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Ni-catalyzed cross-coupling of aryl thioethers with alkyl Grignard reagents via C–S bond cleavage

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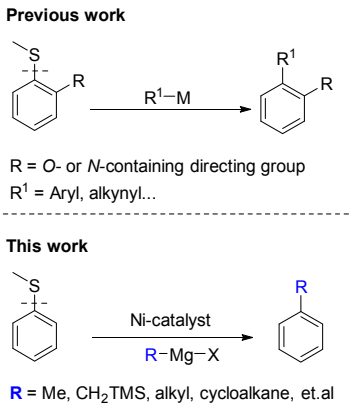
A Ni-catalyzed cross-coupling of aryl thioethers with alkyl Grignard reagents, which accompanied by the cleavage of C(aryl)–SMe bond, has been presented. This method is distinguished by its mild condition, moderate functional groups tolerance, such as hydroxyl, halogen, and heterocycles, which should provide a straightforward access to the modification of sulfur-containing molecules.

Organosulfur compounds are of great value because of its widespread existence in natural products,[1] and versatile functions in pharmaceuticals.[2] Therefore, the highly selective activation of the C–S bond still remains a highly valued synthetic transformation to accurately modify sulfur-containing molecules. During the past several decades, transition-metal-catalyzed cross-coupling reactions have witnessed astounding development in the construction of carbon-carbon bonds.[3] So far, multiple coupling partners such as Mg-, Li-, Zn-, Sn-, B-, and Si-based organometallic species have been applied in different metal-catalyzed C–C bond forming protocols. Among them, the Grignard reagents, discovered in 1900,[4] have attracted considerable interest since the incredible breakthrough work of Kumada and Tamao.[5] More importantly, concurrent with the emergence of Pd-catalyzed cross-coupling, the application of catalytic Kumada-Tamao-Corriu (KTC) reaction to aryl methyl ether via a counterintuitive Ni-catalyzed C(sp^2)–OMe bond cleavage discovered by Wenkert and coworkers[6] made the Grignard reagents particularly active in cross-coupling reactions with unconventional coupling partners that would otherwise be too inert to the construction of carbon-carbon bonds.[7-11] Over the past decade, the means to utilize C(aryl)–O electrophiles has undoubtedly gained considerable momentum.[12] Various nucleophiles, including organoboron, organozinc, organolithium, hydride, amine, and carbon nucleophiles can be conducted smoothly in the C(sp^2)–O functionalization.[13] Sulfur is in the same main-group member with oxygen, however, the activation of the C(sp^2)–S bond was comparatively scanty due to its bad smell and strong affinity to transition metals, although the C–S bond has relatively lower bond dissociation enthalpies (BDE) than C–O bond.[14] Especially, the published carbon nucleophiles that can be coupled with aryl thiol ethers have been primarily limited to C(sp^2)- or C(sp)-based nucleophiles.[15] Meanwhile, there was needed an *O*- or *N*-containing group to exist in the aryl thiol ethers as the directing group with respect to coupling reaction (As shown in Scheme 1).[15c-h] Herein, we reported a nickel-catalyzed KTC-type cross-coupling of aryl thiol ethers with various inexpensive and nontoxic alkyl Grignard reagents, in which a sulfur methyl group is eliminated.



Scheme 1 Transition-metal-catalyzed cross-coupling of aryl thiol ethers

We firstly proceed to examine the reaction compatibility of the aryl thioethers with MeMgBr by using $NiCl_2(PPh_3)(IPr)$ as the catalyst in toluene at room temperature. As shown in Table 1, thiomethyl-naphthalenes can perform high reactivity

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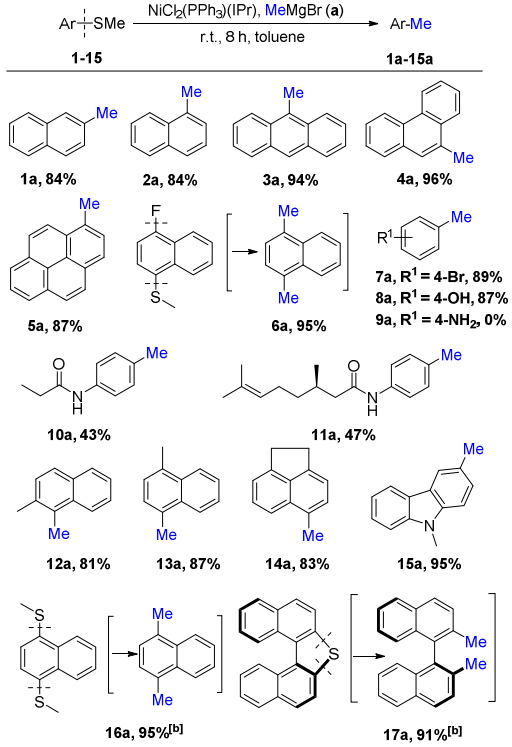
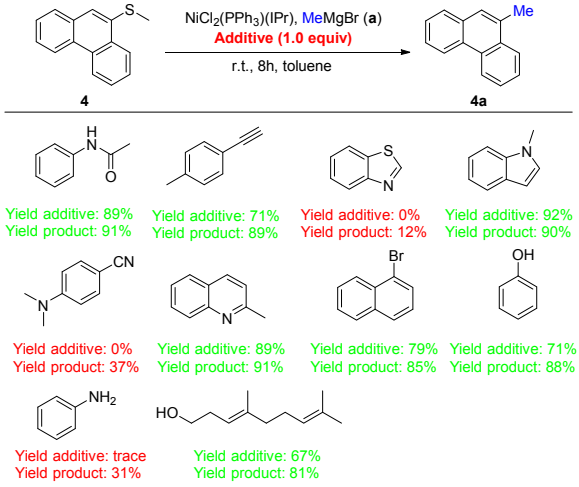
and be attacked by methyl group with excellent yields to produce

Table 1 Ni-Catalyzed methylation of aryl thioethers[a]



[a]Reaction conditions: **1** (0.20 mmol), MeMgBr (0.40 mmol), and $NiCl_2(PPh_3)(IPr)$ (0.002 mmol) in toluene (1.0 mL) at room temperature for 8 h; yield refers to isolated yield. [b]Grignard reagent (0.60 mmol) was added.

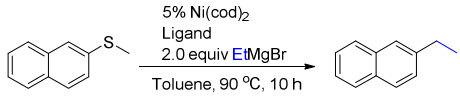
Table 2 Additive-based robustness screen[a]



[a]The related experiment was carried out according to the general procedure except the addition of the respective additive (0.2 mmol, 1.0 equiv); the yield of the product **4a** and the remaining additives refer to isolated yield.

the corresponding products under the mild conditions. Besides naphthalene groups, we observed that a thiomethyl substituent on an array of aromatic rings including anthracene (**3**), phenanthrene (**4**) and pyrene (**5**) could be accommodated to

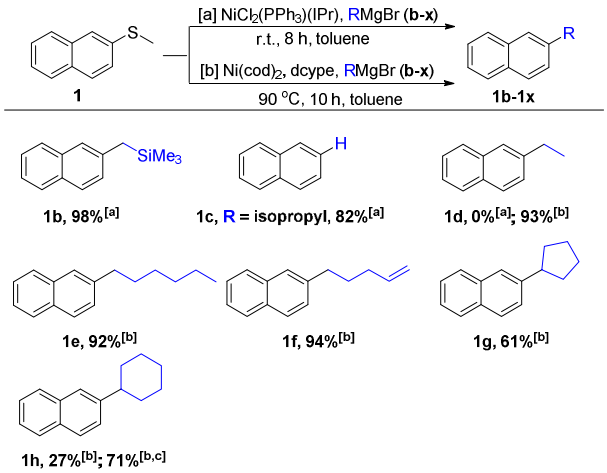
Table 3 Screening of ligands[a]



Entry	Ligand (x mol%)	Yield (**1d**)
1	PCy_3(10)	0
2	IPr·HCl (10) (R = ^{i}Pr)	0
3	IMes·HCl (10) (R = 2,4,6,-$Me_3C_6H_2$)	0
4	IMe·HCl (10) (R = Me)	0
5	dcype (5)	93

[a]Reaction conditions: 1 (0.20 mmol), EtMgBr (0.40 mmol), $Ni(cod)_2$ (0.01 mmol), and Ligand in toluene (1.0 mL) at 90 °C; yield refers to isolated yield.

Table 4 Scope of Grignard reagents[a]



[a]Reaction conditions: **1** (0.20 mmol), RMgBr (0.40 mmol), and $NiCl_2(PPh_3)(IPr)$ (0.002 mmol) in toluene (1.0 mL) at room temperature for 8 h; yield refers to isolated yield. [b]Reaction conditions: **1** (0.20 mmol), RMgBr (0.40 mmol), $Ni(cod)_2$ (0.01 mmol), and dcype (0.01 mmol) in toluene (1.0 mL) at 90 °C for 10 h; yield refers to isolated yield. [c]MgI_2 (0.40 mmol) was added.

form the methylation products. Moreover, functional groups, such as bromine (**7**), a free hydroxyl group (**8**), amide group (**10**, **11**), and alkenyl (**11**) were found to be compatible and robust enough, in contrast of amino group (**9**). Among these,

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the challenging late-stage application of bioactive citronella derivative (**11**) is also right. Notably, as for fluorine-substituted thiomethyl-naphthalene (**6**), we get the both C(aryl)−F and C(aryl)−S bond cleavage product (**6a**), which is consistent with the reported KTC-type reaction of aryl fluorides.[7] Different steric substituted thiomethyl-naphthalenes (**12**-**14**) were also conducted smoothly under these conditions with similar yields (81-87%). Furthermore, the methylation successfully occurred as well at both substrate containing two thiomethyl groups (**16**) and thiophene analogue (**17**) by simply increasing the amount of the Grignard reagents to 3.0 equiv. Additionally, on the basis of the above results, an additive-based robustness screen reported by Glorius's group[16] has been operated to furtherly explore the reaction compatibility (As shown in Table 2). The screening consists of running the standard Ni-catalyzed cross-coupling in the presence of an additive. The additive was taken to represent a common functionality that could be present in a given target molecule. Through the comparative results gathered by the recovery yields of the additives and the yields of the methylate products, we can evaluate the tolerance of functional groups in this reaction reasonably. As shown in Table 2, 10 additives have been tested. The free amino-group, cyano-group, and thiazolyl were found to be detrimental to the reaction based on the corresponding additives were lost completely. We were pleased to observe that alkene, alkyne and quinoline were generally compatible in the reaction. Some useful functional groups could also be introduced to the reaction, such as, free hydroxyl, amide and bromine.

Encouraged by these results, we then turned our attention to the scope of the Grignard reagents. As shown in Table 4, the Me_3SiCH_2MgBr was also proceeded smoothly to form the corresponding coupling product **1b**. Notably, the $ArCH_2SiMe_3$ were proved to be great synthetic intermediates, which can directly convert into some important substrate classes, such as olefins, amines and alcohols.[17] Unfortunately, the alkyl Grignard reagents bearing a *β*-hydrogen cannot react (EtMgBr, $^nC_6H_{13}MgBr$, and et.al) or just give the undesired reduction product (**1c**) under the above-mentioned condition. In order to realize the expected coupling reaction, we then initially investigated the effect of the ligand on the reaction of the naphthyl sulfide **1** and EtMgBr (**d**) with the use of general $Ni(cod)_2$ as the catalyst precursor (As shown in Table 3). Based on the result, the generally used PCy_3 and a serious of *N*-alkyl-substituted NHC ligands were proved to be noneffective (Entry 1-4, Table 3). Instead of the above most reported ligands for the C(aryl)−heteroatom bond activation, using a bidentate ligand 1,2-bis(dicyclohexylphosphino)ethane (dcype) can directly realize this cross coupling reaction and give the corresponding product **1d** with 93% yield. The result of ligand screening is greatly consistent with Chatani's work on the activation of a C(aryl)-OMe bond.[13j] With the optimized ligand in hand, we then continue the above investigation of the scope of alkyl Grignard reagents bearing a *β*-hydrogen (Table 4). As expected, $^nC_6H_{13}MgBr$ similarly performed well in this condition with excellent yield 92% (**1e**), irrespective of chain length compare to EtMgBr. The Grignard reagent containing a terminal olefin (**f**) was also suitable for this coupling reaction, which provide a practical way for the modification of aryl thioether with the introduction of functional group. Notably, these coupling reaction were also successfully occurred at five (**g**) and six (**h**) cycloalkyl groups to generate corresponding alkylated products **1g** and **1h** respectively. As for ^iPrMgBr, we can still only get the mixture of 2-isopropylnapthalene and naphthalene based on the GC-MS under this optimized condition.

Conclusions

In conclusion, a new and simple Ni-catalyzed cleavage of C–S bonds has been developed by the cross-coupling of aryl thioether with alkyl Grignard reagents. This protocol can be conducted smoothly under mild conditions with diversely substituted aryl thioethers and various Grignard reagents in moderate to excellent yields. Meanwhile, the C–S bond activation also be useful in the modification of sulfur-containing molecules in view of its ubiquity in natural products, pesticides, or proteins. Further investigations will be continued to explore the reaction mechanism and the potential of related transformations in our laboratories.

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Conflicts of interest

There are no conflicts to declare.

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