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Biaryl Construction through Kumada Coupling with Diaryl Sulfates as One-by-One Electrophiles under Mild Conditions

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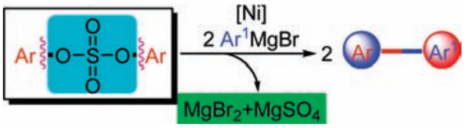
ABSTRACT



Diaryl sulfates were successfully applied as one-by-one organo electrophiles in Kumada coupling to construct biaryls with the emission of harmless inorganic salts.

The construction of C−C bond is the main task of organic synthesis. Due to high efficiency and broad application, transition-metal-catalyzed cross-couplings have become one of the most powerful tools for constructing carbon−carbon bonds in the past half century.[1] With great efforts from different research groups, significant achievements have been made to broaden the substrate scope of organic electrophiles.[2] Very recently, relatively inert aryl chloride,[3] as well as aryl fluoride in some cases,[4] have already been successfully applied as electrophiles. However, most organic halides suffered from sluggish preparation through Sandmeyer processes, which might result in an ecological problem in large-scale syntheses.[5]

Other than organic halides, phenol derivatives are other choices of organic precursors in cross-couplings. Arising from the high bond dissociation energy of C−O of phenol, the preactivation of hydroxyl group to better leaving groups is actually demanded (Scheme 1).[6] In general, sulfonates were great choices to approach such goals. Among various

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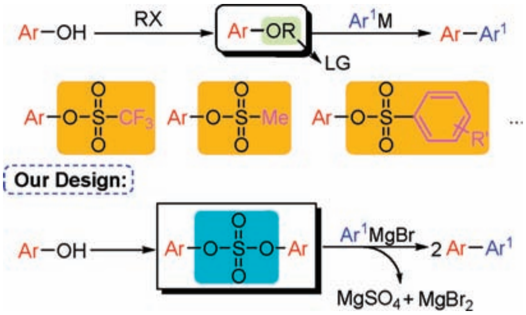
10.1021/ol9028308

Scheme 1



sulfates, triflates were broadly applied into cross couplings, which showed the best reactivity.[7] Recent advances indicated that less reactive mesylates, tosylates, as well as phosphates also showed good reactivities.[8,9] More recently, the carboxylates and methyl ethers were successfully applied into transition-metal-catalyzed Kumada, Suzuki, and Negishi coupling reactions.[10,11] However, relatively high toxicity, low C-atom economy, and sometimes high cost have limited their applications.

Our initial efforts to approach the efficient and environmentally benign cross coupling from phenol derivatives made us believe that diaryl sulfates might be an ideal continuous coupling partner (Scheme 1). Compared with other organic sulfonates, diaryl sulfates might exhibit several advantages: (1) the easy availability from phenols; (2) 100% C-atom economy (if with 100% conversions and yields); (3) harmless inorganic emissions toward the environment. So far, diaryl sulfates have never been applied as electrophiles in cross coupling although the monosulfates were successfully prepared and used in cross couplings.[12] Herein we first demonstrated a highly efficient Kumada coupling with the use of diaryl sulfates as sequential organo electrophiles under mild conditions, leaving inorganic $MgSO_4$ and MgX_2 as byproducts.

With our developed method, diaryl sulfates **1** were easily produced under mild conditions in excellent yields (see the Supporting Information). By a simple scale-up, 100 g of di(*p*-tolyl) sulfate **1a** was produced without a change of the procedure in excellent yield (eq S1, Supporting Information). It is important to note that such diaryl sulfates, different from dialkyl sulfates, are very stable and generally nontoxic and can be stored at room temperature for a long time. These features make such materials potentially applicable in synthetic industry.

Our evaluation to approach the cross coupling of diaryl sulfates was initiated from Ni-catalyzed Kumada coupling (Table 1). As expected, the tentative experiment indicated that a good yield of a desired product **3a** was achieved in the presence of 5 mol % of $Ni(PCy_3)_2Cl_2$ and 10.0 mol % of additional PCy_3 in THF after 2 h at room temperature. A quantitative yield was obtained by the simple promotion of temperature to 70 °C (entry 2). Other solvents, such as toluene, also worked for this transformation but with a lower efficiency (entry 3). Further examination showed diethyl ether (Et_2O) worked as the best solvent at room temperature (entry 4). Different ligands were systematically screened, and the PCy_3 was proved to be the best one. It is important to note that the removal of additional PCy_3 obviously decreased the yield (cf. entries 4 and 6). However, other monodentated and bidentated phosphine ligands, such as PPh_3, dppe, dppp, and dppf, were not efficient (entries 7−10). NHC ligands, such as IMes and IPr, which showed great reactivity in palladium chemistry,[13] also conveyed the cross coupling but only in moderate yields (entries 11 and 12). Furthermore, some common catalysts, which were successfully applied in Kumada-type coupling, such as Pd, Fe, and Co complexes, completely failed (entries 13−15).[14]

Different ArMgBr were further investigated with di(2-naphthyl) sulfates **1b** as substrate (Table 2). We found that steric hindrance did not play a vital role, and comparable yields were achieved with 2-, 3-, and 4-tolyl Grignard reagents (entries 2−4). Most importantly, the extremely steric

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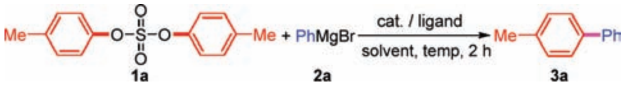
Table 1. Phenylation of 4-Toylsulfate with PhMgBr under Different Conditions[a]



entry	cat. (mol %)	ligand (mol %)	solvent	temp (°C)	yield[b] (%)
1	$Ni(PCy_3)_2Cl_2$ (5.0)	PCy_3 (10.0)	THF	rt	89
2	$Ni(PCy_3)_2Cl_2$ (5.0)	PCy_3 (10.0)	THF	70	99
3	$Ni(PCy_3)_2Cl_2$ (5.0)	PCy_3 (10.0)	toluene	rt	76
4	$Ni(PCy_3)_2Cl_2$ (5.0)	PCy_3 (10.0)	Et_2O	rt	99
5	$Ni(PCy_3)_2Cl_2$ (5.0)	PCy_3 (10.0)	Et_2O	0	29
6	$Ni(PCy_3)_2Cl_2$ (5.0)		Et_2O	rt	81
7	$Ni(PPh_3)_2Cl_2$ (5.0)	PPh_3 (10.0)	Et_2O	rt	9
8	$Ni(dppe)Cl_2$ (5.0)	dppe (5.0)	Et_2O	rt	6
9	$Ni(dppp)Cl_2$ (5.0)	dppp (5.0)	Et_2O	rt	<5
10	$Ni(dppf)Cl_2$ (5.0)	dppf (5.0)	Et_2O	rt	15
11	$Ni(acac)_2$ (5.0)	IMs·HCl (10.0)	Et_2O	rt	42
12	$Ni(acac_2$ (5.0)	IPr·HCl (10.0)	Et_2O	rt	54
13	$Pd(OAc)_2$ (5.0)	PCy_3 (20.0)	Et_2O	rt	<5
14	$Fe(acac)_2$ (5.0)	PCy_3 (20.0)	Et_2O	rt	<5
15	$Co(acac)_2$ (5.0)	PCy_3 (20.0)	Et_2O	rt	<5

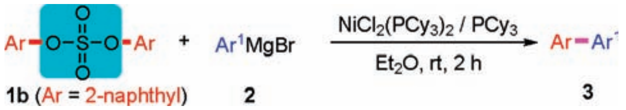
[a] The reactions were carried out on a scale of 0.2 mmol of sulfate **1a** and 0.6 mmol of phenylmagnesium bromide **2a**. [b] GC yield with the use of *n*-dodecane as an internal standard.

hindered 1-mesitylMgBr also showed an excellent efficacy (entry 7). Since the reaction condition is relatively mild, MeO and F survived well although they showed good reactivity in various Ni-catalyzed transformations, which leaves the potential for further functionalization (entries 5 and 8).[4−10] Notably, even more active C−Cl was compatible, while the designed product **3bi** was isolated in a moderate yield (entry 9).

Different diaryl sulfates were further tested for this transformation. Other than naphthyl derivatives, simple phenol derivatives also showed good reactivities (Table 3). Different from ArMgBr, the steric effect played a key role. When di(2-tolyl) sulfates (**1d**) were surveyed as a substrate, the efficiency of the cross coupling was obviously decreased (entry 3). As is known, it is quite challenging to facilitate the cross coupling to construct biaryls from the electron rich aryl electrophiles.[3e,7d] However, electron-rich diaryl sulfates showed great reactivities under the corresponding reaction conditions, and the desired products were afforded in good to excellent yields. In fact, electron-donating groups, such as methoxyl and *N*,*N*-dimethylamino groups, were also beneficial for the preparation of the corresponding diaryl sulfates. Thus, this development became a useful complementary tool for general cross coupling from other electrophiles. On the other hand, the remaining methoxyl group also offered the opportunities to construct polyarenes by our and others' developed method.[10,11]

The proposed pathway of this transformation included two different sulfates as organo electrophiles (**1** and **4**). After the first sequence of oxidative addition, transmetalation and reductive elimination to produce the first molecule of desired product **3**, the new monosulfate **4** was produced in situ, which further underwent a similar sequence to produce the second molecule of **3** to fulfill the complete transformation, producing the final inorganic byproduct **5** (a mixture of $MgSO_4$ and $MrBr_2$) as the waste (Scheme 2).

Table 2. Kumada Coupling with **1b** and Various Aryl Grignard Reagents[a]

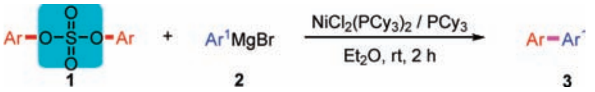


entry	Ar^1 (**2**)	**3** (%)
1	Ph (**2a**)	**3ba** (85)
2	2-tolyl (**2b**)	**3bb** (93)
3	3-tolyl (**2c**)	**3bc** (94)
4	4-tolyl (**2d**)	**3bd** (94)
5	4-$MeOC_6H_4$ (**2e**)	**3be** (88)
6	4-$Me_2NC_6H_4$ (**2f**)	**3bf** (92)
7	2,4,6-$(Me)_3C_6H_2$ (**2g**)	**3bg** (91)
8	4-FC_6H_4 (**2g**)	**3bh** (72)
9	4-ClC_6H_4 (**2i**)	**3bi** (43)

[a] All the reactions were carried out on a scale of 0.2 mmol of diaryl sulfate **1b** and 0.6 mmol of Ar^1MgBr **2** in the presence of 5 mol % of $Ni(PCy_3)_2Cl_2$ and 10.0 mol % of PCy_3 in 2 mL of Et_2O, and isolated yields were reported.

On the basis of this proposal, di(2-naphthyl) sulfate **1b** was tested in the presence of 1.5 equiv of Grignard reagent **2b**. After 2 h of stirring, **1b** was completely consumed and the desired cross-coupling product was detected in 66% GC yield (based on both naphthyl groups from one moleculae

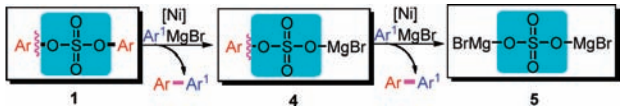
Table 3. Construction of Biaryls through Ni-Catalyzed Kumada Coupling from Diaryl Sulfates **1** with Various Aryl Grignard Reagents **2**[a]



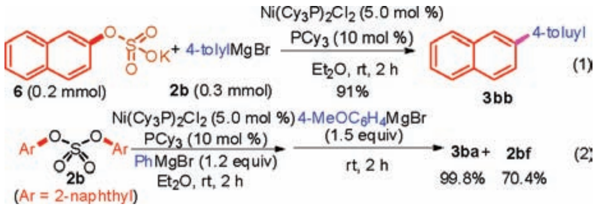
entry	Ar (**1**)	Ar (**2**)	**3** (%)
1	4-tolyl (**1a**)	Ph (**2a**)	**3aa** (99)[b]
2	3-tolyl (**1c**)	Ph (**2a**)	**3ca** (99)[b]
3	2-tolyl (**1d**)	Ph (**2a**)	**3da** (88)[b]
4	Ph (**1e**)	4-tolyl (**2b**)	**3eb** (99)[b]
5	4-$MeOC_6H_4$ (**1f**)	Ph (**2a**)	**3fa** (72)
6	4-$MeOC_6H_4$ (**1f**)	4-tolyl (**2b**)	**3fb** (75)
7	4-$MeOC_6H_4$ (**1f**)	3-tolyl (**2c**)	**3fc** (73)[c]
8	4-$MeOC_6H_4$ (**1f**)	2-tolyl (**2d**)	**3fd** (75)
9	2-$MeOC_6H_4$ (**1g**)	4-tolyl (**2b**)	**3gb** (75)
10	4-$Me_2NC_6H_4$ (**1h**)	Ph (**2a**)	**3ha** (83)
11	4-$Me_2NC_6H_4$ (**1h**)	4-tolyl (**2b**)	**3hb** (81)
12	4-$Me_2NC_6H_4$ (**1h**)	3-tolyl (**2c**)	**3hc** (88)
13	4-$Me_2NC_6H_4$ (**1h**)	2-$C_{10}H_7$ (**2j**)	**3hj** (73)
14	4-$Me_2NC_6H_4$ (**1h**)	1-$C_{10}H_7$ (**2k**)	**3hk** (61)

[a] All the reactions were carried out on a scale of 0.2 mmol of diaryl sulfate **1** and 0.6 mmol of Ar^1MgBr **2** in the presence of 5.0 mol % of $Ni(PCy_3)_2Cl_2$ and 10.0 mol % of PCy_3 in 2 mL of Et_2O, and isolated yields were reported if without further note. [b] GC yield with the use of *n*-dodecane as an internal standard. [c] 17% of 3,3″-dimethylterphenyl was isolated as a byproduct.

Scheme 2

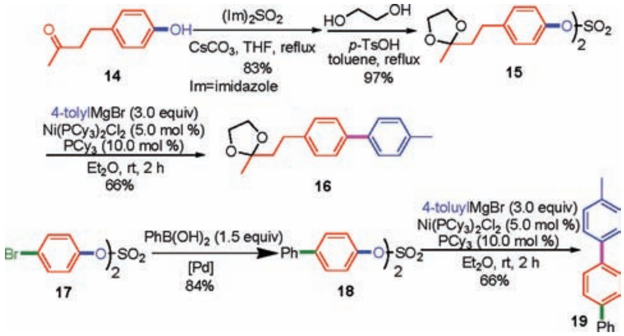


of substrate). It was important to note that the monosulfate species was observed by ESI mass spectroscopy (Supporting Information). This result indicated that the monosulfate salt **4** was a key intermediate after the first catalytic cycle as proposed, which showed a lower reactivity under the same conditions. In fact, potassium 2-naphthyl monosulfate **6** was also prepared and tested. The desired product **3bb** was obtained in 91% yield (eq 1). Thus, the different reactivities of sulfate **1** and monosulfate may induce the cross coupling with different nucleophiles at different stages to form two biaryls. As expected, the addition of 1.2 equiv of PhMgBr followed by 1.5 equiv of 4-CH$_3$OC$_6$H$_4$MgBr to **2b** in the presence of the developed catalytic system resulted in both **3ba** and **3bf** in 99% and 70% isolated yield, respectively (eq 2). Those results strongly supported the hypothesis of two catalytic cycles.



To expand the application of the developed method, acidic and basic conditions and possible orthogonal cross coupling were tested. Through the ketalization under an acidic condition,[15] the sulfate **15** was formed by keeping the sulfate ester group untouched, which underwent the developed coupling to form biaryl adduct **16** (Scheme 3). Further orthogonal cross coupling also indicated that the biaryl sulfate functional group even survived under basic condition for the traditional Suzuki coupling (Supporting Information),[16] which offered a great chance to make different scaffolds via sequential C−C bond formations by cross couplings. During those transformations, diaryl sulfates may play dual roles as both the protecting group of phenol and the leaving group in the sequential cross coupling.

Scheme 3



In summary, we have developed a novel nickel-catalyzed Kumada coupling of diaryl sulfates. Given the value of the products, not only do these observations offer a new synthetic protocol for constructing biaryls but they also show the potential of using sulfates as a new kind of efficient, green, and consecutive organic electrophiles in various cross couplings. Combined with other developed methods, polyarenes could be readily synthesized through one-pot sequential cross coupling, which might be broadly used in the synthesis of interesting molecules.

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Supporting Information Available: Brief experimental details and other spectral data for products. This material is available free of charge via the Internet at http://pubs.acs.org.

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