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Cross-coupling of Aryl/Alkenyl Silyl Ethers with Grignard Reagents through Nickel-catalyzed C–O Bond Activation

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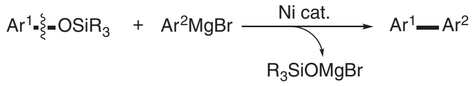
C–O activation and its application have drawn much attention since oxygen-based electrophiles are easily available, less toxic, and more environmentally benign. This letter presents systematically results on the Ni-catalyzed Kumada–Tamao–Corriu coupling based on siloxy arenes/alkenes, which provides a new strategy of silyl protection/C–C bond formation sequence in organic synthesis.

Cross-coupling reaction has become one of the most powerful tools for C–C bond construction in organic synthesis.[1] Among the developments of this area, C–O bond activation has recently drawn more attention since the easy availability, low toxicity, and environmental friendliness of starting materials.[2] Since Wenkert and co-workers reported the first example of nickel-catalyzed inert C–O bond cleavage in 1979,[3] this field has been increasingly developed in recent years. Besides a few examples of stoichiometric cleavage of inert C–O bonds,[4] various transition-metal-catalyzed C–O transformations including C–OMe,[5] C–OOCR,[6] and C–ONa[7] bonds of phenol derivatives have been reported sequentially.

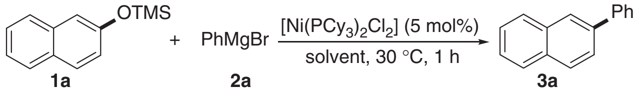
As a ubiquitous protecting group of phenols and alcohols, silyl groups are widely used in organic synthesis.[8] In general, siloxy groups are deprotected to give free OH after transformations. It could be a useful synthetic strategy to break the C–OSi bond followed by the formation of a C–C bond after the designed transformations in the presence of silyl ether as protecting groups. Hayashi and Kumada systematically studied nickel-catalyzed alkenyl C–OSiMe$_3$ bond activation in 1980.[9] In previous work, only a few examples of aryl C–OSiMe$_3$ bond activation have been reported.[3b,5a,5d,5e] Herein, we report a systematic study of the Kumada–Tamao–Corriu coupling reaction via nickel-catalyzed C–O bond activation of aryl/alkenyl silyl ethers (Scheme 1).



Scheme 1. C–O bond activation of siloxy arenes.

Previous work indicated that [Ni(PCy$_3$)$_2$Cl$_2$] is one of the most effective catalyst for the C–O bond activation.[5a,5d,5e,6a–6c,6e,6h,6m,6n,7] Thus, we ran the first try of the Kumada–Tamao–Corriu reaction by using 2-trimethylsiloxynaphthalene (**1a**) as the substrate and [Ni(PCy$_3$)$_2$Cl$_2$] as the catalyst. In the presence of 2.0 equiv of PhMgBr (**2a**) as the nucleophile, the desired cross-coupling worked well in arene or ether as solvents (Table 1). Actually, toluene (Entry 1) and THF (Entry 9) gave the best results under mild conditions and good to excellent yields of the product **3a** were obtained in 1 h at 30 °C under various conditions.

Table 1. Cross-coupling between 2-trimethylsiloxynaphthalene and PhMgBr under different conditions



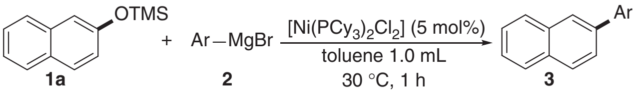
Entry	Equiv of PhMgBr	Solvent	Yield/%[a]
1	2.0	toluene	95 (80)[b]
2	1.5	toluene	95
3	1.2	toluene	66
4	2.0	benzene	92
5	2.0	*o*-xylene	88
6	2.0	mesitylene	93
7	2.0	DME	92
8	2.0	dioxane	88
9	2.0	THF	96
10	2.0	*n*-Bu$_2$O	76
11	2.0	(EtO)$_2$CH$_2$	92

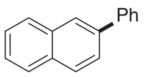
[a]Yields determined by GC using *n*-dodecane as an internal standard. [b]Isolated yields in parenthesis.

Different Grignard reagents were tested under the standard conditions (Table 2). Most of the aryl Grignard reagents gave good to excellent yields. However, aryl C–F bonds on Grignard reagents were not compatible. It is noticed that *o*-substituted phenyl Grignard reagents required a higher temperature and longer time to complete the reaction (**3c** and **3d**). Methoxy and dimethylamino groups on aryl Grignard reagents survived well (**3e** and **3f**). Unfortunately, alkenyl, allyl, benzyl, and most alkyl Grignard reagents failed at this stage while MeMgBr gave the product **3i** in an almost quantitative yield.

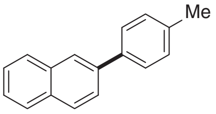
We then tested the variation of siloxy groups (Table 3). Trialkylsiloxy (Entries 1–4), triarylsiloxy (Entry 5), mixed alkyl/aryl siloxy groups (Entry 6), including bulky groups such as –OSi*t*-BuMe$_2$ (Entry 4), were efficient leaving groups during this transformation. To our interest, the presence of vinyl substituent on silyl group failed producing the desired product (Entry 7). In this case, Si–O was cleaved and the phenylated product PhSiMe$_2$(vinyl) was found in a good yield (GC yield ca. 90%), indicating that PhMgBr attacked the silicon center beyond the desired cross-coupling.[10] This inversion of the reactivity is probably due to the Lewis acidity of vinylsilane[11] and/or the coordinative ability of vinyl groups toward the Ni center. As a

Table 2. Cross-coupling between 2-trimethylsiloxynaphthalene and various Grignard reagents[a,b]

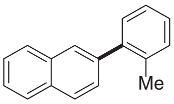




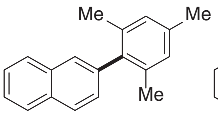
3a (80%)



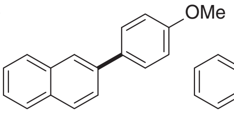
3b (81%)



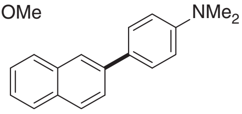
3c (74%)[c]



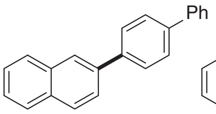
3d (73%)[c]



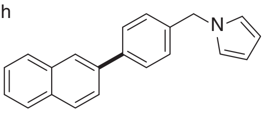
3e (70%)



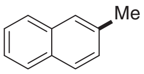
3f (63%)



3g (84%)



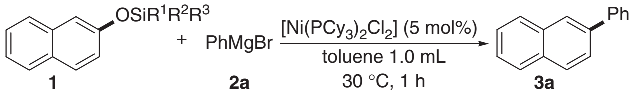
3h (69%)

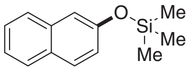
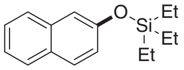
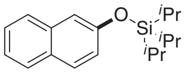
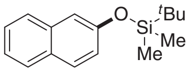
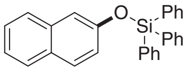
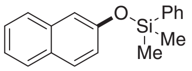
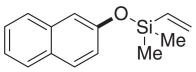


3i (>99%)

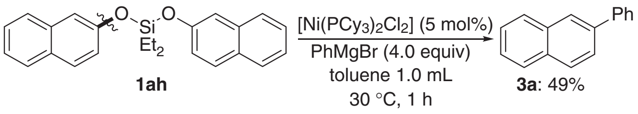
[a] All the reactions were carried out in the scale of 0.2 mmol of **1a** and 0.4 mmol of **2**. [b] Isolated yields. [c] Conditions: 80 °C, 10 h.

Table 3. Cross-coupling between various 2-siloxynaphthalene and PhMgBr[a]



Entry	Substrate		Yield/%[b]
1	**1a**		80
2	**1ab**		76
3	**1ac**		89
4	**1ad**		85
5	**1ae**		80
6	**1af**		88
7	**1ag**		0

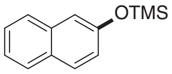
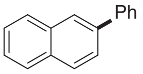
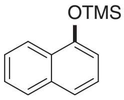
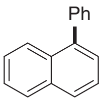
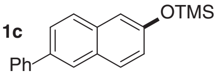
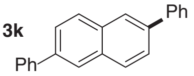
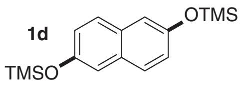
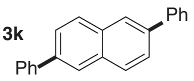
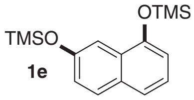
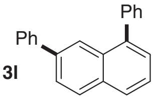
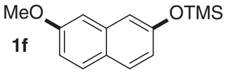
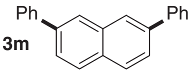
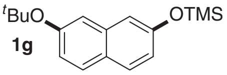
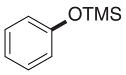
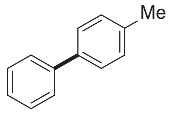
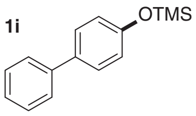
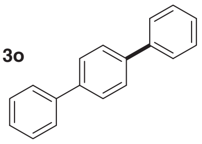
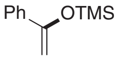
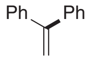
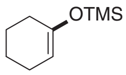
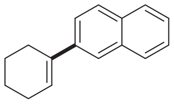
[a] All the reactions were carried out in the scale of 0.2 mmol of 2-siloxynaphthalene and 0.4 mmol of PhMgBr. [b] Isolated yields.



Scheme 2. C–O bond cleavage in bis(2-naphthoxy)diethylsilane.

Table 4. Cross-coupling between various aryl/alkenyl silyl ether and Grignard reagents[a]

$$\mathrm{Ar^1\text{–}OTMS} + \mathrm{Ar^2\text{–}MgBr} \xrightarrow[\text{toluene 1.0 mL, 30 °C, 1 h}]{[\mathrm{Ni(PCy_3)_2Cl_2}]\ (5\ \mathrm{mol\%})} \mathrm{Ar^1\text{–}Ar^2}$$

Entry	Substrate		Product		Yield/%[b]
1	**1a**		**3a**		80
2	**1b**		**3j**		73
3	**1c**		**3k**		70
4[c]	**1d**		**3k**		71
5[c]	**1e**		**3l**		71
6[c]	**1f**		**3m**		54
7[c]	**1g**		**3m**		59
8[d,e]	**1h**		**3n**		47
9[f]	**1i**		**3o**		46
10	**1j**		**3p**		77
11[g,h]	**1k**		**3q**		32

[a] All the reactions were carried out in the scale of 0.2 mmol of **1** and 0.4 mmol of PhMgBr unless otherwise noticed. [b] Isolated yields. [c] 0.8 mmol of PhMgBr was used. [d] Using *p*-tolylmagnesium bromide as Grignard reagent, the yield is determined by GC. [e] Conditions: 80 °C, 24 h. [f] Conditions: 110 °C, 24 h. [g] Using 2-naphthylmagnesium bromide as Grignard reagent. [h] Conditions: 80 °C, 10 h.

result, the naphthoxy group performed as a leaving group. Notably, when bis(2-naphthoxy)diethylsilane served as the substrate, only one C–OSi bond was cleaved even at a higher temperature (Scheme 2).[12]

Finally, different functional groups on the naphthalene moiety of naphthyl trimethylsilyl ether were surveyed (Table 4, Entries 1–7). 1-Siloxynaphthalene **1b** gave a similar result as 2-siloxynaphthalene **1a** (Entry 2). It is important to note that disilyl ethers of different naphthalenediols at 1,7- or 2,6-position lead the diphenylation products in good yields in the presence of 4.0 equivalent of PhMgBr (**2a**), companied with a small amount of monophenylated products as by-products (Entries 4 and 5). Moreover, even methoxy and *tert*-butoxy groups could not be well discriminated beyond siloxy groups and only diphenylated products were isolated in good yields in the presence of large amount of **2a** (Entries 6 and 7). Moreover, phenyl and biphenyl trimethylsilyl ether required higher temperature and longer time to yield cross-coupling products in moderate yields, probably due to their better aromaticity (Entries 8 and 9). It is noteworthy that vinyl silyl ether, which could be easily prepared from carbonyl compounds,[13] also leads to such a cross-coupling. It should be noticed that α-siloxystyrene showed much higher reactivity than inactivated 1-siloxycyclohexene (Entries 10 and 11).

In summary, we have systematically invested nickel-catalyzed cross-coupling of aryl/alkenyl silyl ether with Grignard reagents via C–OSi bonds activation.[14] With this investigation, siloxy groups are not the ubiquitous protection group of oxygen-contained molecule in organic synthesis but also a leaving group for further organic transformations. This study could offer a new strategy of silyl protection/C–C bond formation sequence in organic synthesis. Further studies on exploring other transformations of siloxy group and their application are under investigation.

This paper is in celebration of the 2010 Nobel Prize awarded to Professors Richard F. Heck, Akira Suzuki, and Ei-ichi Negishi.

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