

meta-substituted anilines

up to 91% vield

Synthesis of *meta*-Substituted Anilines via Copper-Catalyzed [1,3]-Methoxy Rearrangement

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Cite This: https://dx.doi.org/10.1021/acs.orglett.0c01009 **Read Online** ACCESS Metrics & More Article Recommendations Supporting Information ABSTRACT: meta-Substituted anilines were efficiently synthe-.OMe NH cationic NHC-Cu catalvs sized via copper-catalyzed [1,3]-methoxy rearrangement of N-EDG EDG + Nu-H methoxyanilines followed by Michael addition of nucleophiles to [1.3]-Methoxy Rearrangement Michael Addition Cascade the in situ generated ortho-quinol imine. The present reaction

Thus, the present rearrangement can resolve problems stemming from oxidation reactions, such as the use of stoichiometric amounts of oxidants and low compatibility of electron-withdrawing groups.

niline derivatives have been utilized for a wide variety of **A**purposes, such as pharmaceuticals, agrochemicals, dyes, and organic electronic devices.¹ Therefore, it has been of great importance to develop synthetic methods for functionalized anilines in order to impart desired biological and physical properties. In particular, due to inherent ortho- and parapreference of anilines in electrophilic substitution reactions, effective and selective preparation for meta-substituted anilines are still a fundamental challenge in the synthetic community. Although protocols from nitrobenzenes including electrophilic substitution followed by reduction of the nitro group have been conventionally utilized for meta-substituted aniline synthesis (Scheme 1a), the process severely suffered from harsh conditions and narrow scope of substituents on the aniline ring because the strong electron-withdrawing nitro group significantly decelerates the electrophilic substitution reactions. Transition-metal-catalyzed cross-coupling reactions of *meta*-haloanilines and Buchwald–Hartwig amination² of meta-haloarenes have been practically employed as an efficient tool to prepare meta-substituted anilines under mild conditions (Scheme 1b). However, these processes often face the similar selectivity issue since meta-substituted substrates are preprepared typically through electrophilic substitution. Accordingly, the development of a reaction system, namely, other than protocols involving electrophilic substitution reactions is highly desirable. Transition-metal-catalyzed direct meta-C-H functionalization reactions of anilines have been recently gathering much attention for this purpose (Scheme 1c),^{3,4} realizing various functionalization reactions, such as arylation, borylation, alkylation, chlorination, and olefination, using welldesigned ligands and directing groups. However, this stateof-the-art methodology still has some drawbacks, such as overfunctionalization due to equal reactivity between the two meta positions and low efficiency in the reactions of the parasubstituted anilines presumably due to the steric repulsion

exhibits excellent applicability of para-substituents, such as vinyl,

methylthio, ester, and bromo, and carbon nucleophiles, such as 1,3,5-trimethoxybenzene, *N*-methylindole, and dimethyl malonate.

Scheme 1. Synthesis of meta-Substituted Anilines

a) Electrophilic substitution-reduction from nitroarenes



b) Cross-coupling reaction



×low selectivity in preparation of substrates via electrophilic substitution

c) Directed meta C-H functionalization



d) Cu-catalyzed reaction between *ortho*-substituted *N*-methoxyanilines **1** and carbon nucleophiles **2** (This work)



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between the neighboring *para*-substituent and the metal catalyst bound at the *meta* position in the arylmetal intermediate. Here we demonstrate the new approach to *meta*-substituted aniline derivatives by the Cu-catalyzed cascade reaction between *N*-methoxyanilines 1 having an electron-donating group (EDG) at the *ortho* position and carbon nucleophiles 2 (Scheme 1d), which can overcome the aforementioned problems.

That is to say, we have recently disclosed that the [1,3]alkoxy rearrangement of *N*-alkoxyanilines was efficiently promoted by cationic copper catalysts ligated to an *N*heterocyclic carbene (NHC) ligand with high functional group compatibility (Scheme 2, route a).⁵ Moreover,

Scheme 2. Synthesis of *meta*-Substituted Anilines 3 through Cu-Catalyzed [1,3]-Methoxy Rearrangement from *N*-Methoxyanilines 1



substrates 1 having electron-donating alkyl and aryl groups at the ortho position of the N-methoxyanilines underwent a domino rearrangement of the methoxy group and the orthosubstituent, leading to 3-substituted 2-anisidines (Scheme 2, route a to b).⁶ Our experimental studies firmly proved that the ortho-quinol imine intermediate A was efficiently generated through copper-catalyzed [1,3]-rearrangement of the methoxy group to the ortho position bound to the electron-donating group. Accordingly, we envisioned that catalytically generated ortho-quinol imine A would serve as a Michael acceptor to react with suitable nucleophiles, leading to meta-monosubstituted anilines (Scheme 2, route a to c); since the quinol imine A generates just one time from the starting material 1 in the catalytic cycle, the process is essentially free from overreaction. It should be mentioned that Michael addition to ortho-⁷ and para-quinol imines,⁸ which are preprepared^{7,8a-g} or catalytically generated^{8h} through oxidation of anilines,⁹ has been studied for a long time (Scheme 2, route a' to c). However, the synthetic value of this approach has been severely discounted because the process requires stoichiometric amounts of strong oxidants and therefore inevitably suffers from incompatibility of oxidant-sensitive functional groups as well as electron-withdrawing groups (EWGs). Thus, the catalytic methoxy rearrangement (Scheme 2, route a), which is the key step of the present cascade process, would overcome intrinsic problems stemming from the oxidation process.

The *meta*-selective functionalization of aniline derivatives was realized when a mixture of *N*-methoxy-2-methylaniline 1a, in which the nitrogen atom was protected by a benzyloxycarbonyl (Cbz) group, and 1,3,5-trimethoxybenzene 2a (2 equiv) was treated under the optimized reaction conditions (see Supporting Information) with catalytic amounts of IPrCuBr [IPr: N,N'-bis(2,6-diisopropylphenyl)-imidazol-2-ylidene, 10 mol %] and AgSbF₆ (10 mol %) in chlorobenzene (1.0 M) at 80 °C (Table 1, entry 1). The reaction was completed within 20 h, affording the corresponding 5-arylated aniline **3aa** in 91% isolated yield. It should be noted that only

Table 1. Scope of the Nucleophile 2^a

Cbz N	DMe Me	. No.11	10 mol % IPrCuBr 10 mol % AgSbF ₆	NHCbz	
1a		+ NU-H 2 (2 equiv)	PhCl, 80 °C 20-35 h	Nu 3	
entry	2		NuH	3 (yield / %) ^{<i>b</i>}	
1	2a	MeC	OMe H OMe	3aa [91%, (82%) ^c]	
2	2b	Ме	OMe H	3ab (62%)	
3	2c	_	ОН	3ac / 3ac' [84% (4/1)]	
4	2d	L	OMe S H	3ad (40%)	
5	2e		H	3ae (74%) ^{d}	
6	2f	Me	O H	3af (44%)	
7	2g	١	H	3ag (76%) ^e	
8	2h		H Ph	3ah (60%)	
9	2i		м М	3a i (59%)	
10	2j	F	$\oplus_{\substack{O \\ = 2^{B} \\ O \\ O$	3a j (47%)	
11	2k	N	√ MeO₂C ∕ MeO₂C	3ak (74%)	

^{*a*}The reactions of **1** (0.2 mmol) and **2** (0.4 mmol) were carried out in the presence of IPrCuBr (10 mol %) and AgSbF₆ (10 mol %) in PhCl (0.2 mL) at 80 °C for 20–35 h. ^{*b*}Isolated yields. 'Yield for gram-scale reaction.¹¹ ^{*d*}**6ae** was obtained in 8% yield. ^{*e*}**6ag** was obtained in 8% yield.



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trace amounts of 4a and 5a, which were derived from the domino [1,3]/[1,2] rearrangement and [1,3]-methoxy rearrangement to the unsubstituted ortho position, respectively, were observed as byproducts. The reaction was applicable to various sp²-carbon nucleophiles, such as electron-rich arenes (2a and 2b), 2-methylfuran (2c), 3-methoxythiophene (2d), and N-methylindoles (2e-i) (entries 2-9). 2-Methylfuran 2c reacted with 1a at the 5 position of the furan ring, affording a 4:1 mixture of the 2,5-disubstituted aniline 3ac and 2,3disubstituted aniline 3ac' (entry 3). It should be noted that the reactions employing strong indole nucleophiles, such as 2e and 2g, with 1a were accompanied by formation of small amounts (ca. 8%) of **6ae** and **6ag**, respectively, which were derived from addition to the para position, as byproducts (entries 5 and 7). Notably, a difluoroboron β -diketonate 2j, which often exhibited rich photophysical properties,¹⁰ underwent arylation at the central diketone moiety by the present reaction, affording 3aj in an acceptable yield (entry 10). Moreover, an sp³-carbon nucleophile, such as dimethyl malonate 2k, was employed as an efficient nucleophile to furnish the arylated malonate 3ak in good yield (entry 11). Notably, the gram-scale reaction of 1a and 2a effectively afforded the desired product 3aa in good yield.¹¹

Next, the substituent effect on the N-methoxyaniline 1 was examined (Table 2 and Scheme 3). Not only methyl (1a) but also p-anisyl (1b), 2-furyl (1c), cyclopropyl (1d), and ethyl groups (1e) were employed as electron-donating substituents at the ortho position of the N-methoxyaniline 1 (Table 2, entries 1-4). In addition, a methoxy group (1f) was tolerated as the ortho substituent (entry 6). Moreover, various functional groups were tolerated at the para position such as methylthio (1n, entry 20) and vinyl (1o, entry 21) groups, which are labile under typical oxidation conditions, as well as chloro (1k, entries 16-17) and methoxycarbonyl (1m, entry 18), which decelerate oxidation reactions, in the present rearrangement-Michael addition cascade. In addition, the present reaction showed high compatibility of reactive functional groups, such as bromo (11, Table 2, entry 18) and iodo (2g, Table 1, entry 7) groups. It should be noted the substrates having an ethyl group at the ortho position, such as 1e and 1h, involved formation of the undesired byproducts 4e and 4h, respectively, due to the higher migrating ability of the ethyl group in the reaction with 1,3,5-trimethoxybenzene 2a (Table 2, entries 4 and 11). However, the reactions using a stronger nucleophile, such as N-methylindole 2e, gave the desired product 3ee and 3he, respectively, with high product selectivities (entries 5 and 12). More interestingly, a fluoro group at the para position (1j) was effective to afford the desired product 3ja, in good yield (entry 15). The 2,3- (1p) and 2,6-dimethyl-Nmethoxyaniline (1q) were converted to the desired products 3pa and 3qa, respectively, in good yields (Scheme 3). Furthermore, the reaction between 2,4,6-trimethyl-N-methoxyaniline 1r and 1,3,5-trimethoxybenzene 2a produced the biaryl 3ra, in which four ortho positions were fully substituted, in good yield. In addition, substrate 1s, in which the 5-position was substituted by a methoxycarbonyl group, reacted with 2a at the 3-position, affording 3sa' in an acceptable yield.

We experimentally proved the intermediacy of the *ortho*quinol imine intermediate A (Scheme 2) by using the dimer 7qof a quinol imine, as illustrated in Scheme 4. We previously reported that 7q, which was obtained by the reaction of the 2,6-dimethyl-*N*-methoxyaniline 1q in the presence of cationic IPrCu catalysts, was dissociated to the *ortho*-quinol imine 8q at Table 2. Scope of the Substituent at the *ortho* and *para* Positions of *N*-Methoxyanilines 1^a

Cbz OMe			10 mol % IPrCuBr 10 mol % AgSbEr	NHCbz	
	K	+ Nu-H	PhCl, 80 °C	Nu	Ŷ
 R ² 1		2 (2 equiv)	13-24 h	R ² 3	
entry	1	\mathbb{R}^1	\mathbb{R}^2	2	3 (%) ^b
1	1b	<i>p</i> -MeOC ₆ H ₄	Н	2a	3ba (53)
2	1c	2-furyl	Н	2a	3ca (55)
3	1d	cyclopropyl	Н	2a	3da (88)
4	1e	Et	Н	2a	3ea (56) ^c
5	1e	Et	Н	2e	3ee $(61)^d$
6	1f	MeO	Н	2a	3fa (86)
7	1g	Me	Me	2a	3ga (74)
8	1g	Me	Me	2c	3gc (84)
9	1g	Me	Me	2e	3ge (82)
10	1g	Me	Me	2k	3gk (74)
11	1h	Et	Et	2a	3ha (13) ^e
12	1h	Et	Et	2e	3he (58) ^f
13	1i	Me	F	2a	3ia (82)
14	1i	Me	F	2k	3ik (60)
15	1j	Et	F	2a	3ja (82) ^g
16	1k	Me	Cl	2a	3ka (82)
17	1k	Me	Cl	2k	3kk (61)
18	11	Me	Br	2a	3la (60)
19 ^h	1m	Me	CO ₂ Me	2a	3ma (56)
20	1n	Me	SMe	2a	3na (61)
21	10	Me	vinyl	2a	30a (51)

^{*a*}The reactions of 1 (0.2 mmol) and 2 (0.4 mmol) were carried out in the presence of IPrCuBr (10 mol %) and AgSbF₆ (10 mol %) in PhCl (0.2 mL) at 80 °C for 13–24 h. ^{*b*}Isolated yields. ^{*c*}4e was obtained in 22% yield. ^{*d*}4e and 6ee were obtained in 6% and 11% yield, respectively. ^{*c*}4h and 5h were obtained in 25% and 43% yields, respectively. ^{*f*}5h and 6he' were obtained in 10% and 12% yields, respectively. ^{*g*}5j was obtained in 5% yield. ^{*h*}118 h.





^aThe reactions of 1 (0.2 mmol) and 2a (0.4 mmol) were carried out in the presence of IPrCuBr (10 mol %) and $AgSbF_6$ (10 mol %) in PhCl (0.2 mL) at 80 °C for 15–24 h. Isolated yields.

130 °C in the absence of the copper catalyst (Scheme 4a).⁶ Thus, we preheated 7q at 130 °C for 4 h to form the mixture of 7q and 8q (ca. 6:4), which was then treated with 1,3,5-trimethoxybenzene 2a (4 equiv) and the cationic copper catalyst (Scheme 4b). To our delight, the one-pot reaction afforded the corresponding product 3qa, albeit in low chemical yield (29%). In contrast, when the mixture of 7q/8q and 2a was heated without the cationic IPrCu catalyst, the desired product 3qa was not obtained (Scheme 4c). These results

Scheme 4. Intermediacy of ortho-Quinol Imine 8



clearly indicate that the present transformation proceeds via the *ortho*-quinol imine **8**. Moreover, the cationic copper catalyst plays a dual role to promote not only the former [1,3]methoxy rearrangement but also the latter Michael addition, realizing efficient functionalization at the *meta* position.

A proposed mechanism for the present cascade reaction is illustrated in Scheme 5. First, the cationic NHC copper catalyst

Scheme 5. A Proposed Mechanism



coordinates to the substrate 1 to form the chelate complex 9. Then, the N-O bond would be ionically cleaved to form the arylnitrenium intermediate 10, in which the positive charge is developed on the benzene ring. The C-O bond formation preferentially occurs at the more hindered ortho-position because of stabilization of the process by the electron-donating group, leading to the ortho-quinol imine 8. The copper catalyst simultaneously coordinates to the imine nitrogen atom of the key intermediate 8, facilitating Michael addition of the carbon nucleophile 2 to the less hindered meta position. Finally, elimination of methanol and proton transfer give the metasubstituted aniline 3 while regenerating the cationic copper catalyst. The fact that the reaction between N-methoxyaniline 1a and a strong nucleophile, such as 2e and 2g, afforded the para isomer 6 as a byproduct implies intermediacy of the Narylnitrenium intermediate 10, which was captured at the para position through electrophilic substitution on the nucleophilic indole.¹² Moreover, the substrates 1e and 1j, which have a highly migrative ethyl group at the *ortho* position, preferentially underwent the [1,3]-rearrangement/Michael addition cascade

 $(1 \rightarrow 8 \rightarrow 3)$ rather than undesired [1,3]/[1,2] rearrangement $(1 \rightarrow 8 \rightarrow 4)$. These results clearly indicate that the generated *ortho*-quinol imine 8 (Scheme 5) can serve as a useful synthetic intermediate like *ortho*-quinols, which have been widely utilized in organic synthesis.¹³

In conclusion, we have developed novel approach to *meta*substituted anilines via a copper-catalyzed [1,3]-methoxy rearrangement—Michael addition cascade. Since the *N*methoxy anilines are readily prepared from reduction of commercially available nitroarenes with inexpensive zinc, the present process efficiently synthesizes multiply substituted anilines with a wide variety of functional groups at the *meta* and other desirable positions in a unique and selective manner.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01009.

Experimental procedure and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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