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Metal-Free Synthesis of *ortho*-CHO Diaryl Ethers by a Three-Component Sequential Coupling

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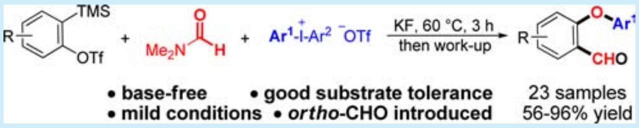
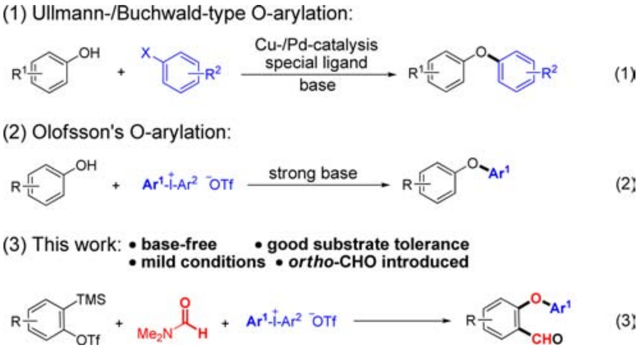
Supporting Information



ABSTRACT: A practical, metal-free, and highly chemoselective approach was developed for the synthesis of *ortho*-CHO diaryl ethers by a three-component sequential coupling of arynes, *N*,*N*-dimethylformamide (DMF), and diaryliodonium salts. Diverse functional groups including halo, nitryl, and bulky substituents and heteroaromatics are well tolerated. Mechanistically, isotopic tracer experiments reveal that the diaryliodonium salt serves as an electrophile to trap the transient intermediates generated from the [2 + 2] cyclization of an aryne and DMF.

Diaryl ethers are prominent structural motifs found in numerous natural products with vital biological activities, drug candidates, high-selling medicines, and relevant materials used in life science and industry.[1] Consequently, for more than a century continuous endeavors have been made toward the efficient synthesis of the unique unit. Ullmann-type diaryl synthesis represents a classical method although stoichiometric amounts of copper reagents and harsh conditions are often required.[1b,2] In recent decades, significant progress has been achieved by Cu-[3] and Pd-catalyzed[4] cross-coupling reactions of phenols with aryl halides or arylboronic acids (Scheme 1, eq 1).

Scheme 1. Profile for the Synthesis of Diaryl Ethers



Nevertheless, such transition-metal catalyses always rely on the use of noncommercially available or expensive ligands and generally suffer from the use of excess amounts of reagents, limited substrate tolerance, high temperatures, and long reaction times, which severely restrict application in organic and pharmaceutical synthesis. Therefore, considerable effort has been directed toward the discovery of a metal-free strategy.[5] Among these attempts, the S_NAr reaction is useful but mostly limited to the coupling of electron-rich/neutral phenols with highly activated aryl fluorides.[6] Recently, Olofsson and coworkers described an elegant protocol, wherein 1 equiv of a strong base, such as NaH, *t*-BuOK, and NaOH, is essential to deprotonate phenols followed by O-arylation with diaryliodonium salts (Scheme 1, eq 2).[7] Despite these important advances, the development of a practical methodology for the synthesis of *ortho* substituted and sterically hindered diaryl ethers remains a challenge. Particularly, exploration for a mild synthesis of *ortho*-CHO diaryl ethers is of great interest and significance because such ethers are very useful to making diverse interesting compounds.[8] Herein, we report a practical and highly chemoselective approach for the synthesis of *ortho*-CHO diaryl ethers by a novel three-component sequential coupling of arynes,[9] DMF,[10] and diaryliodonium salts (Scheme 1, eq 3).

Inspired by the pioneering results from the Miyabe group, in which highly reactive intermediates benzoxetene **A** and its isomer *ortho*-quinone methide **B** might form by [2 + 2] π-bond cyclization of an aryne with DMF,[11] we speculate that an extra electrophile (E^+) could trap **A**/**B** at the oxygen position to furnish **C** involving formation of a new O−E bond and an *ortho*-imine group that leads to an *ortho*-CHO group formation on the aryl ring after simple workup (Scheme 2). Importantly, the process avoids the use of stoichiometric amounts of dangerous strong bases or Lewis acids that is necessary for CHO group introduction by traditional approaches.[12] Reasonably, diaryliodonium salts ($E^+ = Ar^+$, herein) that have been widely utilized as excellent electrophilic arylation reagents[7] were selected for the hypothesis.

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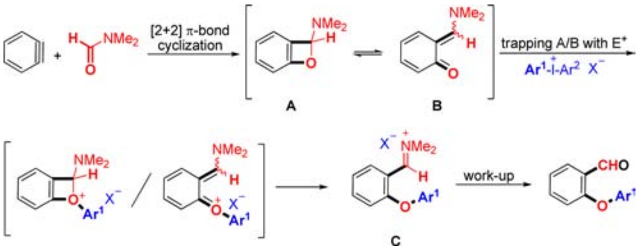
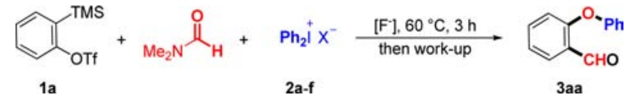
Scheme 2. Hypothetical Reaction Pathway



Indeed, this hypothesis guided our initial screening experiments (Table 1). To our delight, the treatment of the readily accessible aryne precursor 2-(trimethylsilyl)aryl triflate **1a** with diphenyliodonium triflate $Ph_2I^+OTf^-$ **2a** (1.2 equiv) and tetrabutylammonium fluoride (TBAF) (3.0 equiv) in DMF at 60 °C for 3 h facilitated the desired product 2-phenoxybenzaldehyde **3aa** in 70% yield predominantly (entry 1). Stimulated by the preliminary result, further optimization to improve the chemical yield was conducted. Using CsF and KF instead of TBAF improved the yield of **3aa** to 73% and 79%, respectively (entries 2 and 3). Gratifyingly, enlarging the loading of KF to 4.0 equiv gave the best result and afforded **3aa** in 87% yield (entry 4). Lowering the temperature to 50 °C decreased the yield somewhat (entry 5). A brief screening of solvents revealed that DMF is optimal (entries 4, 6–9). The reactions were completely suppressed in THF and CH_2Cl_2 due to the substrate insolubility (entries 6 and 7). Changing the solvent to toluene and acetonitrile (CH_3CN) lowered the yield of **3aa** to 15% and 66%, respectively (entries 8 and 9). The anion effect of diphenyliodonium salts has also been investigated. Accordingly, the replacement of **2a** by **2b–2f** decreased the yield of **3aa** to 83–50% (entries 10–14).

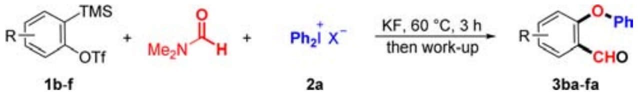
Table 1. Optimization of Reaction Conditions[a]

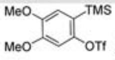
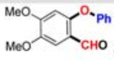
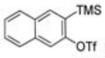
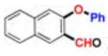
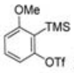
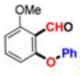
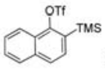
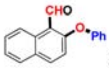
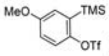
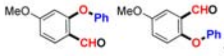
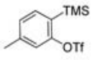
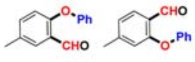
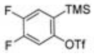
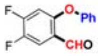


entry	Ph_2I^+ X^-	$[F^-]$ (equiv)	solvent	yield (%)
1	Ph_2I^+ OTf^- **2a**	TBAF (3.0)	DMF	70
2	**2a**	CsF (3.0)	DMF	73
3	**2a**	KF (3.0)	DMF	79
4	**2a**	KF (4.0)	DMF	87
5[b]	**2a**	KF (4.0)	DMF	61
6[c]	**2a**	KF (4.0)	THF	N.R.[d]
7[c]	**2a**	KF (4.0)	CH_2Cl_2	N.R.[d]
8[c]	**2a**	KF (4.0)	toluene	15
9[c]	**2a**	KF (4.0)	CH_3CN	66
10	Ph_2I^+ PF_6^- **2b**	KF (4.0)	DMF	83
11[d]	Ph_2I^+ AsF_6^- **2c**	KF (4.0)	DMF	69
12[e]	Ph_2I^+ NO_3^- **2d**	KF (4.0)	DMF	71
13	Ph_2I^+ Cl^- **2e**	KF (4.0)	DMF	80
14	Ph_2I^+ Br^- **2f**	KF (4.0)	DMF	50

[a] Reaction conditions: **1a** (0.15 mmol), **2** (1.2 equiv), $[F^-]$ (3.0–4.0 equiv), solvent (1.0 mL), 60 °C, 3 h; all yields are isolated. [b] At 50 °C. [c] DMF (10.0 equiv). [d] N.R. means no reaction.

Table 2. Substrate Scope of Arynes[a]



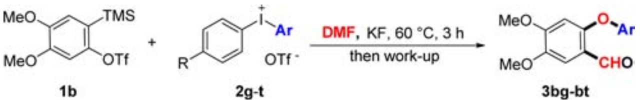
entry	aryne	product	yield (%)
1	 **1b**	 **3ba**	91
2	 **1c**	 **3ca**	82
3	 **1d**	 **3da**	78
4	 **1e**	 **3ea**	84
5	 **1f**	 **3fa/3fa′**	90 (1.2:1)
6	 **1g**	 **3ga/3ga′**	96 (1:1)
7	 **1h**	 **3ha**	72

[a] Reaction conditions: **1b–f** (0.15 mmol), **2a** (1.2 equiv), KF (4.0 equiv), DMF (1.0 mL), 60 °C, 3 h; all yields are isolated.

Under the optimized reaction conditions, we next examined the substrate scope with respect to both aryne precursors and diaryliodonium salts to the novel sequential coupling reaction. First, several *ortho*-silyl aryl triflates were employed and the representative results were summarized in Table 2. In addition to **1a**, symmetric *ortho*-silyl aryl triflates **1b** and **1c** were well tolerated and provided adducts **3ba** and **3ca** in 91% and 82% yields, respectively (entries 1 and 2). Notably, asymmetric *ortho*-silyl aryl triflates **1d** and **1e** gave exclusively **3da** and **3ea** in 78% and 84% yields that exhibit excellent regioselectivity (entries 3–4).[13] In contrast to **1d–e**, the aryne procurers **1f** and **1g** decreased regioselectivity, leading to regioisomers **3fa**/**3fa**′ and **3ga**/**3ga**′ in 90% and 96% yields with ratios of 1.2:1 and 1:1, respectively (entries 5–6). It is noteworthy that both mixtures of **3fa**/**3fa**′ and **3ga**/**3ga**′ can be facilely separated by single flash column chromatography. Importantly, for an aryne precursor having electron-withdrawing groups, 4,5-difluoro-substituted 2-(trimethylsilyl)phenyl triflate **1h** is also tolerated in the reaction to afford the desired product **3ha** in 72% yield smoothly (entry 7).

Next, a wide range of diaryliodonium salts was employed under the standard reaction conditions. Remarkably, we were pleased to find that a large variety of diaryliodonium salts are quite applicable to the three-component coupling reaction. As demonstrated in Table 3, using **1b** as the aryne precursor, diverse diaryliodonium salts gave the desired products in good yields. Symmetric diaryliodonium salts **2g–i** bearing a halogen (Cl and Br) and *tert*-butyl substituted at the *para* position furnished **3bg–bi** in 78–83% yields (entries 1–3). Encouraged by Olofsson's arylation with unsymmetrical diaryliodonium salts, in which an interesting result of "dummy groups"-controlled chemoselectivity was confirmed,[7d] a series of asymmetric diaryliodonium salts **2j–u** with one *para*-$CH_3OC_6H_4$ as the "dummy group" were prepared and reacted with **1b** under the standard reaction conditions (entries 4–15). Remarkably, excellent chemoselectivity was observed regardless of the electronic and steric properties of the other aryl group. For instance, triflate salts **2k–m** having a *para*-halogen (F, Cl, and Br) and even strong electron-withdrawing substituents CF_3 (**2n**) and NO_2 (**2o**) are all suitable for the three-component

Table 3. Substrate Scope of Diaryliodonium Salts[a]



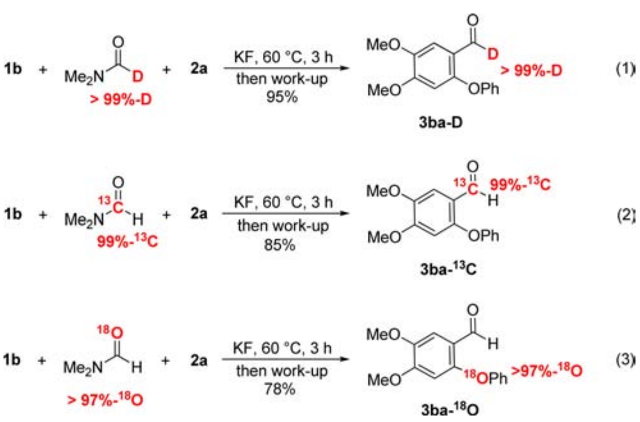
entry	diaryliodonium salts	product	yield (%)
1	R = Cl, Ar = *p*-ClC$_6$H$_4$ **2g**	**3bg**	78
2	R = Br, Ar = *p*-BrC$_6$H$_4$ **2h**	**3bh**	81
3	R = ^{t}Bu, Ar = *p*-^{t}BuC$_6$H$_4$ **2i**	**3bi**	83
4	R = OMe, Ar = C$_6$H$_5$ **2j**	**3ba**	84
5	R = OMe, Ar = *p*-FC$_6$H$_4$ **2k**	**3bk**	61
6	R = OMe, Ar = *p*-ClC$_6$H$_4$ **2l**	**3bg**	65
7	R = OMe, Ar = *p*-BrC$_6$H$_4$ **2m**	**3bh**	83
8	R = OMe, Ar = *p*-CF$_3$C$_6$H$_4$ **2n**	**3bn**	88
9	R = OMe, Ar = *p*-NO$_2$C$_6$H$_4$ **2o**	**3bo**	65
10	R = OMe, Ar = *o*-MeC$_6$H$_4$ **2p**	**3bp**	84
11[b]	R = OMe, Ar = *m*-MeC$_6$H$_4$ **2q**	**3bq**	56
12[b]	R = OMe, Ar = *p*-MeC$_6$H$_4$ **2r**	**3br**	85
13	R = OMe, Ar = 2,4,6-Me$_3$C$_6$H$_2$ **2s**	**3bs**	72
14	R = OMe, Ar = 3-pyridyl **2t**	**3bt**	76
15	R = OMe, Ar = 2-(6-Cl)pyridyl **2u**	**3bu**	68

[a] Reaction conditions: **1b** (0.15 mmol), **2** (1.2 equiv), KF (4.0 equiv), DMF (1.0 mL), 60 °C, 3 h; all yields are isolated. [b] Reaction time was prolonged to 8 h.

coupling reaction and provided **3bk–bo** in 61–88% yields (entries 5–9). In contrast to **2p** with an *ortho*-methyl group (entry 10), **2q** and **2r** containing a methyl group at the *meta*- and *para*-position that seem less reactive proceeded in the reaction with a prolonged reaction time of up to 8 h, affording **3bq** and **3br** in 56% and 85% yields, respectively (entries 11 and 12). Significantly, highly substituted salt **2s** is also compatible with this transformation, and the reaction enabled the formation of **3bs** in 72% yield smoothly (entry 13). Importantly, *ortho*-CHO pyridyl ethers **3bt** and **3bu** can be isolated in 76% and 68% yields with pyridyliodonium salts **2t** and **2u** as electrophiles (entries 14 and 15).

In order to explore the reaction mechanism, isotopic tracer experiments were executed. As shown in Scheme 3, the reactions proceeded in D-DMF (eq 1), ^{13}C-DMF (eq 2), and ^{18}O-DMF (eq 3), delivering the corresponding isotope labeled products **3ba-D**, **3ba-^{13}C**, and **3ba-^{18}O** in high yields, respectively. Reasonably, these observations reveal that such a three-component sequential coupling reaction should go through the postulated pathway demonstrated at Scheme 2, in which the diaryliodonium salt acts as an electrophile to trap the transient intermediates generated from the [2 + 2] π-bond cyclization of aryne and DMF.

Scheme 3. Isotopic Tracer Experiments



In summary, we have realized a useful approach for the synthesis of *ortho*-CHO diaryl ethers by a three-component sequential coupling reaction of arynes, DMF, and diaryliodonium salts. Remarkably, a C–C bond and two new C–O bonds simultaneously formed in the transformation. Mechanistically, isotope experiments disclose that the diaryliodonium salt functions as an electrophile to trap the active intermediates generated from the [2 + 2] cyclization of an aryne and DMF. Further applications of the practical method to some interesting natural products and diaryl ether materials are under investigation in our laboratory and will be reported in due course.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Complete experimental details and characterization data for the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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