a] Naphthalen-2-ol (**1a**, 0.2 mmol), methylation reagent (0.6 mmol), $Ni(cod)_2$ (5 mol%), ligand (20 mol%), solvent (1 mL), 80 °C, 12 h. GC yield was used. [b] MeLi, $ZnMe_2$, or $AlMe_3$ was used. [c] $Ni(OAc)_2$ was used.

We initiated our studies with 2-naphthol (**1a**) as the model substrate since it showed the best reactivity in previous reports.[7b-d] Unfortunately, methyl lithium, methyl zinc, and methyl aluminium reagents completely failed in the cross coupling reactions under different conditions (entry 1). To our delight, the product was observed when MeMgBr was used in the presence of Sphos (dicyclohexyl(2',6'-dimethoxy-[1,1'-biphenyl]-2-yl)phosphine) as ligand (entry 2). In previous studies[8], solvent was proved to be crucial to the cross coupling of *O*-based electrophiles. Unfortunately, the solvents did not show their significance in this case and we did not even observe the desired product in the etheric solvent, despite the fact that they were broadly used in many transformations (entry 3). Although the yield was promoted to 14% in hexane, the reaction mixture was too sluggish to stir, making the further screenings difficult (entry 4). When toluene was used as solvent, the mixture kept well stirring during the reaction time.

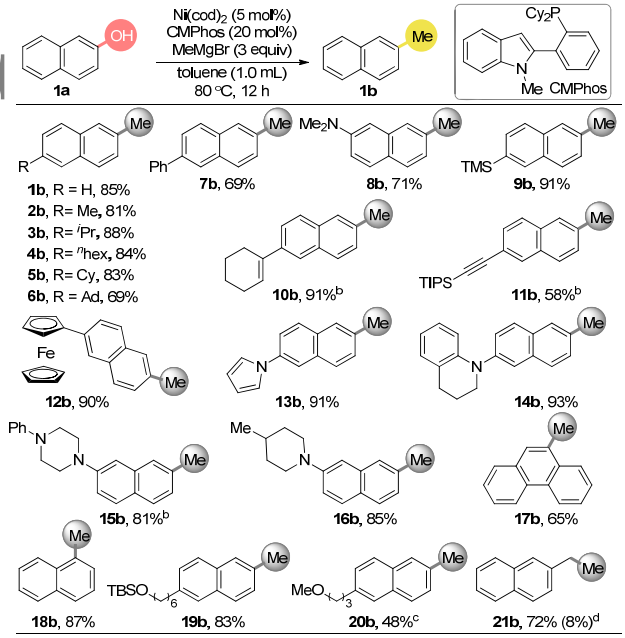
As proposed, the oxidative addition of phenolic C-O bond to the Ni(0) center must be the most difficult step in the catalytic cycle[7b]. We envisioned that a bulky and electron-rich ligand may be beneficial for promoting the oxidative addition. Since many nitrogen-containing ligands[11] were tested but not effective (entry 5), we focused our screening on phosphine ligands. We found that the monodentated Xphos (dicyclohexyl(2',4',6'-triisopropyl-[1,1'-biphenyl]-2-yl)phosphine) with a big bite angle was invalid (entry 6), while CyJohnPhos ((1,1'-biphenyl)-2-yldicyclohexylphosphine) with a smaller one slightly promoted this coupling (entry 7). Although Sphos presented effective in many transformations as a ligand, we speculated that the present methoxyl group might be methylated by the Ni(0)-phosphine-MeMgBr cocktail system under the direction of phosphorus atom and most of the Sphos may be consumed under the current conditions. Thus, Mephos (dicyclohexyl(2'-methyl-[1,1'-biphenyl]-2-yl)phosphine) was subjected to the reaction. A similar efficiency was obtained (entry 8). We further inspected the coordination ability and the steric effect of the phosphine ligand with Davephos (2'-(dicyclohexylphosphino)-*N*,*N*-dimethyl-[1,1'-biphenyl]-2-amine), and the yield was not significantly improved (entry 9). Fortunately, the yield was dramatically increased when PCy_3 was used (entry 10). However, no conversion was observed with the bidentated analogues. For example, dcype (1,2-bis(dicyclohexylphosphino)ethane)) (entry 11). The *tert*-butyl substituted phosphine ligand ^{t}BuDavePhos (2'-(di-*tert*-butylphosphino)-*N*,*N*-dimethyl-[1,1'-biphenyl]-2-amine) shut down the reaction (entry 12).

In line with these observations, we estimated that an increase of both steric hindrance and stability of the ligand may generate the more robust, stable and reactive catalyst system. Thus we tested other different ligand sets. To our satisfactory, NHC ligand I^{t}Bu (1,3-di-*tert*-butyl-2,3-dihydro-1*H*-imidazole) afforded **1b** in a high yield (entry 13). Considering that I^{t}Bu was expensive and sensitive to air and moisture, we extended to develop another stable phosphine ligand. Inspired from the recent successes with the use of CMPhos (2-(2-(dicyclohexylphosphino)phenyl)-1-methyl-1*H*-indole) in the cross couplings of arenol derivatives[6h], we synthesized this ligand and delivered it to this methylation reaction. To our satisfactory, an excellent yield of methylated product **1b** was obtained with the full conversion of starting material **1a** (entry 14). Finally, we found MeMgBr was the best nucleophile (entries 15-16). Moreover, the air and moisture stable Ni(II) catalyst also afforded a good yield (entry 17).

With the optimized conditions in hand, we investigated the substrate scope of arenols (**Table 2**). Different alkyl groups were tolerated in high yields (**2b**-**6b**). Arenol with aryl substituents afforded the product in 69% yield, probably due to its worse solubility (**7b**). The tertiary amino group, which could be further transformed into different functionalities through arylation, borylation, animation reactions,[12] survived well (**8b**). To our delight, the reaction took place in an excellent yield with the silyl group (**9b**), which paved the way for the diversification to complex molecules.[13] Methylation was highly efficient with the styrene moiety[14] and the alkenyl group kept untouched (**10b**). The alkyne functionality was compatible in a synthetic useful yield (**11b**) with some starting martial remained, probably due to the strong coordination interaction between Ni(0) species and alkynyl group.[6d]

To our delight, this protocol was suitable to ferrocene motif (**12b**), that was frequently used in a range of fields, including material science[15], medicinal chemistry[16], organic catalyst and ligand scaffold.[17] Another feature of this method was its good compatibility in the nitrogen-containing heterocycles, such as pyrrolyl (**13b**), tetrahydroquinolinyl (**14b**), piperazinyl (**15b**), and piperidinyl (**16b**). On the other hand, a good yield was obtained with the extented π-conjugated system (**17b**).This protocol was also robust for more steric hindered α-arenol (**18b**). The perfect compatibility of the traditional alcohol protecting group left the room for the synthesis of complicated molecules (**19b**). Etheric group survived under the finely modified conditions and the desired product **20b** was obtained in a moderate yield. The reaction was also applicable to benzyl alcohol in a good yield (**21b**), albeit with a small amount of reductive product.

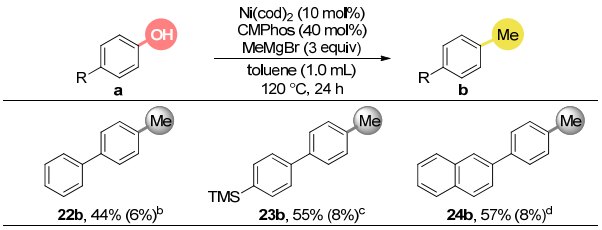
Table 1. Substrate scope of naphthol derivatives and 2-naphthylmethyl alcohol.[a]



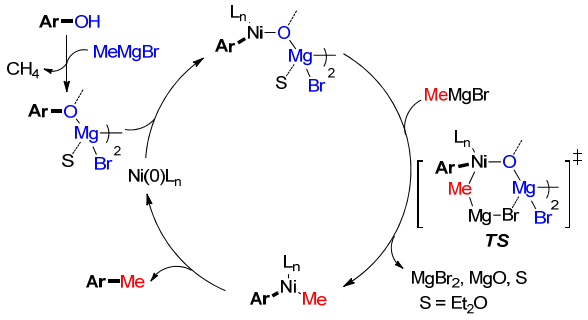
[a] Arenols (**1**, 0.2 mmol), MeMgBr (0.6 mmol), $Ni(cod)_2$ (5 mol%), CMphos (20 mol%), toluene (1 mL), 80 °C, 12 h. [b] 24 h. [c] I^{t}Bu (20 mol%) was used. [d] A mixture of **21b** (72%) and 2-methylnaphthalene (8%) was obtained.

Encouraged by the success with 2-naphthol derivatives, we intended to extend our protocol to the simple but more challenging phenol substrates. Similar as the previous results before, simple phenol and its derivatives showed lower reactivity over other arenols with extended π systems,[18] probably due to the high energy requirement to compensate the loss of the aromaticity of phenyl ring during the oxidative addition. Although biphenols were inactive with aryl Grignard reagents in our previous work,[7b] we found these units were suitable in this methylation under the finely modified conditions in acceptable yields (**Table 3**). The non-substituted biphenol could be methylated in a moderate yield, albeit with a small amount of reductive product (**22b**). A better yield was obtained in the presence of silyl group, which can be further functionalized (**23b**). Furthermore, biphenol with π-extended substituent group also showed good performance (**24b**). It should be noted that in the methlylation of biphenols, the stable and bulky phosphine ligand, CMPhos, showed its power while I^{t}Bu was invalid. The study on the methylation of the simple phenol was still underway.

Table 2. Substrate scope of biphenols [a]



[a] biphenols (0.2 mmol), MeMgBr (0.6 mmol), $Ni(cod)_2$ (10 mol%), CMphos (40 mol%), toluene (1 mL), 120 °C, 24 h. [b] A mixture of **22b** (44%) and 1,1'-biphenyl (6%) was obtained. [c] [A mixture of **23b** (55%) and [1,1'-biphenyl]-4-yltrimethylsilane (8%) was obtained. [d] A mixture of **24b** (57%) and 2-phenylnaphthalene (8%) was obtained.



Scheme 3. The proposed mechanism.

Based on current studies and previous reports, we proposed the mechanism as **Scheme 3**. After deprotonation of arenol by MeMgBr, the dimeric magnesium phenolic salt was formed.[7b] Owing to the Lewis acidity and oxophilicity of magnesium ions, the energy

barrier of the oxidative addition became much lower by the coordination of Mg^{2+} to the phenolic species, as demonstrated by our previous single crystal of 2-NapOMgBr complex. The formed magnesium salts, such as $MgBr_2$ and MgO, could also increase the leaving ability of Ar-OMgBr. The transmetalation step became energetically favored by the interaction of magnesium ions with the oxygen anion *via* six-membered (or fused 4,4-bicyclic) transition state (**TS**) and the formation of magnesium salts [10a]. The desired methylated product was obtained through reductive elimination with the regeneration of Ni(0) species to fulfill the catalytic cycle. During this process, the electron-rich, bulky and stable ligand was required to improve the abilities of the nickel catalyst at the oxidative addition and reductive elimination steps.

In summary, we for the first time developed the nickel-catalyzed methylation of arenols with methyl Grignard reagent under mild conditions. This protocol was featured as good functional group tolerance. The NHC ligand was also a good choice to the extended π system, while the stable, electron-rich and bulky phosphine ligand CMPhos was more robust in our protocol. Benzyl alcohol and biphenols were also methylated with CMPhos as a ligand. Further extension of substrate scope to the alkylation of arenols and other alcohols is underway.Main Text Paragraph.

Experimental Section

General procedure for the methylation of arenols: To an oven-dried schlenk tube with a stirring bar was added **1a** (28.8 mg, 0.2 mmol) in the air. The tube was removed to the glove box and then CMPhos (16.2 mg, 0.04 mmol, 20 mol%) and $Ni(cod)_2$ (2.8 mg, 0.01 mmol, 5 mol%) were added, followed by the sequential injections of toluene (1 mL) and MeMgBr (0.2 mL, 3 equiv, 0.6 mmol). The tube was sealed by plastic septa and moved out of the glove box. The mixture was stirred at 80 °C for 12 h. Then the mixture was cooled to room temperature and directly purified by column chromatography with hexane as the eluent to afford **1b** as a white solid (24.2 mg, 85%).

Acknowledgements

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Keywords: arenol • methylation • nickel • catalysis • cross coupling

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Entry for the Table of Contents (Please choose one layout)

Layout 2:

COMMUNICATION

The nickel-catalyzed direct methylation of arenols with methyl Grignard reagent was solved under mild conditions. The transformation was compatible with various functional groups. Benzyl alcohol and biphenols were also suitable substrates.

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Cross Coupling of Arenols with Methyl Magnesium Bromide through Ni-catalyzed C-O Activation