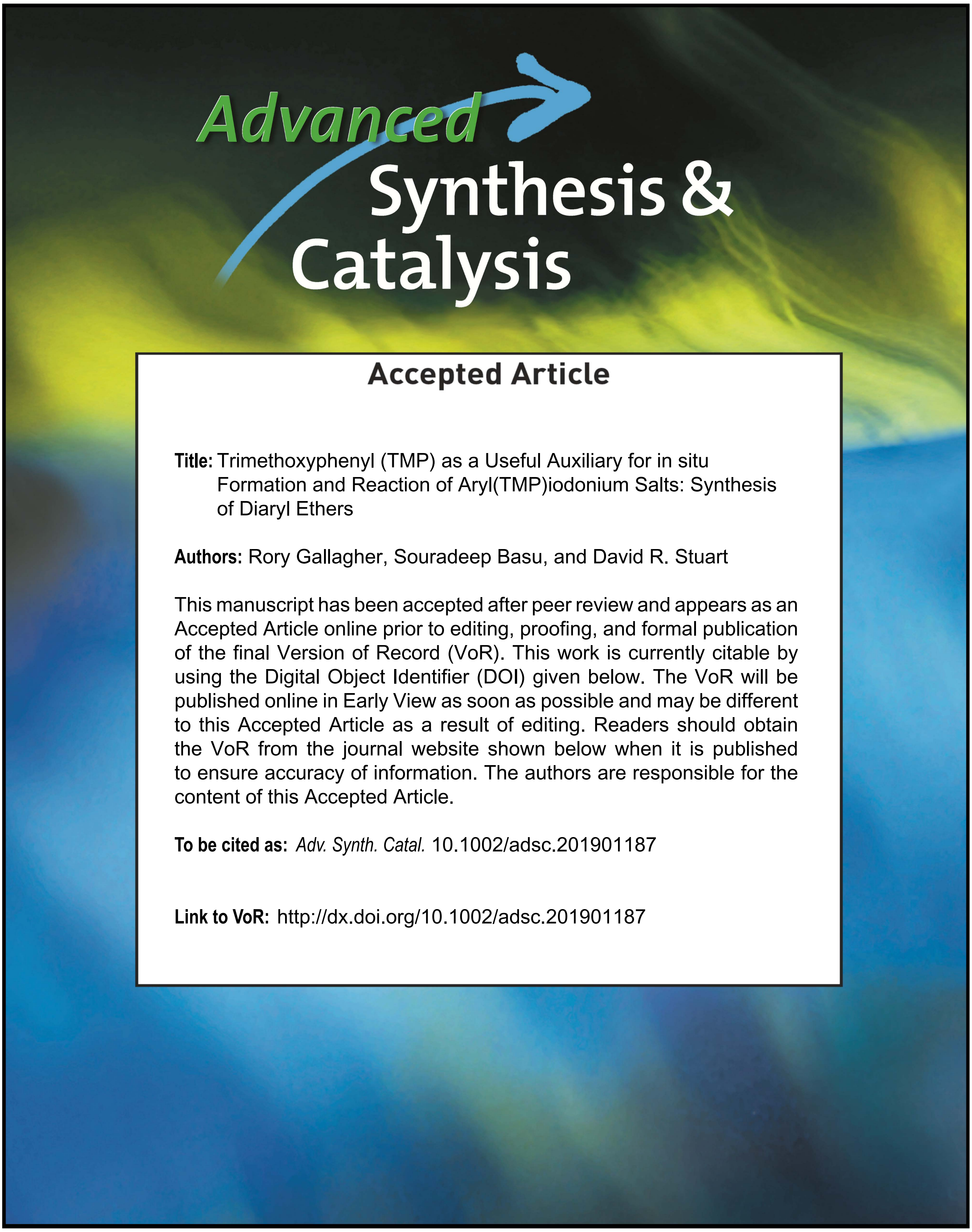

Advanced Synthesis & Catalysis

Title: Trimethoxyphenyl (TMP) as a Useful Auxiliary for in situ Formation and Reaction of Aryl(TMP)iodonium Salts: Synthesis of Diaryl Ethers

Authors: Rory Gallagher, Souradeep Basu, and David R. Stuart

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Trimethoxyphenyl (TMP) as a Useful Auxiliary for *in situ* Formation and Reaction of Aryl(TMP)iodonium Salts: Synthesis of Diaryl Ethers

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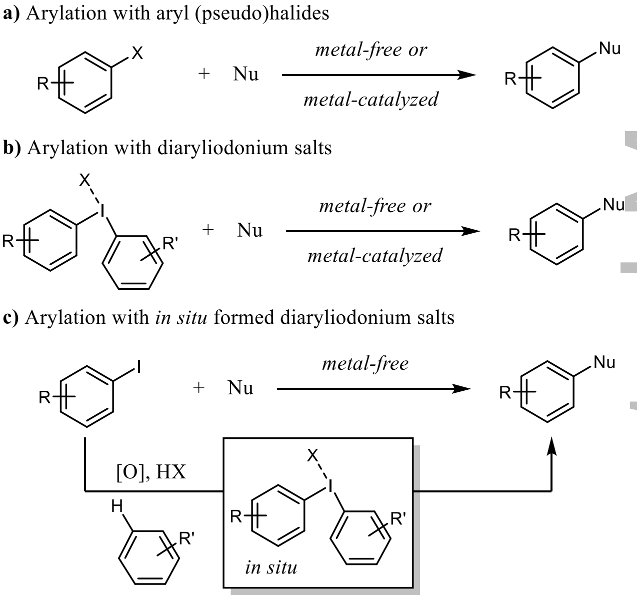
Abstract. Herein, we describe a synthetic approach for arylation that exploits the *in situ* formation and reaction of an unsymmetrical diaryliodonium salt. In this way, aryl iodides are used as reagents in a metal-free reaction. A trimethoxyphenyl (TMP) group is used as a "dummy" group to transfer a wide range of aryl moieties. The scope of aryl electrophiles and phenol nucleophiles is broad (>30 examples) and the yields are high (52-95%, 80% avg.). One-pot coupling reactions avoid the synthesis of diaryliodonium salts and provide opportunities for sequential reactions and novel chemoselectivity.

Keywords: C-O cross-coupling; telescoping; hypervalent iodine; diaryliodonium; diaryl ether

Aromatic rings abound in pharmaceuticals, agrochemicals, and novel materials. Consequently, synthetic chemists have devoted significant resources to devising innovative and practical arylation strategies. Aryl electrophiles bearing leaving groups feature prominently and both metal-free[1] and metal-catalyzed[2] reactions of aryl (pseudo)halides with nucleophiles are well established (Scheme 1a). Diaryliodonium salts contain an aryliodonium leaving group that facilitates mechanistic advantages over traditional halides: facile oxidative addition to first-row metals (i.e., copper) and increased scope in metal-free reactions (Scheme 1b).[3] However, despite these advantages, the need to synthesize diaryliodonium salts is often viewed as a drawback. A potential solution is to form the diaryliodonium *in situ* and exploit the aforementioned advantages of the iodonium leaving group while using more readily abundant starting materials (Scheme 1c).[4]

Unsymmetric diaryliodonium salts are desired over symmetric ones, especially for the transfer of even moderately complex aryl moieties, and many auxiliary aryl groups have been described and aryl transfer selectivity reviewed.[5] Of note, in 2013, Olofsson and co-workers reported a chemoselectivity study and found that the 2,4,6-trimethoxyphenyl (TMP) group is useful for promoting exclusive transfer of the other aryl group of aryl(TMP)iodonium salts,[6] and use of these reagents has continued to emerge over a range of mechanistically distinct reactions.[7-9] We have an ongoing interest in the development of reactions to synthesize[10,11] and use[7b-d] aryl(TMP)iodonium salts, and herein we describe a methods to generate and use them *in situ* for phenol arylation.



Scheme 1. General arylation strategies.

Diaryl ethers are important motifs in pharmaceuticals and agrochemicals and have been synthesized by the strategies presented in Scheme 1a and 1b. The use of both symmetrical and unsymmetrical diaryliodonium salts to synthesize diaryl ethers is precedented, as early as 1953, and is particularly relevant to this work.[6,10a,12] To the best of our knowledge there is no report on the synthesis of diaryl ethers from aryl iodides with *in situ* formation of a diaryliodonium salt. Herein, we use the synthesis of diaryl ethers as a platform to demonstrate an arylation strategy using aryl iodides and exploiting an

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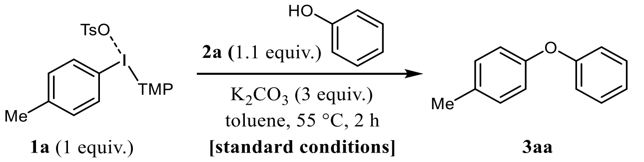
in situ generated aryl(TMP)iodonium salt. Moreover, we highlight the functional group compatibility with sequential reactions and novel chemoselectivity.

At the outset of our investigation we found that there were relatively few examples of diaryl ether synthesis from aryl(TMP)iodonium salts; in fact, there were only four scope examples in total found in three published papers.[6,10a,12l] Therefore, we viewed this as an opportunity to optimize the second step of our telescoped reaction and identify reaction conditions that are specifically suited to the coupling of aryl(TMP)iodonium salts and phenols (Table 1). Our survey of reaction conditions included the structure of the aryl(TMP)iodonium salt (**1a**), the identity of base and solvent, the reaction temperature and time. The conditions that we refer to hereafter as "standard conditions" include 1.1 molar equivalents of phenol coupling partner, 3 equivalents of K_2CO_3 as base, toluene as solvent, 55 °C as reaction temperature, for 2 hours, and result in 99% ^{1}H NMR yield and 91% isolated yield of **3aa** (Table 1, entry 1). We found that using the symmetrical variant of **1a** ([di-(4-tolyl)]iodonium tosylate) resulted in notably lower yield (76%) under identical conditions (Table 1, entry 2). Moreover, anisyl as an auxiliary resulted in lower yield and ~ 8: 1 selectivity for transfer of tolyl *vs* anisyl to the phenol (Table 1, entry 3). This result is consistent with that previously observed by Togo and co-workers,[12h] and underscores that anisyl is an inferior auxiliary to TMP in this case. Additionally, variation of the counter anion of **1a** to either OTf or BF_4 revealed that triflate may be a suitable replacement, though tetrafluoroborate resulted in lower yield (Table 1, entry 4 and 5). We found that reducing the equivalents of K_2CO_3 only marginally affected the yield of **3aa** (88%; Table 1, entry 6). However, a screen of other bases that have been used to couple diaryliodonium salts and phenols resulted in generally lower yields (Table 1, entry 7 and 8). The solvents THF and MeCN also provided high yield of **3aa**, and may be useful alternatives to toluene (Table 1, entry 10 and 11). Finally, we found that moderate heating at 55 °C provided higher yield than 21 or 80 °C (Table 1, entry 12 and 13).

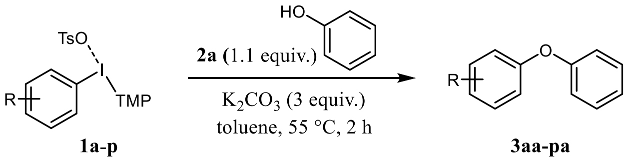
Table 1. Influence of reaction conditions on coupling.[a]

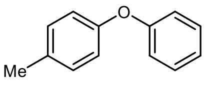


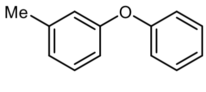
Entry	Deviation from standard conditions	Yield[b]
1	none	99%(91%)[c]
2	[di-(4-tolyl)]iodonium tosylate instead of **1a**	76%
3	(4-tolyl)(4′-anisyl)iodonium tosylate instead of **1a**	83%[d]
4	OTf as counter anion of **1a**	94%
5	BF_4 as counter anion of **1a**	70%
6	1 equiv. of K_2CO_3	88%
7	KO*t*-Bu instead of K_2CO_3	79%
8	$NaHCO_3$/TBAF instead of K_2CO_3	29%
9	NaOH instead of K_2CO_3	97%
10	THF instead of toluene	93%
11	MeCN instead of toluene	85%
12	80 °C as reaction temp.	96%
13[e]	21 °C as reaction temp.	25%

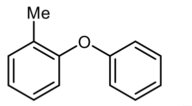
[a] Reaction conditions: **1a** (0.1 mmol, 1 equiv.), **2a** (0.11 mmol, 1.1 equiv.), K_2CO_3 (0.3 mmol, 3 equiv.), toluene (0.5 mL), 55 °C, 2 h; see table for deviations. [b] Yield determined by ^{1}H NMR spectroscopy with 2,4-dichlorobenzaldehyde as internal standard. [c] Isolated yield. [d] 11% of **3ja** detected. [e] 24 hour reaction time.

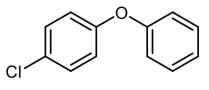
Table 2. Scope of aryl(TMP)iodonium salts.[a)]

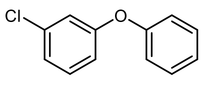


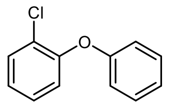

3aa, 91%

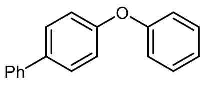

3ba, 88%

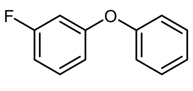

3ca, 91% (90,[b)] 78[c)])

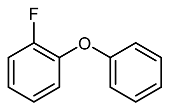

3da, 81% (99,[c)] 97[d)])

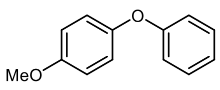

3ea, 88%

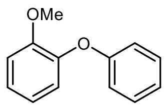

3fa, 87%

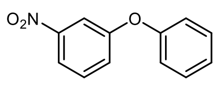

3ga, 77%

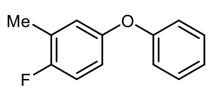

3ha, 75%

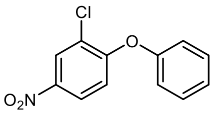

3ia, 75% (72)[e)]

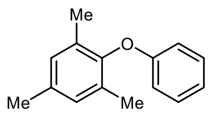

3ja, 85% (90[d)])

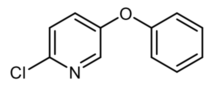

3ka, 56%


3la, 86%


3ma, 84%


3na, 73%

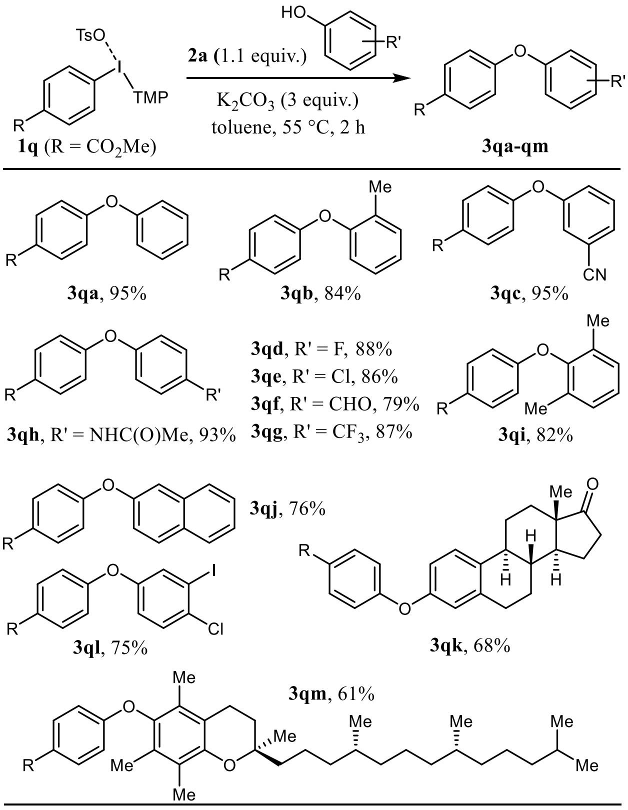

3oa, 84%


3pa, 91%

[a)] Reaction conditions: **1** (0.5 mmol, 1 equiv.), **2a** (0.55 mmol, 1.1 equiv.), K_2CO_3 (1.5 mmol, 3 equiv.), toluene (2.5 mL), 55 °C, 2 h. See the SI for specific deviations in conditions. [b)]Yields from ref. [12f]. [c)]Yields from ref. [12j]. [d)]Yields from ref [12h]. [e)]Yields from ref [12e]

Tables 2 and 3 contain representative examples of diaryl ethers that may be prepared from aryl(TMP)iodonium tosylates and phenols under the standard conditions described above. The substrate scope is generally tolerant of both electronic and steric effects on both the aryl electrophile and phenol nucleophile (Table 2 and 3). The high yields observed for *p*-, *m*-, *o*-tolyl and *p*-, *m*-, *o*-chlorophenyl series highlight the tolerance for steric and electronic effects on the aryl electrophile (**3aa-fa**, Table 1). Other electron donating (Ph, **3ga**) and electron withdrawing (F, NO_2; **3ha**, **3ia**, and **3la**) substituents are also compatible in this coupling reaction. Notably, even very electron rich rings are transferred preferentially over the TMP group. Compound **3ja** is synthesized in 85% yield by preferential transfer of *p*-anisole over TMP. Although the selectivity of aryl group transfer for starting material **1j** is high, this electron rich substrate required longer reaction time (24 hours) than other substrates in Table 2. The use of unsymmetrical aryl(TMP)iodonium salts also facilitates the transfer of elaborate aryl groups (**3ma** and **3na**), sterically congested aryl groups (**3oa**), and heterocyclic aryl groups (**3pa**; Table 2). Notably, the yields obtained here are similar to those previously reported.[12e,f,h,j]

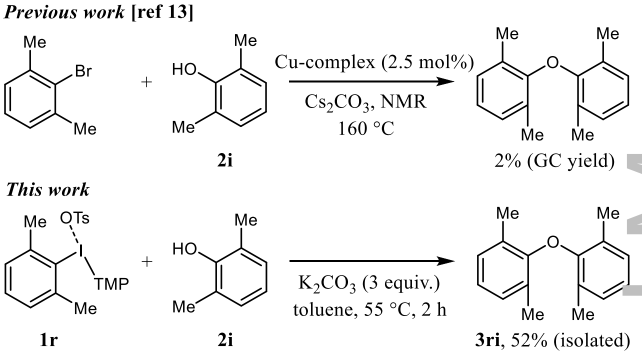
Table 3. Scope of phenols.[a)]



[a)] Reaction conditions: **1q** (0.5 mmol, 1 equiv.), **2** (0.55 mmol, 1.1 equiv.), K_2CO_3 (1.5 mmol, 3 equiv.), toluene (2.5 mL), 55 °C, 2 h. See SI for specific deviations from standard conditions.

Steric and electronic effects are also well-tolerated on the phenol coupling partner (Table 3). Aryl(TMP)iodonium tosylate **1q** was used as the standard electrophile to assess the scope of phenols in this reaction. Electron rich (**2b**, **2h**, **2j**) and electron deficient (**2c-g**) phenols are compatible, which includes aldehyde groups (**3qf**) and N-H bonds (**3qh**). Several other notable examples are provided in Table 3. The sterically encumbered phenol, 2,6-dimethylphenol **2i** couples with **1q** to produce **3qi** in 82% yield (Table 3). Additionally, aryl iodides are well tolerated on the phenol coupling partners (**3ql**) which is distinct from metal-catalyzed reactions and may be used for further functionalization. Finally, elaborate phenols (estrone, **2k** and α-tocopherol, **2m**) are well-tolerated and undergo *O*-arylation in moderate yield (68%, **3qk**, and 61%, **3qm**, respectively).

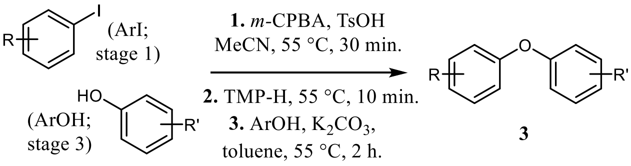
We have also demonstrated that the use of aryl(TMP)iodonium tosylates is compatible with a combination of both sterically encumbered aryl electrophile and phenol nucleophile. The symmetrical, and highly sterically congested, 2,2′,6,6′-tetramethyldiphenyl ether (**2ri**) has only been described in the literature on one other occasion,[13] and in ~2% yield by GCMS (Scheme 2). The coupling of **1r** and **2i** proceeded in 52% isolated yield under our standard conditions to deliver **3ri** (Scheme 2).

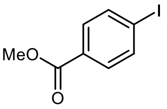
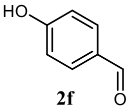
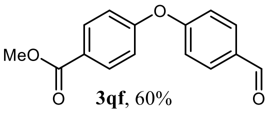
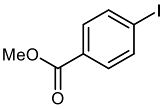
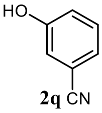
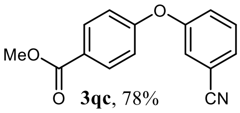
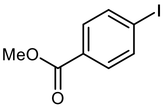
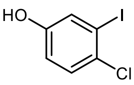
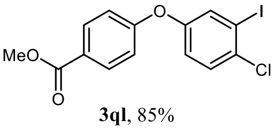
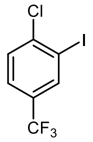
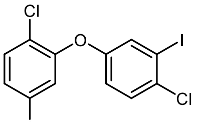


Scheme 2. Access to sterically hindered diaryl ethers.

In line with our overall goal to capitalize on aryl(TMP)iodonium salts as reaction intermediates, we have developed a method to telescope three reactions together: 1) aryl iodide oxidation, 2) installation of the TMP auxiliary, and 3) C-O coupling. The result is a direct coupling of aryl iodides with phenols that takes place under relatively mild temperature (55 °C), short reaction time (< 3 hours), and without a metal catalyst. We have previously telescoped the first two reactions together (aryl iodide oxidation and installation of TMP auxiliary),[10a,c] but to the best of our knowledge this is the first example wherein the synthesis of aryl(TMP)iodonium salts from aryl iodides and subsequent reactions are combined in a single pot. During development we found that the C-O coupling reaction was relatively insensitive to the solvent (MeCN) and the by-products (H_2O and *m*-ClC_6H_4COOH) of the first two reactions. Indeed, MeCN was found to be a suitable solvent for this reaction, albeit in slightly lower yield than toluene as solvent (Table 1, compare entries 1 and 11). We also found that increasing the stoichiometry of base (4 equiv.) was necessary to neutralize the carboxylic acid produced from *m*-CPBA, but we did not observe any competitive C-O coupling with the carboxylate nucleophile. Four examples of this strategy are shown in Table 4. The first three examples replicate products that were synthesized directly from aryl(TMP)iodonium salts (**3qf**, **3qc**, **3ql**) and are formed in synthetically useful yields (60-85%) directly from the aryl iodides (Table 4). On average, the yields of diaryl ethers (**3qf**, **3qc**, **3ql**) formed from aryl iodides are lower than those from aryl(TMP)iodonium salts (74% *vs*. 83%, respectively), but the telescoped approach reduces both solvent volume and time associated with purification of the aryl(TMP)iodonium salt. The fourth example yields a more structurally elaborate and functionalized diaryl ether in 68% yield (Table 4, **3tl**) and highlights not only the importance of an unsymmetrical aryl(TMP)iodonium intermediate, but also the compatibility of this approach for iodo-functional handles on the phenol nucleophile.[12m]

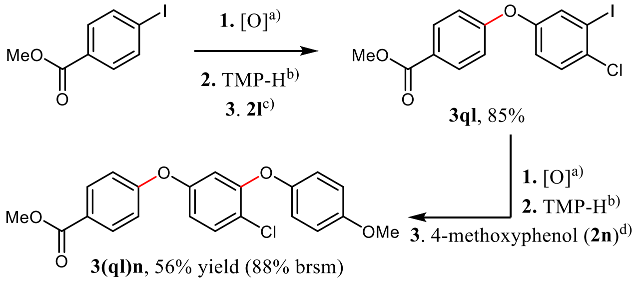
Table 4. Telescoped reactions.[a)]



ArI	ArOH	Diaryl ether
	 **2f**	 **3qf**, 60%
	 **2q**	 **3qc**, 78%
	 **2l**	 **3ql**, 85%
	**2l**	 **3tl**, 68%

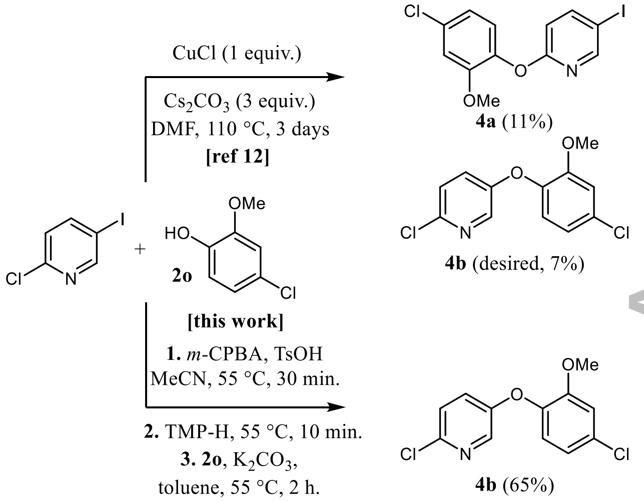
[a)] Reaction conditions: **1.** Aryl iodide (0.5 mmol, 1 equiv.), *m*-CPBA (0.5 mmol, 1 equiv.), TsOH•H_2O (0.5 mmol, 1 equiv.), MeCN (0.5 mL), 55 °C, 30 min.; **2.** TMP-H (0.5 mmol, 1 equiv.), 10 min.; **3. 2** (0.55 mmol, 1.1 equiv.), K_2CO_3 (2 mmol, 4 equiv.), toluene (2.5 mL), 55 °C, 2 h.

In an additional example, we demonstrate how the compatibility of iodo functional handles on the nucleophile can be used for sequential reactions to synthesized polyaryl ethers (Scheme 3). In this way product **3ql** was produced in 85% yield and in a second pot **3(ql)n** was obtained in 56% isolated yield with 36% of unreacted **3ql** also isolated (88% based on recovered start material).



Scheme 3. Sequential coupling reactions. [a)] Aryl iodide (0.5 mmol, 1 equiv.), *m*-CPBA (0.5 mmol, 1 equiv.), TsOH•H_2O (0.5 mmol, 1 equiv.), MeCN (0.5 mL), 55 °C, 30 min. [b)] TMP-H (0.5 mmol, 1 equiv.), 10 min. [c)] **2l** (0.55 mmol, 1.1 equiv.), K_2CO_3 (2 mmol, 4 equiv.), toluene (2.5 mL), 55 °C, 2 h. [d)]4-methoxyphenol **2n** used as the phenol.

Finally, we show in Scheme 4 that this reaction is highly chemoselective for aryl iodides even in the presence of more electrophilic groups. Classic nucleophilic substitution (S_NAr) of halogenated pyridines occur fastest at the 2- and 4-positions relative to the 3-position.[14] Indeed, several examples of S_NAr on 2-chloro-5-iodopyridine with *O*-nucleophiles show a high preference for substitution of the 2-chloro over the 5-iodo moiety.[15] Diaryl ethers containing a pyridyl group have been investigated for their antibacterial activity,[16] and copper-mediated coupling was used to form the diaryl ether C-O bond (Scheme 4). In the case of 2-chloro-5-iodopyridine the reaction is relatively unselective, low-yielding, and required high temperature and long reaction times. Our telescoping approach is selective for the iodo group, occurs under much more mild temperature, and in shorter reaction time (Scheme 4).[17]



Scheme 4. Chemoselective coupling of 2-chloro-5-iodopyridine.

In conclusion, we have developed a mild and efficient method to synthesize diaryl ethers from aryl iodides and phenols that takes advantage of aryl(TMP)iodonium salts as a key reaction intermediate. This method does not require a metal catalyst and has broad substrate scope. We are further evaluating this chemistry in the context of functionalizing biomolecules and as a broader arylation strategy.

Experimental Section

Synthesis of diaryl ethers from aryl(TMP)iodonium tosylate and phenols.

Aryl(TMP)iodonium tosylate (0.5 mmol, 1 equiv.), potassium carbonate (1.5 mmol, 3 equiv.), phenol (0.55mmol, 1.1 equiv.), and toluene (2.5 mL) were added to an 8 mL vial, equipped with a magnetic stir bar and sealed with a cap. The reaction was placed in a preheated aluminum block set to 55 °C and stirred vigorously for 2 hours. The reaction was removed from heat and partitioned between dichloromethane and saturated aqueous ammonium chloride. The organic phase was evaporated under reduced pressure and the residue purified using flash column chromatography.

Synthesis of diaryl ethers from aryl iodides and phenols via telescoped reactions.

Aryl iodide (0.5 mmol, 1 equiv.) and acetonitrile (0.5 mL) were added to an 8 mL vial equipped with a magnetic stir bar. *p*-Toluenesulfonic acid (0.55 mmol, 1.1 equiv.) was added in one portion, followed by one portion of *m*-CPBA (0.55 mmols, 1.1 equiv.). The vial was sealed with a cap and transferred to a preheated aluminum block set to 55 °C and stirred vigorously for 30 minutes. Trimethoxybenze (0.5 mmols, 1 equiv.) was added in one portion and stirring was continued at 55 °C for 10 minutes. Toluene (2.5 mL) was added to the vial, followed by potassium carbonate (2.0 mmol, 4 equiv.) and phenol (0.55 mmol, 1.1 equiv.). The reaction was stirred at 55 °C for 2 hours. The reaction was removed from heat and partitioned between dichloromethane and saturated aqueous ammonium chloride. The resulting organic solution was evaporated under reduced pressure and purified using flash column chromatography.

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COMMUNICATION

Metal-Free Cross-Coupling of Aryl Iodides and Phenols with Aryl(TMP)iodonium Tosylates as Intermediates

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