Organocopper Reagents

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A Cobalt-Catalyzed Sulfonate/Copper Exchange for the Preparation of Highly Functionalized Electron-Deficient Aryl Copper Reagents**

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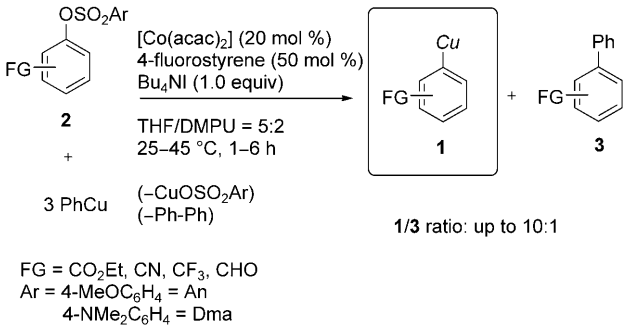
Dedicated to Dr. Klaus Römer on the occasion of his 70th birthday

The preparation of highly functional aryl organometallics is of great importance for the synthesis of drugs, agrochemicals and materials.[1] Recently, copper-catalyzed reactions[2] and highly chemoselective functionalized copper reagents[3–5] have attracted great attention.[6] A direct copper insertion,[3] an iodine–copper exchange[4] or a directed cupration[5] have been used to prepare functionalized aryl copper reagents from the corresponding aryl bromides or iodides. Alternatively, phenol derivatives, such as sulfonates, have been seldomly used for the preparation of aryl organometallics owing to the strength of the carbon–oxygen bond.[7,8] A transition-metal-catalyzed activation of the aryl group–oxygen bond has been envisioned to achieve this goal; cobalt has been the metal of choice because of to its high reactivity and moderate price.[9,10]

Herein, we report a novel preparation of highly functionalized aryl copper reagents **1** bearing a range of sensitive functional groups (esters, nitriles, or aldehydes) starting from aryl sulfonates **2** using a cobalt-catalyzed sulfonate/copper exchange reaction mediated by phenylcopper (PhCu) (Scheme 1).[11]



Scheme 1. The cobalt(II)-catalyzed aryl sulfonate/copper exchange reaction.

In the course of our studies on cobalt-catalyzed cross-couplings,[12] we observed that the reaction of electron-deficient aryl *p*-tolylsulfonates (ArOTs) with PhCu produced, together with the cross-coupling product **3**, an aryl copper compound **1**, which is the result of a OTs/Cu exchange. Although this was a minor product under standard cross-coupling conditions,[12] we were able to optimize its formation. By replacing the tosyl group by an aryl sulfonate bearing a donor substituent in the *para* position (OMe, NMe_2), using a higher catalyst loading (from 7.5 mol% to 20 mol%), and performing the reaction in a 5:2 THF:DMPU mixture (DMPU = *N*,*N*′-dimethyl-*N*,*N*′-propylene urea), the sulfonate/copper exchange became the major reaction pathway (ratio of **1**:**3** up to 10:1; Scheme 1). Thus, the reaction of 1,3-dicarbethoxy benzenesulfonate (**2a**, 1 equiv) with PhCu (3 equiv)[11] in the presence of $[Co(acac)_2]$ (20 mol%), 4-fluorostyrene (50 mol%),[13,14] and Bu_4NI[14] (1.0 equiv) in a THF/DMPU mixture (5:2) furnishes the aryl copper reagent **1a** within 2 h at 25 °C, and provides the aryl iodide (**4a**) after iodolysis in 72% yield (Scheme 2).

Similarly, trapping the aryl copper species **1b** obtained by the reaction of **2b** with PhCu (3.0 equiv after 3 h at 25 °C) with iodine furnishes ethyl 3-cyano-5-iodobenzoate **4b** in 65% yield (Scheme 2b). The copper reagent **1a** could also be trapped by various other electrophiles. Allylation with 3-bromopropene affords the allylated product **4c** in 78% yield (Scheme 2c), and acylation using pivaloyl chloride furnishes the benzophenone **4d** in 61% yield (Scheme 2d). The organocopper reagent derived from **2a** undergoes a smooth substitution reaction with 3-iodocyclohexen-1-one, yielding the cyclohexenone **4e** in 64% yield (Scheme 2e). A carbocupration[15] of ethyl propiolate with **1a** furnishes the alkene **4f** in 61% yield (Scheme 2f). The related copper reagent **1b** undergoes a 1,4-addition with cyclohexenone, yielding the corresponding Michael adduct **4g** in 66% yield. The reaction of **1b** with *S*-methyl thiomethyl sulfonate $MeSSO_2Me$ furnished the thioether **4h** in 73% yield (Scheme 2h).

Further trapping reactions of aryl copper reagents prepared from the aryl sulfonates **2a–g** are summarized in Table 1. 1,3,5-trisubstituted arenes, which are usually difficult to prepare, can also be easily accessed by this method.[16] Thus, 3,5-dicyanophenyl-4-methoxybenzenesulfonate **2c** reacts under standard conditions within 6 h at 45 °C, leading to the corresponding copper reagent that was quenched with iodine to yield 5-iodo isophthalonitrile **4i** (Table 1, entry 1). Other

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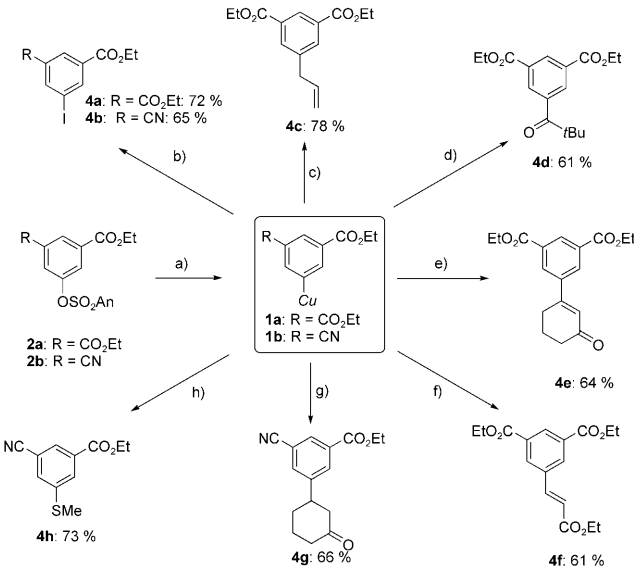
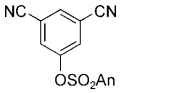
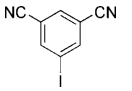
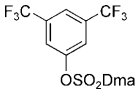
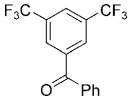
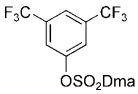
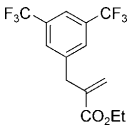
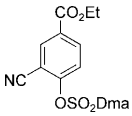
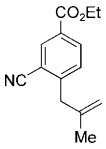
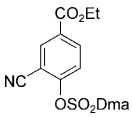
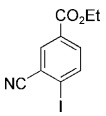
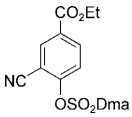
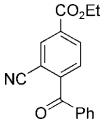
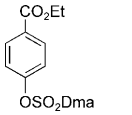
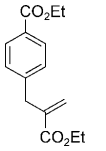
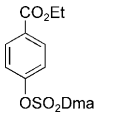
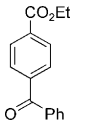
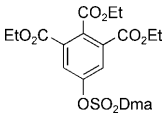
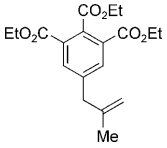
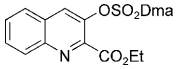
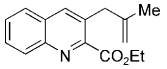


Scheme 2. Aryl sulfonate/copper exchange of the sulfonates **2a**,**b** and trapping with various electrophiles. Reagents and conditions: a) PhCu (3.0 equiv) $[Co(acac)_2]$ (20 mol%), 4-fluorostyrene (50 mol%), Bu_4NI (1.0 equiv), THF/DMPU = 5:2, 25 °C, 2–3 h; b) I_2 (2.0 equiv), −20 °C, 30 min, 25 °C, 2 h; c) 3-bromopropene (2.0 equiv), −20 °C, 30 min, 25 °C, 2 h; d) *t*BuCOCl (2.0 equiv), −20 °C, 30 min, 25 °C, 2 h, e) 3-iodocyclohexen-1-one (2.0 equiv), −20 °C, 30 min, 25 °C, 2 h; f) ethyl propiolate (2.0 equiv), −40 °C, 30 min, 25 °C, 2 h; g) cyclohexenone (2.0 equiv), TMSCl (2.0 equiv), −20 °C, 30 min, 25 °C, 2 h; h) MeS-SO_2Me (2.0 equiv), −20 °C, 30 min, 25 °C, 2 h.

aryl sulfonates bearing electron-withdrawing groups are readily converted into the corresponding copper species. Thus, 3,5-bis(trifluoromethyl)phenyl-4-(dimethylamino)benzenesulfonate **2d** gave the aryl copper reagent **1d** within 4 h at 25 °C. Benzoylation yielded the benzophenone **4j** in 71% yield; alternatively, allylation with ethyl 2-(bromomethyl)-acrylate[17] gave the 1,3,5-trisubstituted arene **4k** in 71% yield (Table 1, entries 2 and 3). The *ortho*-substituted sulfonate **2e** also reacted well, providing the aryl copper reagent **1e**, which was then allylated with 3-bromo-2-methylpropene to yield the ethyl benzoate **4l** in 69% yield (Table 1, entry 4). Reaction with iodine or benzoyl chloride gave the iodo derivative **4m** and ketone **4n** in 69% and 70% yields, respectively (Table 1, entries 5 and 6). Monosubstituted aryl sulfonates, such as **2f**, readily led to aryl sulfonate/copper exchange (5 h at 50 °C). The resulting aryl copper **1f** was trapped with ethyl 2-(bromomethyl)acrylate[17] or benzoyl chloride, furnishing the *para*-disubstituted arenes **4o** and **4p** in up to 62% yield (Table 1, entries 7 and 8).

1,2,3,5-tetrasubstituted arenes are also accessible. Triester **2g** affords the expected aryl copper reagent **1g** within 1 h at 25 °C. Allylation with 3-bromo-2-methylpropene furnished the 1,2,3-triester **4q** in 72% yield (Table 1, entry 9). The compatibility of our method with N heterocycles is also shown: the substituted quinoline **2h** reacts with PhCu in the presence of $[Co(acac)_2]$ at 25 °C within 3 h to give copper reagent (**1h**), which was allylated with methallyl bromide, leading to the functionalized quinoline **4r** in 53% yield (Table 1, entry 10).

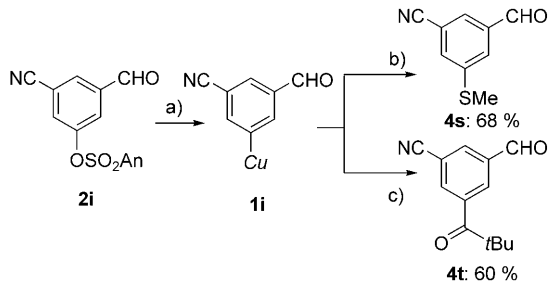
Table 1: Synthesis of products **4** obtained by the reaction of aryl sulfonates with PhCu subsequent quenching with an electrophile.

Entry	Substrate[a]		E^+	Product		Yield [%][b]
1		**2c**	I_2		**4i**	64
2		**2d**	PhCOCl		**4j**	71
3		**2d**			**4k**	71
4		**2e**			**4l**	69
5		**2e**	I_2		**4m**	69
6		**2e**	PhCOCl		**4n**	70
7		**2f**			**4o**	62
8		**2f**	PhCOCl		**4p**	61
9		**2g**			**4q**	72
10		**2h**			**4r**	53

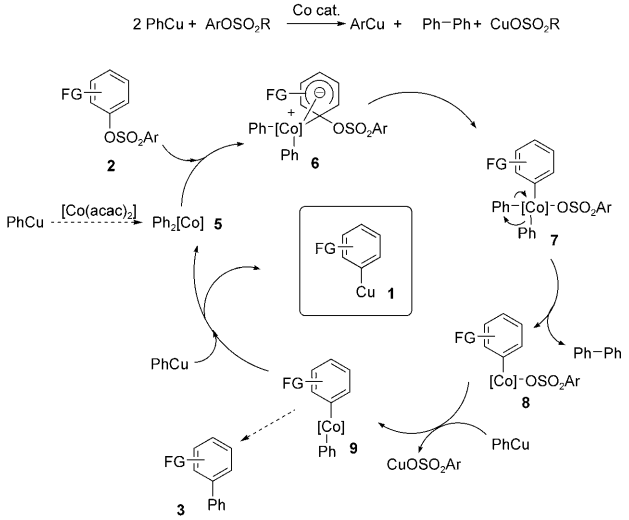
[a] An = 4-$MeOC_6H_4$, Dma = 4-$Me_2NC_6H_4$. [b] Yield of isolated analytically pure product.

Remarkably, an aldehyde function was also tolerated during the exchange reaction. For example, 3-cyano-5-formylphenyl 4-methoxybenzenesulfonate (**2i**) afforded **1i** under standard conditions, which was then trapped with *S*-methyl thiomethylsulfonate to give thioether **4s** in 68% yield. Acylation of **1i** furnished the ketone **4t** in 60% yield (Scheme 3).

A catalytic cycle is proposed for the reaction mechanism (Scheme 4). PhCu initially undergoes a transmetalation to the corresponding cobalt derivative Ph_2Co (**5**). Nucleophilic addition of **5** to an electron-deficient aryl sulfonate **2** would



Scheme 3. Aryl sulfonate/copper exchange on substituted benzaldehydes. Reagents and conditions: a) PhCu (3.0 equiv) [Co(acac)$_2$] (20 mol%), 4-fluorostyrene (50 mol%), Bu_4NI (1.0 equiv), THF/DMPU = 5:2, 25 °C, 1 h; a) $MeSSO_2Me$ (2.0 equiv), −20 °C, 30 min, 25 °C, 2 h, b) *t*BuCOCl (2.0 equiv), −20 °C, 30 min, 25 °C, 2 h.



Scheme 4. Proposed mechanism for the sulfonate/copper exchange reaction.

then lead to a cobalt(IV) intermediate **6** that is stabilized by a η^5-complexation. This type of complexation may explain why electron-poor aromatic systems react faster. After re-aromatization, this cobalt complex produces a cobalt(IV) intermediate[16] **7**. Reductive elimination of the cobalt reagent **7** would then affords biphenyl[18,19] and the aryl cobalt(II) reagent **8**. The reaction of this intermediate with PhCu results in the formation of compound **9**, which only slowly undergoes a reductive elimination to ArPh (**3**). A subsequent transmetalation with PhCu leads to the aryl copper reagent **1** and regenerates Ph_2Co[19] (**5**). This pathway is preferred over the formation of **3**, as ratios of 10:1 are obtained (Scheme 1). Alternatively, a reduction of [Co(acac)$_2$] to a reactive cobalt(I) intermediate[9e] may be envisioned, leading to a similar sequence as shown in Scheme 4.

In summary, we have developed a novel sulfonate/copper-exchange that allows phenol derivatives (aryl sulfonates) to be converted into the corresponding copper reagents. This cobalt-catalyzed reaction tolerates sensitive functional groups, such as an aldehyde, a nitrile, or an ester. The synthetic scope of this new reaction is currently being investigated in our laboratories.

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