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New copper-mediated O-arylations of phenols with arylstannanes

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Abstract—A novel method for the synthesis of diaryl ethers with phenols and arylstannanes under mild conditions is described. This copper-mediated O-arylation is feasible using DMAP in acetonitrile and is complementary to the use of boronic acids as aryl donors. The reaction is tolerant of a wide range of substituents and sterically hindered coupling partners.
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The development and design of a reliable and efficient method for the construction of the C(aryl)–O bond has attracted the attention of many chemists during the last century.[1] This important transformation has been developed to include a wide range of compounds. Since the pioneering works by Ullmann and Goldberg, the copper-mediated cross-coupling reactions have become a powerful tool for the synthesis of complex molecules.[2] In addition to the classical conditions, by the reaction of a phenol with aryl halide as an aryl donor, the scope of the copper-promoted methodology was extended mainly to other organometalloids such as organobismuth,[3] organotrifluoroborate[4] reagents and arylboronic acids.[5] In particular, the recent introduction of boronic acids as an aryl donor has been a significant discovery such that the synthesis of diaryl ethers as a long-standing problem seems to have been solved. Nevertheless, the applicability is limited if the synthesis of the boronic acids is troublesome or complicated, for instance, the transformation of an *ortho*- or *para*-substituted electron poor aryl triflate into the corresponding aryl boronic acid is far from trivial.[6]

Although the use of aryl stannanes as coupling partners in the C(aryl)–N bond formation was recently described by Lam et al., the application to the construction of diaryl ethers failed.[7] In the context of synthetic efforts in this field, we had an occasion to investigate copper-mediated coupling reactions. In order to synthesize diaryl ether **5**,[8] we intended to prepare a boronic acid from triflate **1a**, but no method was found for this transformation. With a view to exchange triflate **1a** for an aryl iodide, we generated trimethylstannane adduct **2** in good yield. To our surprise, treatment with iodine in dichloromethane provided chlorophenylstannane **3**,[9] which was immediately and without rigorous analysis subjected to an Ullmann reaction with phenol **4** (Table 1, entry 1). The desired highly functionalized cross-coupling product **5** was obtained in low yield, even though three *ortho*-substitutions of the diaryl ether unit are occupied. Considering the fact that the coupling between neither an *ortho*- or *para*-substituted electron poor aryl boronic acid and a phenol, nor a stannane and phenol is not documented, this finding may represent a good complement in the synthesis of diaryl ethers. The subsequently conducted characterisation of **3** demanded a detailed examination for this kind of coupling reaction type.

An attempt to effect the coupling by 2,2,6,6-tetramethylheptane-3,5-dione (TMHD) as a promoter[10] only yielded trace amounts of the desired product (entry 2). However, replacing the copper source and the base with copper acetate and Et_3N, as the impressive works by Chan, Evans and Lam revealed, the reaction yields are comparable to entry 1. To our surprise, the adaptation of the original protocol from these groups by using **2** as an aryl donor and dichloromethane as a solvent failed, even at elevated temperatures (entries 4 and 5). To our relief, we found that aryl stannane **2** can be coupled with phenol **4** using acetonitrile as a solvent as carried out with chlorostannane **3** in entry 3. Reducing the amount of the base was achieved by using DMAP (entry 7).

As expected, the major side reaction in this ether formation is the reduction of aryl stannane to arene (Ar–SnR_3

Keywords: Synthesis of diaryl ethers; O-Arylation; Cross-coupling; Copper.

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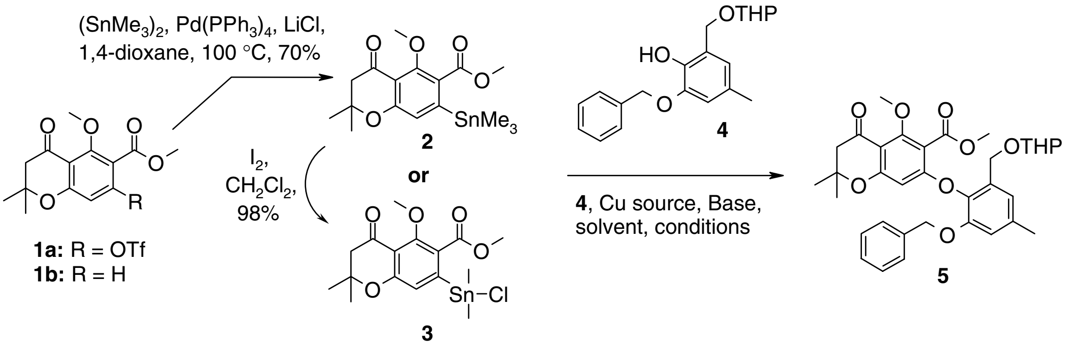
Table 1. Synthesis of diaryl ether **5** through copper-mediation



Entry	Stannane (1 equiv)	Phenol **4** (equiv)	Cu source (equiv)	Base (equiv)	Conditions	Yield (%)	
						5	**1b**
1	**3**	2	Cu/CuO (2.5/2.5)	DMAP (3)	MeCN, 81 °C, 2 h, Ar	23	
2	**3**	2	CuCl/TMHD[a] (0.5/0.1)	Cs_2CO_3 (2)	NMP, 100 °C, 3.5 h, Ar	7	
3	**3**	4	$Cu(OAc)_2$ (1.1)	Et_3N (40)	MeCN, 4 Å MS, 81 °C, 1.5 h, air	24	
4	**2**	2	$Cu(OAc)_2$ (1.1)	Et_3N (10) + Pyridine (10)	CH_2Cl_2, 4 Å MS, 22 °C, 2 h, air	0	
5	**2**	2	$Cu(OAc)_2$ (1.1)	Et_3N (20)	CH_2ClCH_2Cl, 4 Å MS, 60 °C, 15 h, Ar	<5	
6	**2**	2	$Cu(OAc)_2$ (1.1)	Et_3N (20)	MeCN, 4 Å MS, 81 °C, 1.5 h, air	25	
7	**2**	2	$Cu(OAc)_2$ (1.5)	DMAP (3)	MeCN, 4 Å MS, 81 °C, 1.5 h, air	25	
8	**2**	4	$Cu(OAc)_2$ (1.1)	DMAP (8)	MeCN, 4 Å MS, 81 °C, 1.5 h, air	58	21
9	**2**	4	$Cu(OAc)_2$ (1.1)	DMAP (8)	MeCN, 4 Å MS, 81 °C, 1.5 h, Ar	22	75

[a] TMHD: 2,2,6,6-Tetramethylheptane-3,5-dione.

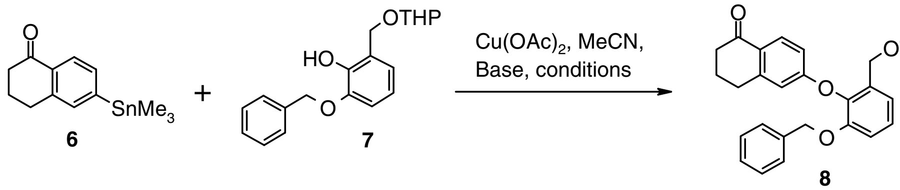
to Ar–H, **1b**). Therefore, excess amounts of phenol were necessary for a higher-yielding coupling reaction to circumvent this side reaction (entry 8). Most of the excess phenol could be recovered after chromatography. Further investigations revealed that better results are observed in the presence of atmospheric air or even oxygen (entries 8 and 9), especially for larger scales, which is in accordance with the results from the Evans group. This finding supports the original investigations and proposal by Evans et al.[5b] dealing with the intermediacy of hypervalent copper(III) species in this type of reaction. It seems that the presence of an oxidizing atmosphere improves the process of the arylation reaction and lends some substantial supporting evidence that perhaps an arylcopper(I) phenoxide intermediate can be oxidized to an arylcopper(III) species prior to the reductive elimination. Although, as yet, no experimental evidence exists for this unresolved issue, this rationalization can be supported. In our case, however, the presence of sensitive benzylic positions required careful control of the amount of oxygen introduced to the reaction.

Further experimentation provided additional insight (not shown): a brief screening of solvents showed that toluene, DMF and pyridine were less effective than acetonitrile. Other bases such as KO-*t*-Bu, Cs_2CO_3 and piperidine were also less effective. We also found that the reactions carried out with other copper sources such as $Cu(acac)_2$, $Cu((CO_2)_2)$ and $Cu(phen)Br_2$ also gave inferior results. Copper acetate is the best choice as has been previously reported in the cross-coupling reactions with boronic acids and phenols.

The cross-coupling reaction of stannane **6** and phenol **7** following our protocol afforded diaryl ether **8** in moderate yield (Table 2, entry 1). Lam's previous experience using TBAF both as a base and an accelerator for the transmetallation by forming a hypervalent stannane led us to try this combination of reagents (entry 2). We observed that DMAP in acetonitrile furnished a better reaction outcome than TBAF, leading to almost double the yield in the formation of **8**. Presumably, DMAP in the acetonitrile solvent plays an important dual role as a base and as a participating ligand to form a possible organocopper species in the reaction medium. On the other hand, using DMAP at 30 °C the reaction time was extended and did not achieve the yield observed at elevated temperature (entry 3). Interchanging the excess amount of the phenol by an excess of stannane **6** led to a slight increase of the yield (entries 4 and 5).

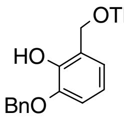
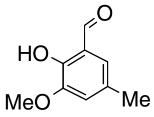
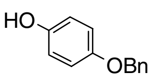
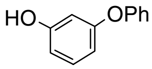
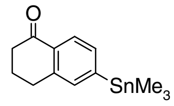
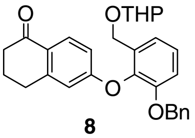
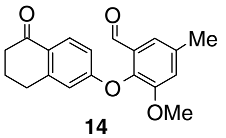
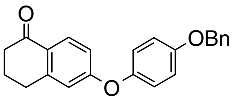
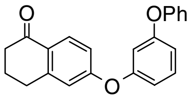
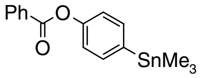
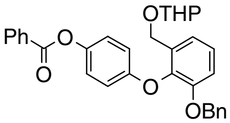
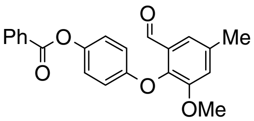
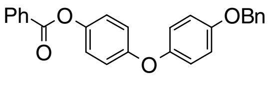
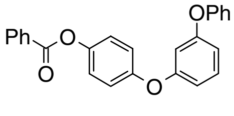
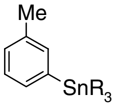
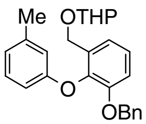
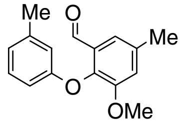
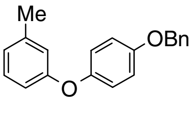
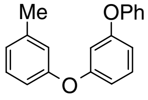
In order to investigate the scope and limitation of our protocol, we applied similar conditions to cross copper-mediated reactions between a variety of stannanes (**6**, **12**, **13**) and phenols (**7**, **9**–**11**) leading to the coupling products **8**, **14**–**24** (Table 3). Methods A and B and C and D are, respectively, very similar. As the reaction yields in the syntheses of **8** and **21** are similar, methods C and D are interchangeable in most cases. However, as applied in methods B, a large excess of DMAP might impact the reaction outcome (e.g., sensitive group in **17**). In case of doubt, method A and D can be preferred. In addition to that the availability of phenols and stannanes determines whether method A or D is favourable. The reactions described in Table 3 follow the general trend that electron-donating groups on the phenol furnish moderate yields in very short reaction times. This fact acts accordingly to the well-established trend in copper- and palladium-catalyzed ether formation reaction. However, an electron-withdrawing group on the

Table 2. Effect of base, temperature and excess amounts on the coupling of **6** with **7**



Entry	Stannane **6** (equiv)	Phenol **7** (equiv)	$Cu(OAc)_2$ (equiv)	Base (equiv)	Conditions	Yield (%)
1	1	4	1.1	DMAP (4)	MeCN, 81 °C, 1.5 h, air	44
2	1	4	1.1	TBAF (4)	MeCN, 4 Å MS, 81 °C, 30 min, air	24
3	1	4	1.6	DMAP (4)	MeCN, 30 °C, 72 h, air	25
4	2	1	2	DMAP (2)	MeCN, 81 °C, 2 h, air	49
5	3.5	1	3.5	DMAP (2)	MeCN, 81 °C, 2 h, air	55

Table 3. Yields of diaryl ethers **8**, **14**–**24** ($Ar_1–SnR_3 + Ar_2–OH \rightarrow Ar_1–O–Ar_2$)

Stannane	Phenol			
	 **7**	 **9**	 **10**	 **11**
 **6**	 **8** 55% (Method D) 49% (Method C)	 **14** 0% (Method B)	 **15** 41% (Method C)	 **16** 52% (Method A)
 **12**	 **17** 43% (Method A) 30% (Method B)	 **18** trace (Method B)	 **19** 59% (Method A)	 **20** 48% (Method C)
 **13**	 **21** R = Me: 42% (Method D) 38% (Method C)	 **22** R = n-Bu: 29% (Method D)	 **23** R = Me: 52% (Method D)	 **24** R = Me: 39% R = Et: 43% R = n-Bu: 45% (Method D)

Method A: 1 equiv stannane, 4 equiv phenol, 1.6 equiv $Cu(OAc)_2$, 4 equiv DMAP, 4 Å MS, air, 81 °C, 40 min; Method B: 1 equiv stannane, 4 equiv phenol, 1.1 equiv $Cu(OAc)_2$, 8 equiv DMAP, 4 Å MS, air, 81 °C, 40 min; Method C: 2 equiv stannane, 1 equiv phenol, 2 equiv $Cu(OAc)_2$, 2 equiv DMAP, 4 Å MS, air, 81 °C, 40 min; Method D: 3.5 equiv stannane, 1 equiv phenol, 3.5 equiv $Cu(OAc)_2$, 2 equiv DMAP, 4 Å MS, air, 81 °C, 40 min.

phenol, such as an aldehyde, slows down the reaction as expected. For example, the reaction of **9** with the electron poor or neutral stannanes **6** and **12** failed,[11] while stannane **13** provided diaryl ether **22** in moderate yield. The reaction is general with respect to the aryl stannane component. The reaction yields are not reduced if the coupling partners bear sensitive groups, such as the benzoate leaving group in **12**. Furthermore, different alkyl substituents in the stannane moiety (Me, Et, *n*-Bu) resulted in comparable isolated yields of **24**.[12] Moreover, small amounts of water did not impede the reaction, whereas molecular sieves were added at larger scales.

In summary, we developed a reliable synthesis to substituted diaryl ethers using aryl stannanes and phenols. In general, the reactions are complete within one hour under mild conditions. The coupling partners are valuable as a result of their air and moisture stability, availability and compatibility with a variety of functionalities. A wide range of electron neutral and rich phenols were applicable in an easy to use procedure.[13] Structurally and electronically diverse trialkylstannanes enhance the scope in this formation reaction. Despite the moderate yields (40–60%), this general method is complementary to the use of boronic acids as aryl donors, as it tolerates substrates bearing an *ortho*- or/and *para*-carbonyl group.

Acknowledgements

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References and notes

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13. Representative experimental procedure for **23**: To a 10 mL vial were added 4-(benzyloxy)phenol (25 mg, 0.12 mmol), trimethyl(3-methylphenyl)stannane (124 mg, 0.42 mmol), 4-(dimethylamino)-pyridine (30 mg, 0.24 mmol), powdered 4 Å molecular sieves and 1 mL of acetonitrile. The resulting solution was stirred in an oil bath preheated to 81 °C for 3 min. Copper acetate (77 mg, 0.42 mmol) was added quickly in one portion and the resulting mixture was stirred for 40 min at 81 °C under ambient atmosphere. The reaction was cooled, filtered and diluted with EtOAc. The organic solution was washed with H_2O and brine, dried over Na_2SO_4 and concentrated. The residue was purified by silica gel chromatography (eluent 10% EtOAc/hexane) to give 19 mg (52%) of **23**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48–7.29 (m, 5H), 7.18 (t, 1H), 7.00–6.90 (m, 4H), 6.85 (d, 1H), 6.78–6.70 (m, 2H), 5.05 (s, 2H), 2.31 (s, 3H); MS (DCI) *m*/*z* 308 $(M+NH_4)^+$.