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DEVELOPMENT OF A COPPER-CATALYZED *META*-ARYLATION OF AN ARYL *O*-CARBAMATE

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Abstract

The importance of the aromatic motif cannot be overstated in modern organic chemistry. Despite many years of research, the *meta*-functionalization of arenes remains a significant challenge in synthetic chemistry. Here we report the development of a *meta*-selective arylation of an aryl *O*-carbamate via copper catalysis.

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Introduction

Decorated aromatic rings are critically important functional groups in pharmaceutical compounds, natural products and other molecules of human interest.[1] A few pharmaceutical compounds of note are shown in Figure 1 to demonstrate the ubiquity of the aromatic motif. Some of the most common ways to decorate aromatic rings (en route to a pharmaceutical or natural product, for example) include electrophilic aromatic substitution,[2] directed *ortho*-metallation (DoM) chemistry[3] and more recently, palladium-mediated C-H functionalization processes.[4,5] While all these methods facilitate the substitution of arenes at the *ortho* and/or *para* position, substitution at the *meta* position remains a challenge in modern synthetic chemistry (Figure 2).

Recently, developments in the 1,3-substitution of arenes have been published.[6,7,8] Seminal publications by the Gaunt[7] and Yu[8] groups represent a significant advance in arene substitution chemistry (Figure 3). Two particularly relevant examples are from the Gaunt laboratory, which reported *meta*-selective C–H arylation for acetanilides[7a] and α-aryl carbonyl compounds[7b] (Figure 3A and 3B). These arylations proceed under copper catalysis and use diaryliodonium triflate as the electrophile. In 2017, the Yu laboratory reported the *meta*-arylation of nosyl-protected phenylethylamines using palladium catalysis and norbornene as a "transient mediator"[8c] (Figure 3C). Notably, all of these examples use very specific nitrogen-based directing groups.

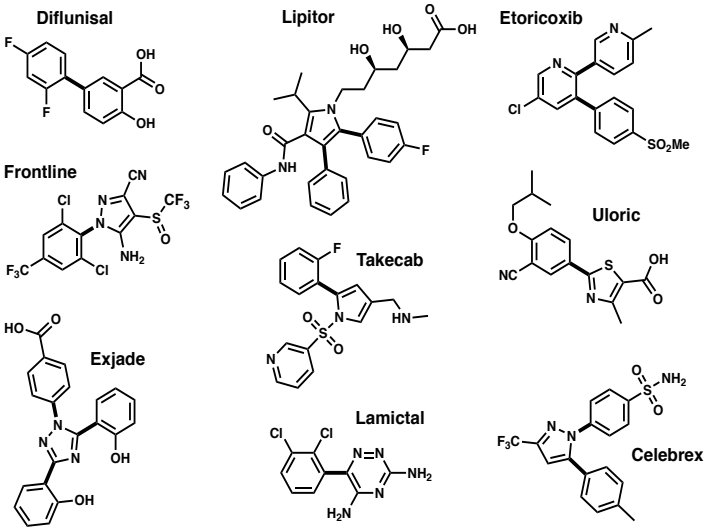


Figure 1. Common Drugs Containing an Aromatic Motif.

Herein we report the development of a copper-mediated *meta*-arylation of an oxygen-based directing group, the *N,N*-diethyl

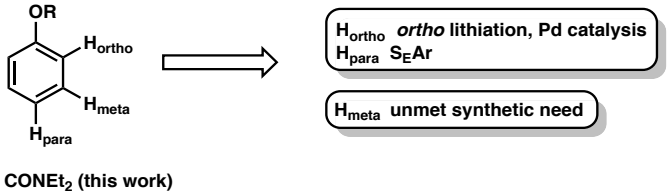


Figure 2. The Remaining Challenge in Aromatic Substitution.

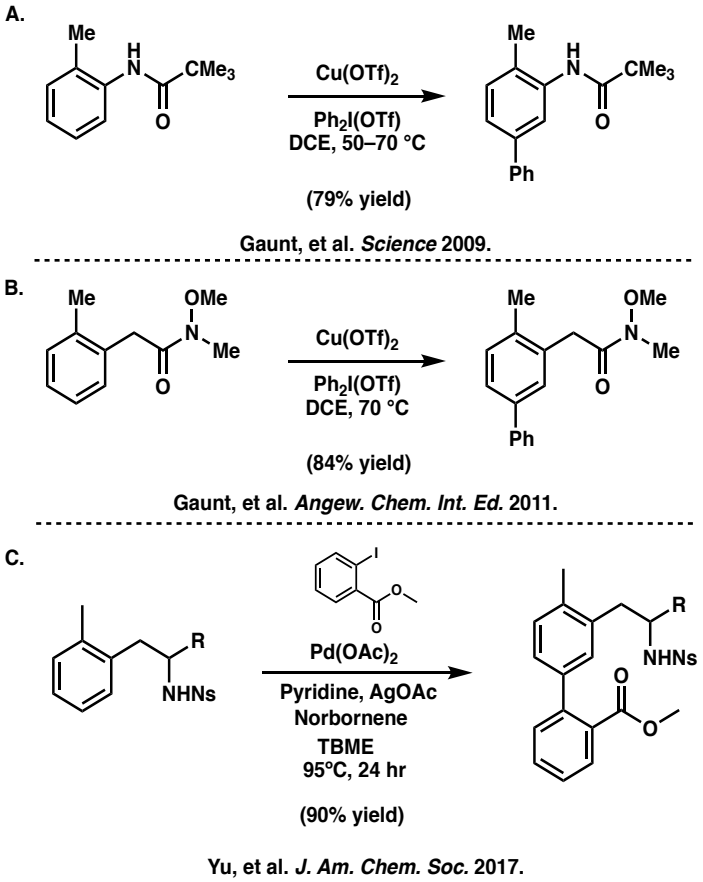


Figure 3. Examples of *Meta*-Arylations.

aryl *O*-carbamate. As a directing group, the aryl *O*-carbamate has a number of advantages. Carbamates are easy to synthesize[9] from commercially available materials, stable toward wide variety of reaction conditions including low reactivity toward Pd(0),[10] and can direct the installation of substituents onto the aromatic ring, via electrophilic aromatic substitution,[11] directed *ortho*-metallation (DoM) chemistry,[12] or palladium-mediated C–H functionalization processes.[13] Furthermore, the aryl *O*-carbamate itself is an excellent cross-coupling partner,[10,14] allowing for straightforward transformation of the erstwhile directing group. In combination, these characteristics render the aryl *O*-carbamate an ideal partner for the multistep synthesis of polysubstituted aromatics, motifs routinely encountered in drug scaffolds, ligands for catalysis, and materials chemistry.

The Loh laboratory made use of the practical properties of aryl *O*-carbamates in their recent report on the copper-catalyzed *meta*-arylation of phenol derivatives.[15] Interestingly, the Loh group observed a significant amount of cleavage of the (*N,N*-dimethyl) carbamate to deliver a mixed product of arylated phenol and arylated aryl *O*-carbamate – a challenge they addressed by hydrolyzing the carbamate to supply only the arylated phenol as isolated product. Here we report our development of a *meta*-selective arylation of *N,N*-diethyl aryl *O*-carbamate and our exploration of the necessary reaction parameters.

Experimental

Unless stated otherwise, reactions were conducted in flame-dried glassware under an atmosphere of nitrogen. Reagents were ordered from Sigma–Aldrich and VWR, and then used as received. Prior to use, 1,2-dichloroethane was purified by distillation from CaH_2. 1,2-dimethoxyethane and other solvents were dried and degassed on a solvent purification system. Reaction temperatures were controlled using an IKAmag temperature modulator, and unless stated otherwise, reactions were performed at room temperature (approximately 23 °C). Thin-layer chromatography (TLC) was conducted with EMD gel 60 F254 pre-coated plates (0.25 mm) and visualized using UV light. J.T. Baker silica gel (170-400 mesh, 60 Å) was used for flash column chromatography. ^{1}H NMR spectra were recorded on a Bruker spectrometer (at 400 MHz) and are reported relative to residual solvent signals.

*Synthesis of Carbamate **2** (Scheme 1):*

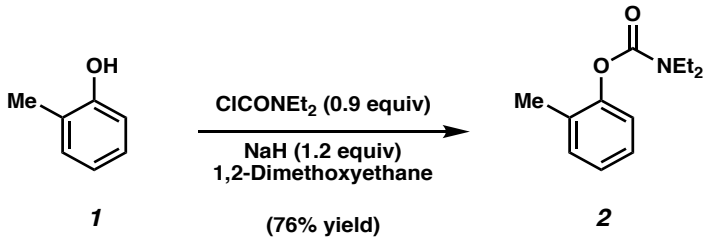
A flame-dried round-bottom flask was charged with sodium hydride (1.2 equiv.) and evacuated and backfilled with N_2 three times. The flask was cooled to 0°C as a solution of *o*-cresol (**1**) (1 equiv.) in 1,2-dimethoxyethane (approx. 0.3 M) was slowly added via cannulation. When bubbling ceased, a solution of *N,N*-diethyl carbamoyl chloride (0.9 equiv.) in 1,2-dimethoxyethane (approx. 0.7 M) was also added to the flask via cannulation. (Total molarity of the final reaction = 0.22 M.) The reaction was warmed to room temperature and stirred at room temperature until completion. The reaction was monitored via thin layer chromatography. Upon completion, the reaction was quenched with water. The 1,2-dimethoxyethane was then removed under reduced pressure. The remaining aqueous solution was diluted with ethyl acetate and washed with aqueous 2M potassium hydroxide (3x), followed by brine (1x). The combined aqueous layers were washed with ethyl acetate (2x). The combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. The resulting crude carbamate was purified via flash chromatography (4:1 hexanes:ethyl acetate) to afford a clear oil in 76% yield. R_f (4:1 hexanes:ethyl acetate)= 0.43. The identity of the product was confirmed to be 2-methylphenyl carbamate ***2*** via ^{1}H-NMR. Spectral data matches that previously reported in the literature.[16]

*General Procedure for the Synthesis of Arylated Carbamate **4** (Scheme 2):*[17]

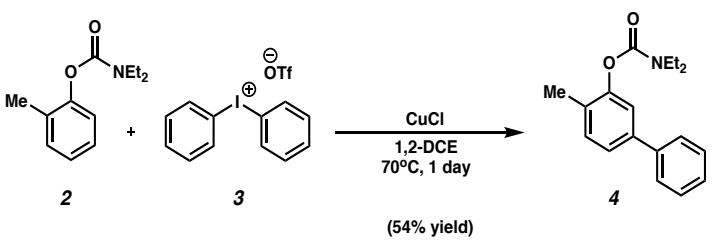
A flame-dried 1.5 dram vial was charged with 2-methylphenyl carbamate (**2**) (0.5 mmol, 1 equiv.), CuCl (10 mol%), and diphenyliodonium triflate (**3**) (1 mmol, 2 equiv.) and then evacuated and backfilled with N_2 (3x). 1,2-Dichloroethane (2.5 mL, 0.2M) was then added and the vial was sealed with a Teflon-lined cap. The reaction was stirred at 70°C. Upon completion, the reaction solution was allowed to cool, diluted with dichloromethane, and washed with aqueous saturated sodium bicarbonate (1x). The resulting aqueous layer was washed with CH_2Cl_2 (1x) and the combined organic layers were dried over magnesium sulfate. The solvent was evaporated under reduced pressure, affording arylated carbamate **4** as a crude yellow-gold oil. 54% yield was determined via ^{1}H-NMR using 10 µL styrene as an internal standard. ^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.57 (dt, J=7.1, 1.4Hz, 2H), 7.40 (t, J=7.4Hz, 2H), 7.30–7.37 (m, 3H), 7.26 (d, J=7.6Hz, 1H), 3.37–3.55 (m, 4H), 2.25 (s, 3H), 1.18–1.33 (m, 6H).

Results and Discussion

Aryl carbamate **2** was considered an ideal initial test substrate. The presence of the *ortho*-methyl substituent both promotes arylation at the desired position, due to electron-donation and provides a convenient handle by which to identify the desired product via NMR. Reaction development began with an extensive survey of copper catalysts. As seen in Table 1, many copper catalysts gave comparable yields in the 40-55% range.[18] This was true for both copper(I) and copper(II) catalysts. Notably, copper sulfates produced lower yields. Importantly, the reaction does proceed (in 26% yield) without the presence of catalyst to the desired *meta*-arylated product (final entry, Table 1). However, the consistently higher yields produced in the presence of certain copper species suggests



Scheme 1. Synthesis of Carbamate **2**.



Scheme 2. Synthesis of Arylated Carbamate **4**.

the copper catalyst does play a role.

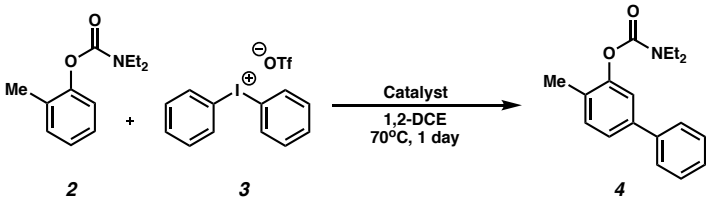
Proceeding with CuCl as the catalyst, we addressed the question of catalyst quantity. As seen in Table 2, the best yield is observed with 10 mol% catalyst loading. Interestingly, doubling catalyst loading to 20% did not correspond with higher yield. Gratifyingly however, catalyst loadings as low as 2 mol% were still effective in promoting this reaction. For practical reasons, we proceeded with 10 mol% CuCl as our standard condition.

Solvent conditions were next explored. Literature precedent[7] suggested that chlorinated solvents were likely to work, so experiments began with a variety of readily available chlorinated solvents. Dichloroethane isomers produced the best yields (see Table 3) with 1,2-dichloroethane ultimately chosen as the solvent. Some non-halogenated solvents of similar polarity and/or boiling point were tried, as well as mixtures of chlorinated and non-halogenated solvents. As seen in Table 3, non-halogenated solvents completely suppressed the reaction. Furthermore, mixtures of solvents containing 50% 1,2-dichloroethane (the best solvent for this reaction) were similarly ineffective.

With catalyst and solvent conditions in hand, we considered temperature (see Table 4). The ideal temperature for the copper-catalyzed *meta*-arylation was found to be 70 °C. Lower temperature (60 °C) appears to be insufficient even for the baseline, non-catalyzed arylation. Higher temperatures seem to inhibit the copper catalysis, but allow for the baseline non-catalyzed transformation to occur. (The boiling point of 1,2-dichloroethane is 84 °C. All reactions are run in a sealed reaction vessel.)

The final reaction parameter considered was reaction time. The *meta*-arylation reaches maximum yield in 3 hours and seems to be stable for at least a day (see Table 5). Unsurprisingly, longer reaction times lead to some product loss. Due to the limitations of undergraduate research, reactions are typically run overnight. However, this data suggests that this is not detrimental to product yield.

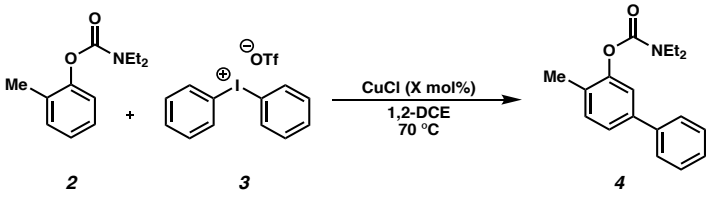
In summary, a moderate yielding copper-catalyzed meta-ary-



2 *3* *4*

Catalyst	Yield
CuCl	54%
CuI	41%
CuBr	41%
CuCN	42%
$CuCl{\cdot}2H_2O$	38%
$CuCO_3$	11%
CuO	42%
$CuCl_2$	39%
$CuBr_2$	40%
$CuSO_4$	11%
$Cu(OAc)_2{\cdot}H_2O$	40%
$CuSO_4{\cdot}5H_2O$	22%
$CuN_2O_6{\cdot}2.5H_2O$	41%
no catalyst	26%

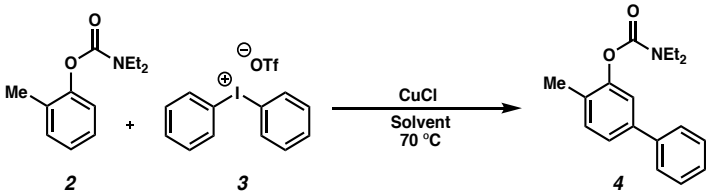
Table 1. Copper Catalysts for the *meta*-Arylation of Carbamate **2**.



2 *3* *4*

CuCl mol%	Yield
0%	26%
2%	42%
5%	39%
10%	54%
20%	46%

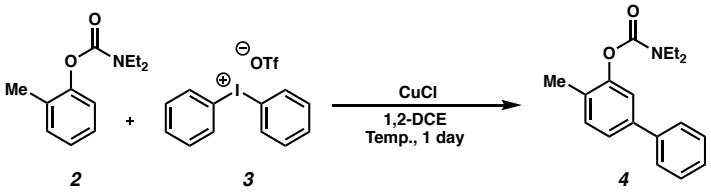
Table 2. Survey of Copper Catalyst Quantity in the *meta*-Arylation of Carbamate **2**.



2 *3* *4*

Solvent	Yield
1,1,1-trichloroethane	14%
Dichloromethane	18%
1,1-Dichloroethane	33%
1,2-Dichloroethane	54%
Chloroform	7%
Acetonitrile	0%
Dioxane	0%
1:1 Chloroform:1,2-Dichloroethane	6%
1:1 1,2-Dichloroethane:1,2-Dimethoxyethane	9%
1:1 Acetonitrile:1,2-Dichloroethane	0%

Table 3. Solvents for the *meta*-Arylation of Carbamate **2**.



2 *3* *4*

Temperature (°C)	Yield
60	7.7%
70	54%
95	26%
105	20%

Table 4. Temperature for the *meta*-Arylation of Carbamate **2**.

lation of an *N,N*-diethyl aryl *O*-carbamate has been developed. A variety of copper catalysts (and catalyst loadings) were explored, as well as solvent, temperature and reaction time. The *meta*-selective functionalization of an arene utilizing an electron-donating *O*-carbamate as the directing group represents a consequential step forward in organic synthesis, by addressing the challenge of *meta*-selective functionalization with a practical and synthetically useful directing group.

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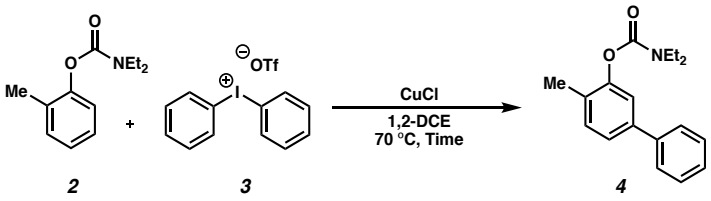

Reaction Time	Yield
1 hour	38%
2 hours	44%
3 hours	56%
1 day	54%
3 days	40%
7 days	47%

Table 5. Reaction Time for the *meta*-Arylation of Carbamate **2**.

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17 The reagents and quantities for the best conditions to synthesize carbamate **4** are shown here, but the same general procedure was used for all *meta*-arylation experiments.

18 The remainder of the mass includes some unreacted carbamate **2** starting material; for the CuCl catalyzed reaction, 12% unreacted carbamate **2** remained. The rest of the mass could not be identified, but is hypothesized to include a phenolic side-product resulting from cleavage of the carbamate.