

the reaction proceeded via a Heck-like pathway.

Copper-Catalyzed Meta-Selective Arylation of Phenol Derivatives: An Easy Access to *m*-Aryl Phenols

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ABSTRACT: Ach challenge. Access incorporation of c meta-arylated phe	nieving selective meta-function ing such compounds gene complex templates. Here, we enols with a simple and co	onalization of j rally needs ele report a gener ommon directin	phenols is a significant evated temperature or ral approach to achieve og group. This copper-		Cu(II) catalysis	

KEYWORDS: carbamates, phenols, aryliodonium salts, copper, C-H functionalization

catalyzed protocol proceeds with complete meta-selectivity and tolerates a variety of functional groups in both coupling partners. Computational studies have revealed that

I n the past 3 decades, enormous growth has been achieved in the area of C-H bond functionalization.¹ Over the past 20 years, directed aryl sp² C-H bond functionalization has captured notable attention; however, this approach has generally been confined to functionalization of the positions ortho to the directing groups on arenes.² In contrast to orthofunctionalization, scope of both transformations and substrates for selective meta-functionalization of an arene C-H bond is still in its infancy.³⁻⁵ Phenol and its derivatives being important arene motifs in pharmaceuticals and natural products are versatile synthetic building blocks for many organic transformation reactions.⁶ Hence, selective functionalization of phenol derivatives has attracted much interest from the synthetic community. Many methods have been reported for the modifications at the ortho/para position of phenols, utilizing the electron donating nature of the hydroxyl group. However, such an electronic property restricts the functionalization at the meta positions of the phenol. In recent years, Yu4a,f,l-n and Larrosa^{5f} independently achieved palladium catalyzed meta-selective arylation and alkenylation of phenol derivatives through the "end-on template" directing group strategy and traceless directing group relay strategy. Recently, Yu's group presented an excellent work of sequential functionalization of a meta C-H bond followed by the catalytic cleavage of an ipso C-O bond in phenols.⁴ⁿ Although significant breakthroughs have been made,40 there is an ongoing search for new approaches for meta C-H functionalization of phenols. Given our continued interest in the direct C-H functionalization and copper catalysis,⁸ our lab has focused on developing new reactions that work with broad substrate scope. Copper, being an earth abundant metal, makes its use more viable and more cost-efficient than precious transition metal catalysts. The first breakthrough in metaactivation of arenes^{5a} was reported by Gaunt, which subsequently led to the development of new concepts for meta-functionalization in synthetic chemistry. Influenced by

the reactivity of anilides in copper-catalyzed reaction^{5a} of diaryliodonium salts, we hypothesized that phenyl carbamates may also react with diaryliodonium salts in a similar manner to provide a meta-arylated product (Scheme 1).^{9,10}

R = CONMe₂

Excellent selectivity scalable mild condition >30 examples

To test this hypothesis, we treated phenyl carbamate 1a with $Ph_2I^+OTf^-$ in the presence of 10 mol % $Cu(OTf)_2$ in the DCE solvent at 70 °C. Arylation took place at the meta position to give 2a and $3a^{7b}$ in a combined yield of 75% (Table 1, entry 1), and in agreement with our hypothesis, products arylated at either para or ortho position were not observed (analyzed by GC). Inspired by this result, we continued with the optimization of the protocol by retaining the o-cresol core as our model substrate. It was revealed that changing the acyl group had a significant effect on the selectivity and yield of the reaction (Table 1, entries 1-5). The reaction proceeds with acetate and pivalate groups, although the selectivity and conversions were moderate and meta-/ortho-arylated products were obtained with a ratio of 2:1 (Table 1, entries 2 and 3). However, when carbonates and esters were screened, the starting materials were retained without affording the desired arylated products (Table 1, entries 4 and 5). Having identified the suitable phenol derivative for arylation, we established a condition for the hydrolysis of carbamates in order to afford meta-arylated phenols in one pot. Initially, we found that treating the reaction crude obtained after reaction with Cu(OTf)₂ with 10 equivalents of NaOH in EtOH at 80 °C for 12 h provided selective meta-arylated phenol 2a in 74% isolated yield after column chromatography (Table 2, entry 1).

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Scheme 1. Design of Meta-Selective Copper-Catalyzed C-H Bond Arylation

(a) General reactivity of phenol



(b) Complementary catalysis between Pd(II) and Cu (II)



(c) This study - meta C-H arylation of aryl carbamates



Table 1. Screening of the Acyl Group^a

o o	Ph ₂ I ⁺ OTf ⁻ (1.2 equiv) Cu(OTf) ₂ (10 mol %)	OH Me		
Me	DCE (2.0 mL) 70 °C, 24 h	Ph	Me Ph	
1а-е		2a	3a-3e	
entry	R	Product	yield (%) ^a	
1 ^b	NMe ₂	2a + 3a	20 + 55	
2 ^c	Me ₂	2a + 3b	13 + 40	
3 ^c	CMe ₂	2a + 3c	12 + 52	
4	OMe	2a + 3d	NIL	
5	Ph	2a + 3e	NIL	

^aYields were determined by GC. ^bIsolated yield. ^cObserved meta-/ ortho-arylated products in 2:1 ratio.

Table 2. Effect of Substituents on the Nitrogen Atom^a



^{*a*}Reaction conditions: (1) **1a** (1 equiv), salt (1.2 equiv), catalyst (10 mol %) in DCE (2.0 mL) for 24 h. (2) NaOH (10 equiv) in EtOH (5 mL) at 80 °C for 12 h. ^{*b*}Isolated yields after column chromatography. ^{*c*}($C_{3}H_{3})_{2}ZrHCl$ (3 equiv) in THF (5 mL) at room temperature for 15 h.

Table 3. Optimization of Arylation of Phenol Carbamates^a

Me	Me N Me 1. lodoniu DCE, 2. NaOH, B	m salt, catalyst Temp, 24 h EtOH, 80 °C, 12	OH Me	
	1a		2	la
Entry	catalyst (10 mol %)	salt	temp [°C]	yield [%] ^b
1	$Cu(OTf)_2$	Ph ₂ I ⁺ OTf ⁻	70	66
2	$Cu(OTf)_2$	$Ph_2I^+BF_4^-$	70	74
3	$Cu(OTf)_2$	Ph ₂ I ⁺ PF ₆ ⁻	70	0
4	$Cu(OTf)_2$	$Ph_2I^+BF_4^-$	60	48
5	$Cu(OTf)_2$	Ph ₂ I ⁺ BF ₄ ⁻	80	56
6	$Cu(OAc)_2$	Ph ₂ I ⁺ BF ₄ ⁻	70	42
7	CuBr ₂	Ph ₂ I ⁺ BF ₄ ⁻	70	63
8	CuI	$Ph_2I^+BF_4^-$	70	64
9	Cu powder	$Ph_2I^+BF_4^-$	70	60
10		$Ph_2I^+BF_4^-$	70	31
11		Ph ₂ I ⁺ BF ₄ ⁻	80	26
12		$Ph_2I^+BF_4^-$	100	24
n			.) 1. (1.0	. \ 1

^{*a*}Reactions were carried out with 1a (1 equiv), salt (1.2 equiv), and catalyst (10 mol %) in DCE (2.0 mL) for 24 h. ^{*b*}Isolated yields after column chromatography.

In our next attempt, using $(C_5H_5)_2$ ZrHCl to hydrolyze the carbamate, we managed to isolate 65% of the arylated phenol product. Subsequently, a survey of different alkyl groups on the nitrogen atom of the carbamate was conducted. Among the alkyl groups screened, *N*,*N*-dimethyl-derived carbamate afforded the desired product in satisfactory yield. We observed that the optimized condition is applicable even for morpholine-(Table 2, entry 4) and pyrrolidine (Table 2, entry 5)-derived carbamates with desired products being formed in 70 and 71% yields, respectively. Further fine tuning of reaction conditions with respect to temperature and catalyst loading was also conducted (Table 3). Among the diaryliodonium salts screened, the tetrafluoroborate salt gave the product **2a** in

Scheme 2. Scope of Meta-Arylation with Phenol Carbamates^a



^aReactions were carried out with 1 (1.0 equiv), salt (1.2 equiv), catalyst (10 mol %) in DCE (2.0 mL) for 24 h. ^bDiphenyliodonium salt (0.5 equiv). ^cDiphenyliodonium salt (3 equiv).

good yield. The source of the Cu catalyst proved crucial for this transformation.

Both Cu(I) and Cu(II) species gave a phenol product in moderate to good yield, with Cu(OTf)₂ leading to the best yields among the catalysts examined. Even simple copper powder can provide a meta-arylated product in moderate yield (Table 3, entry 9). The meta-arylated product was isolated in 31% yield, when the reaction was performed without the catalyst at 70 °C (Table 3, entry 10). Subsequent screening of the reaction in the absence of the copper catalyst at elevated temperatures showed decrease in the yield without compromising the meta-selectivity (Table 3, entries 11–12). To rule out the possible contamination from trace impurities of copper, a catalyst-free reaction at 70 °C was performed in brand new glassware with a new stirrer bar and the meta-arylated product was isolated in 28% yield.

With the optimized conditions in hand, the scope of this copper-catalyzed meta-arylation of phenol derivatives was investigated and the results are summarized in Scheme 2. In general, with respect to phenol carbamates, both electron-

Scheme 3. Scope of Diaryliodonium Salts⁴



^{*a*}Reaction conditions (1) **1a** (1 equiv), salt (1.2 equiv), catalyst (10 mol %), DCE (2.0 mL) 70 °C, 24 h. (2) NaOH (10 equiv), EtOH (5 mL), 80 °C, 12 h.

Scheme 4. Access to Meta-Arylated Carbamates^a



^{*a*}Reaction conditions (1) **1a** (1 equiv), salt (1.2 equiv), catalyst (10 mol %), DCE (2.0 mL) 70 °C, 24 h. (2) Me₂NCOCl (1.2 equiv), K₂CO₃ (1.5 equiv), MeCN (10 mL), 85 °C, 2 h. ^{*b*}Diphenyliodonium salt (0.5 equiv).

Scheme 5. Gram-Scale Synthesis



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Scheme 6. Diversification of *m*-Aryl Carbamate 3a^a



^aReaction conditions: ${}^{a}NiCl_{2}(PCy_{3})_{2}$ (5 mol %), TMDSO (2.5 equiv), $K_{3}PO_{4}$ (4.5 equiv), toluene (1.0 mL), 115 °C. ${}^{b}NiCl_{2}(PCy_{3})_{2}$ (10 mol %), $K_{3}PO_{4}$ (7.5 equiv), PhB(OH)₂ (4 equiv), toluene (1.5 mL), 130 °C.

donating and electron-withdrawing functional groups, regardless of their substitution patterns on the arene moiety, were all well tolerated, affording the desired products in good to excellent yield. A series of ortho-substituted phenol carbamates including electron-releasing and electron-withdrawing substituents provided arylated products (2a, 2f-2j) in moderate

to good yields. Halogen-substituted products offer the opportunity for further synthetic elaborations. Arylation of 2-aryl-substituted (1k and 1m) and 2-cyclohexyl (1l)-substituted phenol carbamates exclusively occurred at the meta position, yielding products (2k, 2l and 2m) in good yields.

Substrates bearing electron-withdrawing and electronreleasing meta-substituents were also reactive in this protocol (2n-2q). Carbamates bearing the 3-OMe group gave the meta-arylated phenol (2p) in 67% yield along with an orthoarylated product (para to the OMe group),^{5b} which was obtained in 19% yield. This may be due to the strong influence exerted by the carbamates over the -OMe group in directing the incoming aryl moiety. The simple phenol carbamate system forms the meta-monoarylated and diarylated products (2r and 2s), which can be selectively accessed by controlling the stoichiometry of the diaryliodonium salt (refer Supporting Information). Gratifyingly, the substituent at C-4 position was also well tolerated, giving the diarylated phenol (2t) in good yield. Pleasingly, this protocol also accommodates 2,4disubstituted phenol carbamate. When 1u was employed as a substrate, the product 2u was obtained in 64% yield. In addition, under the optimized conditions, carbamates derived



(b) Alternative mechanism of copper catalyzed meta-selective C-H arylation

Figure 1. Proposed mechanisms for Cu-catalyzed meta-arylation of anilides.^{5a,12}

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Figure 3. Proposed mechanism for uncatalyzed meta-arylation of aryl carbamates.

from naturally occurring estrone (1v) yielded the corresponding arylation product in 61% with exclusive meta-selectivity.

Next, we extended the scope of our copper-catalyzed metaarylation of carbamates with an array of diaryliodonium salts (Scheme 3). The arylating coupling partners possessing both electron-releasing and electron-withdrawing groups at the para position produced selective meta-arylated products in good to moderate yields (**2w**, **2aa**, and **2af** were obtained in 80, 57, and 69% isolated yields, respectively). Furthermore, salts bearing halides (F, Cl, and Br) were compatible under the optimized reaction conditions, giving monoarylated products (2x, 2y), and 2z in good yield. These results provide a platform for further utilization of meta-arylated products via transition metalcatalyzed cross-coupling reactions. Diaryliodonium salts bearing electron-releasing or electron withdrawing metasubstituents were also effective in this protocol, giving the corresponding products (2ab-2ad). Also, *o*-methoxy iodonium salt reacted smoothly to give meta-arylated carbamate (2ae) in 42% yield.

This arylation method can also be applied to get metaarylated carbamates in quantitative yields. After the first step, treating the crude reaction mixture with Me₂NCOCl and K_2CO_3 in acetonitrile at 80 °C for 2 h, we can access the corresponding carbamates in quantitative yields (Scheme 4).

To explore the utility of this process on a preparative scale, we performed the reaction in gram scale with substrate **1a** and diphenyliodonium tetrafluoroborate salt. Gratifyingly, our copper-catalyzed meta-arylation of carbamates worked well in gram scale to give the desired product **2a** in 72% isolated yield (Scheme 5).

To demonstrate the synthetic utility of this meta-arylation, we attempted diversification of 3r using the carbamate as a synthetic handle (Scheme 6). Carbamate 3r was converted into possible other products in good yields by using the reported methods such as reductive cleavage^{11a} and cross-coupling^{11b} reactions.

In the literature, ^{5a,12} there are two proposed mechanisms for a similar meta-arylation process, as shown in Figure 1. The mechanism (A) shown in Figure 1a proceeds via antioxycupration, whereas mechanism (B) shown in Figure 1b proceeds via a Heck-like four-membered transition state (TS). Li, Wu, and co-workers have performed density functional theory (DFT) calculations for the reaction between acetanilide and PhCu(OTf)₂and demonstrated that mechanism B is much more stable and feasible.¹² To probe the mechanism of the reaction of acyl-type substrates examined in this work, we performed DFT computational studies of the reaction between the acetoxy-substituted substrate (2) and $PhCu(OTf)_2$ using the M06-2X functional.^{13,14} As in the case of anilides,¹³ our DFT results show that the Heck-like mechanism B is much more favored than mechanism A in the reaction of acyl substrates, with the reaction in mechanism B proceeding with a much lower activation barrier. Importantly, the TS for the meta attack (TS1) is lower (11.0 kcal/mol) in energy than the TSs for the ortho and para attacks by >6 kcal/mol. The preference for the meta attack can be attributed to the coordination bond existing between acetoxy oxygen and the Cu^{III} site (Figures 1b and 2), which the other TSs cannot form (Figure S1).

TS1 is followed by a very stable intermediate (Int1), and the subsequent barrier for proton abstraction from the meta carbon via TS2 is rather small (6.8 kcal/mol). Therefore, the selectivity of the reaction is determined by the first C–C bond formation step, and the DFT results explain well why only the meta product is obtained in our experiments. As shown by Li, Wu, and co-workers for anilides, mechanism A has a prohibitively high barrier (Figure S2). For this mechanism, especially for the reaction of 2 and at the level of theory employed here, a Cu^{III}–aryl intermediate could not be obtained, but C–C bond formation occurred directly after the TS in mechanism A. These results suggest that mechanism A is unlikely to operate under actual experimental conditions. It is also interesting to note that the syn analogue of the

reaction is even more favored than the anti attack in mechanism A, as the TS for the syn attack can have some degree of stabilization because of the interaction between the acetoxy oxygen and the Cu^{III} site (Figure S1).

Based on previous literature,¹⁵ it is known that diaryliodonium salts react with electron-rich arenes under metal-free conditions to form arylated products. It is also known that iodine and compounds of iodine behave in a similar manner to the copper-catalyzed transformations.¹⁶ Hence, we speculate that the meta-selective arylation in the absence of copper catalysts proceeds, as shown in Figure 3. As there is no possibility to form a very reactive Cu(III)–aryl intermediate in the absence of the copper catalyst, we support our observation of less yield at 70 °C for the uncatalyzed reaction. At this moment, we are not clear about the exact mechanism for the uncatalyzed reaction, and further investigations are needed to support the proposed mechanism.¹⁷

In summary, we have demonstrated the first example, in the literature, of a meta-selective arylation protocol of phenol derivatives catalyzed by copper. The current method provides room for further functionalization of the obtained products and thus would find applications in pharmaceuticals and complex molecule synthesis. Computational studies showed that the reactions most probably proceeded via Heck-like fourmembered ring TSs.

ASSOCIATED CONTENT

③ Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.0c05481.

Experimental procedures and spectral data for all new compounds (¹H NMR, ¹³C NMR, and HRMS) (PDF)

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Notes

The authors declare no competing financial interest.

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