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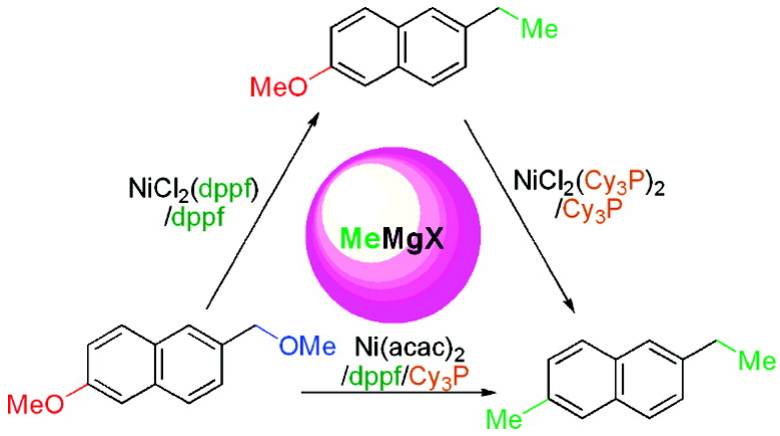

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Direct Benzylic Alkylation via Ni-Catalyzed Selective Benzylic sp³ C−O Activation

Bing-Tao Guan,[†] Shi-Kai Xiang,[†,‡] Bi-Qin Wang,[†,‡] Zuo-Peng Sun,[†,‡] Yang Wang,[§] Ke-Qing Zhao,[‡] and Zhang-Jie Shi*,[†,||]

Beijing National Laboratory of Molecular Sciences (BNLMS) and Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education, College of Chemistry, Peking University, Beijing 100871, China, College of Chemistry and Material Science, Sichuan Normal University, Chengdu, Sichuan 410066, China, and Department of Chemistry, China Agricultural University, Beijing 100094, China, and State Key Laboratory of Organometallic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China

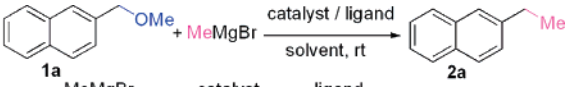
Received December 8, 2007; E-mail: zshi@pku.edu.cn

Kumada coupling is a very useful method to construct C−C bonds by utilizing aryl halides and Grignard reagents via Ni-catalyzation.[1] New developments to apply cheap and easily available aryl chlorides and tosylates into this reaction made it more practical.[2] Recently, Fu and co-workers showed that alkyl halides could be applied into this coupling to construct sp³ C−C bonds.[3] Much attention has also been paid to the activation of the relatively stable but commonly encountered C−O bonds. In direct C−O fuctionalizations, aryl Grignard reagents showed good reactivity to react with sp² C−OMe.[4] Some recent studies showed that Suzuki coupling with methoxyl arenes can be achieved as well.[5] Our recent studies showed that direct methylation of anisole and its derivatives occurred with MeMgBr via Kumada coupling.[6] In this article, we demonstrated the first benzyl alkylation to construct the sp³ C−C bond through Kumada coupling via Ni-catalyzed highly selective benzylic sp³ C−O activation.

Compared to the activation of sp² C−O bonds, sp³ C−O activation was not well studied. Alkyl C−O with good leaving groups, such as OTs, showed satisfying activity in different reactions.[7] However, few cases were reported to selectively activate an sp³ C−O bond in ethers, since, (1) generally, an sp³ C−O bond has a relatively high bond dissociation energy (BDE); (2) the discrimination of two different sp³ C−O bonds of the ether is challenging; and (3) after the cleavage of sp³ C−O bonds, the transformation with other reagents to construct C−C bonds is hard to control. Thus, although the cleavage of the relatively active allylic sp³ C−O bond of allyl ether has been reported via transition-metal catalyzation,[8] the C−C formation directly via etheric sp³ C−O activation is unknown.

We chose first 2-(methoxylmethyl)naphthalene (**1a)** as the substrate (Table 1). Although there are two types of sp³ C−O bonds, they could be differentiated since benzylic C−O is much more active. However, when previous methods to activate aryl sp² C−O bonds were applied, only a very small amount of methylated product **2a** was observed (entry 2). With dppe as the ligand, the methylation was totally shut down (entry 4). Gratifyingly, when dppf was applied as the ligand, the desired product **2a** was isolated in a good yield (entry 5). Both $NiCl_2$ and hydrated $NiCl_2$ were not very efficient for this transformation (entries 11 and 12). $Ni(acac)_2$ showed a better catalytic ability in the presence of bidentated ligands other than dppe in this coupling (entries 9 and 10). It was of great importance to note that the coupling occurred smoothly even in the presence of 2.0 mol % catalyst (entry 6). Other than nickel catalysts, different inorganic salts were investigated but failed (entries 13−17). Further studies showed that the strongly coordinating solvents, such as THF, were not beneficial for this transformation (entry 18). However, this coupling took place quantitively in Et_2O (entry 19).

Table 1. Methylation of 2-(Methoxymethyl)naphthalene (**1a**) under Different Conditions[a]



1a **2a**

entry	MeMgBr (equiv.)	catalyst (5.0 mol%)	ligand (5.0 mol%)	solvent	**2a** (%)[b]
1	1.2	-	-	toluene	0
2[c]	1.2	$NiCl_2(PCy_3)_2$	PCy_3	toluene	9
3[c]	1.2	$NiCl_2(PPh_3)_2$	PPh_3	toluene	12
4	1.2	$NiCl_2$(dppe)	dppe	toluene	0
5	1.2/1.5	$NiCl_2$(dppf)	dppf	toluene	92/>99
6[d]	*1.5*	*$NiCl_2$(dppf)*	*dppf*	*toluene*	*>99*
7	1.5	$NiCl_2$(dppp)	dppp	toluene	97
8	1.5	$Ni(acac)_2$	dppe	toluene	0
9	1.5	$Ni(acac)_2$	dppb	toluene	>99
10	1.5	$Ni(acac)_2$	dppf	toluene	97
11	1.5	$NiCl_2$	dppf	toluene	79
12	1.5	$NiCl_2·6H_2O$	dppf	toluene	14
13	1.5	$FeCl_3$	dppf	toluene	1
14	1.5	$FeCl_2$	dppf	toluene	0
15	1.5	$Pd(PPh_3)_4$	-	toluene	0
16	1.5	$Pd(OAc)_2$	dppf	toluene	0
17	1.5	$PdCl_2$	dppf	toluene	0
18	1.5	$NiCl_2$(dppf)	dppf	THF	19
19	1.5	$NiCl_2$(dppf)	dppf	Et_2O	99

[a] All the reactions were carried out in the scale of 0.5 mmol of **1a** with the corresponding amount of MeMgBr, catalyst, and solvent under N_2. [b] GC yields with the use of *n*-dodecane as an internal standard. [c] 10 mol % of the ligand was used. [d] 2.0 mol % of $NiCl_2$(dppf) and 2.0 mol % of dppf were used in this reaction.

Different protecting groups of benzyl alcohol were detected (Table 2). Alkyl groups were suitable for this transformation regardless of their steric hindrances (entries 1−3). The phenyl group was also checked, and the methylated product was isolated in 75% yield with no observation of methylation on the phenyl ring (entry 4). As a common hydroxyl protecting group, TMS also showed good reactivity (entry 5). However, acetate and free alcohol failed to furnish the desired products, arising from their high reactivity toward Grignard reagents (entries 6 and 7). The derivatives of secondary benzylic alcohol were further investigated. The aryl substituent is helpful for this transformation (entry 8). However, alkyl substituents decreased the yields with the eliminated alkenes as byproducts (entries 9 and 10). Different Grignard reagents were further tested. The results indicated that EtMgBr was good for this coupling (entry 11). However, ^{n}BuMgCl, ^{i}PrMgBr, and PhMgBr showed lower reactivities (entries 12−14).

Various aryl methyl ethers were further surveyed (Table 3). We found that (1) both naphthyl and phenyl groups were perfectly fit

[†] Peking University.
[‡] Sichuan Normal University.
[§] China Agricultural University.
[||] Chinese Academy of Sciences.

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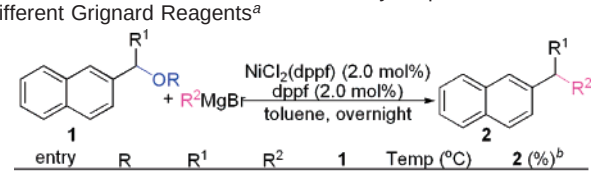
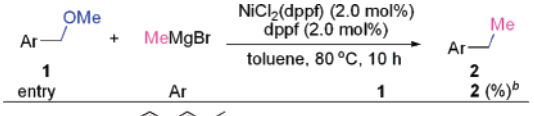
Table 2. Direct Functionalization of Benzylic sp^3 C−OMe with Different Grignard Reagents[a]

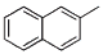
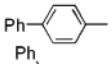
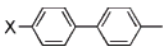


entry	R	R^1	R^2	1	Temp (°C)	2 (%)[b]
1	Me	H	Me	**1a**	25	**2a** (80)
2	Et	H	Me	**1b**	25	**2a** (73)
3	^{t}Bu	H	Me	**1c**	25	**2a** (79)
4	Ph	H	Me	**1d**	25	**2a** (75)
5	TMS	H	Me	**1e**	25	**2a** (76)
6[c]	Ac	H	Me	**1f**	25	**2a** (18)
7[c]	H	H	Me	**1g**	25	**2a** (4)
8	Me	Ph	Me	**1h**	110	**2b** (85)
9[d]	Me	Me	Me	**1i**	110	**2c** (46)
10[d]	Me	Et	Me	**1j**	110	**2d** (45)
11	Me	H	Et	**1a**	70	**2e** (96)
12[d]	Me	H	^{n}Bu	**1a**	80	**2f** (51)
13[d]	Me	H	^{i}Pr	**1a**	70	**2g** (20)
14[d]	Me	H	Ph	**1a**	25	**2h** (22)

[a] All the reactions were carried out with **1** (0.5 mmol) and R^{2}MgBr (0.75 mmol) in the presence of $NiCl_2$(dppf) (2.0 mol %) and dppf (2.0 mol %) in toluene (4.0 mL) at rt under nitrogen atmosphere. [b] Isolated yields unless otherwise noted. [c] GC yields with the use of *n*-dodecane as an internal standard. [d] NMR yields with the use of 1,2-dibromoethane as an internal standard.

Table 3. Benzylic Methylation with Different Substractes via Ni-Catalyzation[a]



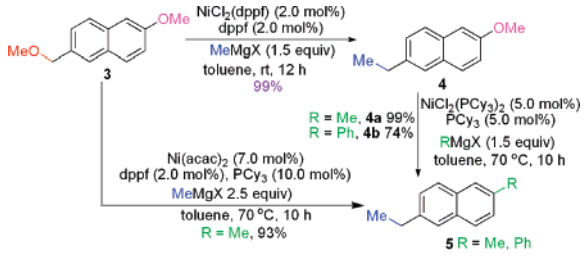
entry	Ar		1	2 (%)[b]
1[c]			**1a**	**2a** (80)
2[c]			**1k**	**2g** (75)
3			**1l**	**2h** (99)
4			**1m**	**2i** (91)
5			**1n**	**2j** (86)
6[d]		X = F	**1o**	**2k** (92)
7		X = OMe	**1p**	**2l** (89)
8		X = Me	**1q**	**2k** (95)
9[e]		X = OH	**1r**	**2m** (70)
10[f]			**1s**	**2n** (> 99)

[a] The reactions were carried out with **1** (0.5 mmol) and MeMgBr (0.75 mmol) in the presence of $NiCl_2$(dppf) (2.0 mol %) and dppf (2.0 mol %) in toluene (2.5 mL) under nitrogen atomosphere. [b] Isolated yields unless otherwise noted. [c] The reactions were carried out at rt. [d] 2.5 equiv of biphenyl (**2k**) was obtained. [e] 2.5 equiv of MgMgBr was used. [f] GC conversion with the use of *n*-dodecane as an internal standard.

for this methylation. The steric effect did not significantly affect the reactivity, and all *para*-, *meta*-, and *ortho*-substituted benzyl substrates could be transformed into the desired products with high efficiency (entries 3−5). (2) Other functionalities, such as the methoxyl and the alkyl group on the phenyl ring survived well (entries 7 and 8). Their electronic properties did not affect the reactivity of the corresponding ethers. However, aryl C−F could not tolerate this condition. It was noteworthy that the free hydroxyl group was compatible with this transformation (entry 9). Furthermore, benzyl methyl ether was also a good substrate for this methylation, which showed the broad substrate scope in this transformation (entry 10).

With this developed method, different methoxyl groups in one molecule were transformed into different functionalities stepwise

Scheme 1. High Chemoselective C−O Activation of Both sp^3 and sp^2 C−OMe



(Scheme 1). Starting from substrate **3**, benzylic sp^3 C−OMe was activated and converted into a methyl group with 99% yield. With Dankwardt's or our developed method, sp^2 C−OMe could be further transformed into a phenyl or a methyl group with high efficiency.[4d,6] Most importantly, these two processes did not crossover each other, which could be well controlled by ligands. These two processes were also combined into one-pot to methylate both sp^3 C−OMe and sp^2 C−OMe in the presence of two ligands with an excellent efficiency.

In summary, we demonstrated an unprecedented cross-coupling of relatively stable benzyl ether via Ni-catalyzed sp^3 C−O activation. This transformation showed high efficiency and excellent chemoselectivity. With this method, sp^2 C−OMe and benzylic sp^3 C−OMe in the same molecule could be differentiated by the methylation tuned by the ligand. It offers new tools for assembling complex molecules.

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Supporting Information Available: Experimental details and other spectral data for products **2** and **4**−**6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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