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Synthesis of *meta*-Aminophenol Derivatives via Cu-Catalyzed [1,3]-Rearrangement—Oxa-Michael Addition Cascade Reactions

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Abstract: Cu-catalyzed reactions of *N*-alkoxy-2-methylanilines and alcohols in the presence of catalytic amounts of IPrCuBr and AgSbF$_6$ afforded the corresponding *meta*-aminophenol derivatives in good to high yields. These reactions proceed via a [1,3]-rearrangement, in which the alkoxy group migrates from the nitrogen atom to the methyl-substituted ortho position, followed by an oxa-Michael reaction of the resulting *ortho*-quinol imine intermediate.

Keywords: anilines; cascade reaction; rearrangement; copper catalysts

1. Introduction

meta-Aminophenol derivatives are frequently used in pharmaceutical science (Figure 1) [1–5]. For example, SEA0400 exhibits inhibitory activity on the Na$^+$/Ca^{2+} exchanger [1], while tetrapetalone A [2] and tenaspimycin [3] inhibit lipoxygenase and Hsp90, respectively. However, performing the synthesis of *meta*-aminophenol scaffolds in an efficient and selective manner has been challenging because electrophilic substitution reactions, the most common approach to the functionalization of anilines and phenols, exhibit ortho/para preference. The radical hydroxylation of nitrobenzene, which occurs at the meta position, has significant drawbacks in terms of regioselectivity, reaction efficiency, and functional group compatibility (Figure 2a) [6–8]. The enzymatic oxidation of nitrobenzene can synthesize *meta*-nitrophenol with excellent site-selectivity, although this method suffers from the poor generality of substrates [9]. In this regard, transition metal-catalyzed cross-coupling reactions using *meta*-haloanilines and *meta*-halophenols are among the most frequently employed methods (Figure 2b) [10–15]. For example, Buchwald–Hartwig amination reactions of *meta*-halophenol derivatives using palladium catalysts [10–13] and Ullman-type reactions using copper catalysts [14,15] have been frequently used for the synthesis of *meta*-aminophenol derivatives. Catalytic C–O bond-forming reactions using *meta*-haloanilines have also been employed as an alternative approach to cross-coupling reactions by employing various transition metal catalysts, such as palladium [16,17], copper [18,19], nickel [20], and gold [21]. However, these reactions are also inherently associated with the selectivity issue in *meta*-haloaniline/phenol preparations. Although other approaches to functionalized *meta*-aminophenol derivatives have been recently reported [22], the development of efficient and robust methods for the synthesis of multiply substituted *meta*-aminophenol derivatives is a pressing issue.
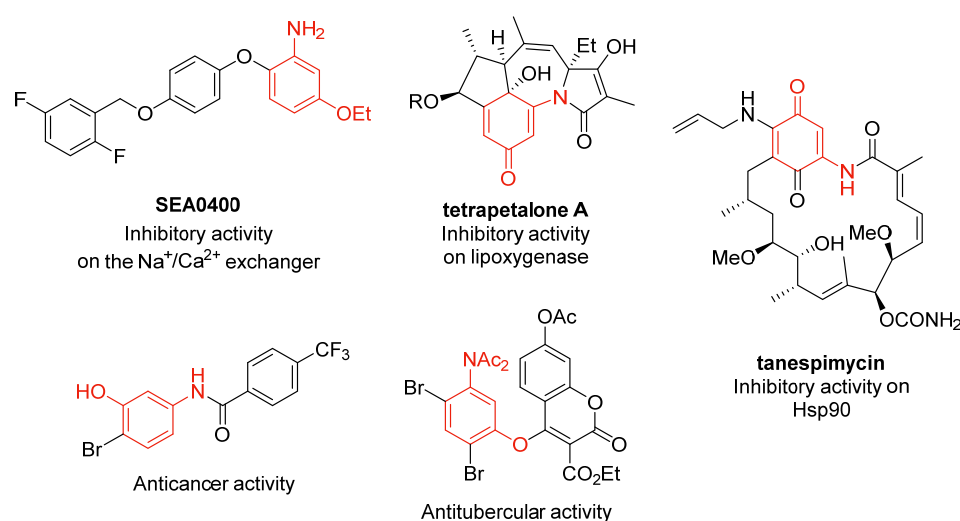
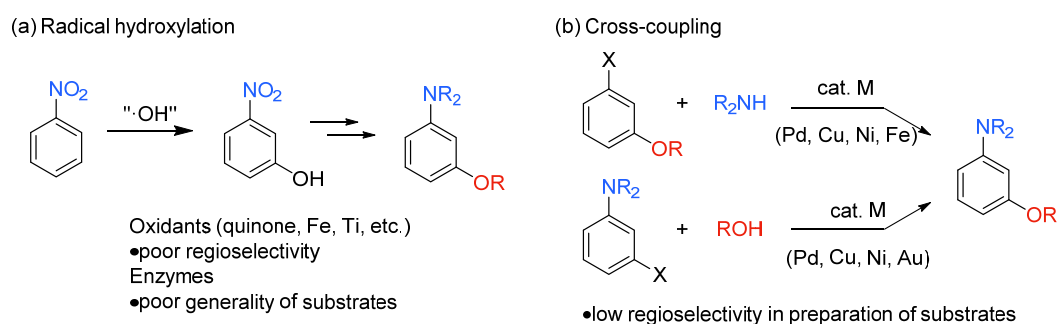**Figure 1.** *meta*-aminophenol derivatives.

Figure 2. Conventional methods for the synthesis of *meta*-aminophenol derivatives.

Against this backdrop, we designed cascade reactions, including the Cu-catalyzed [1,3]-rearrangement, as a potential approach to overcome issues related to selectivity (Figure 3) [23–32]. We have recently reported that *N*-heterocyclic carbene (NHC)-ligated cationic copper catalysts efficiently promote the [1,3]-rearrangement of *N*-alkoxyanilines [23–27]. Specifically, *N*-alkoxyanilines **1** having an electron-donating group (EDG) at the ortho position selectively generated functionalized *ortho*-quinol imine intermediates **A** via a [1,3]-rearrangement of the alkoxy group to the EDG-substituted ortho position [25–28]. *ortho*-quinol imine intermediates **A** underwent favorable transformations, including a [1,2]-rearrangement (Figure 3a) [25]; a Michael addition with carbon nucleophiles such as *N*-methylindole, 1,3,5-trimethoxybenzene, and dimethyl malonate (Figure 3b) [26]; and a Diels–Alder reaction with electron-rich and electron-deficient olefins [27]. It should be emphasized that the Cu-catalyzed [1,3]-rearrangement can generate functionalized quinol imine intermediates **A**, which had been inaccessible via conventional methods, such as thermally induced rearrangement [33] and oxidation [34]. Accordingly, we envisioned that the reactions with alcohols as oxygen nucleophiles would give functionalized *meta*-aminophenol derivatives in a selective manner through an oxa-Michael addition of generated *ortho*-quinol imine intermediates **A** (Figure 3d) [35,36]. Here, we report the Cu-catalyzed [1,3]-rearrangement—oxa-Michael addition—aromatization cascade reactions of *N*-alkoxyanilines **1** and alcohol nucleophiles **2**, which afforded *meta*-aminophenol derivatives **3** in good-to-acceptable yields (Figure 4).
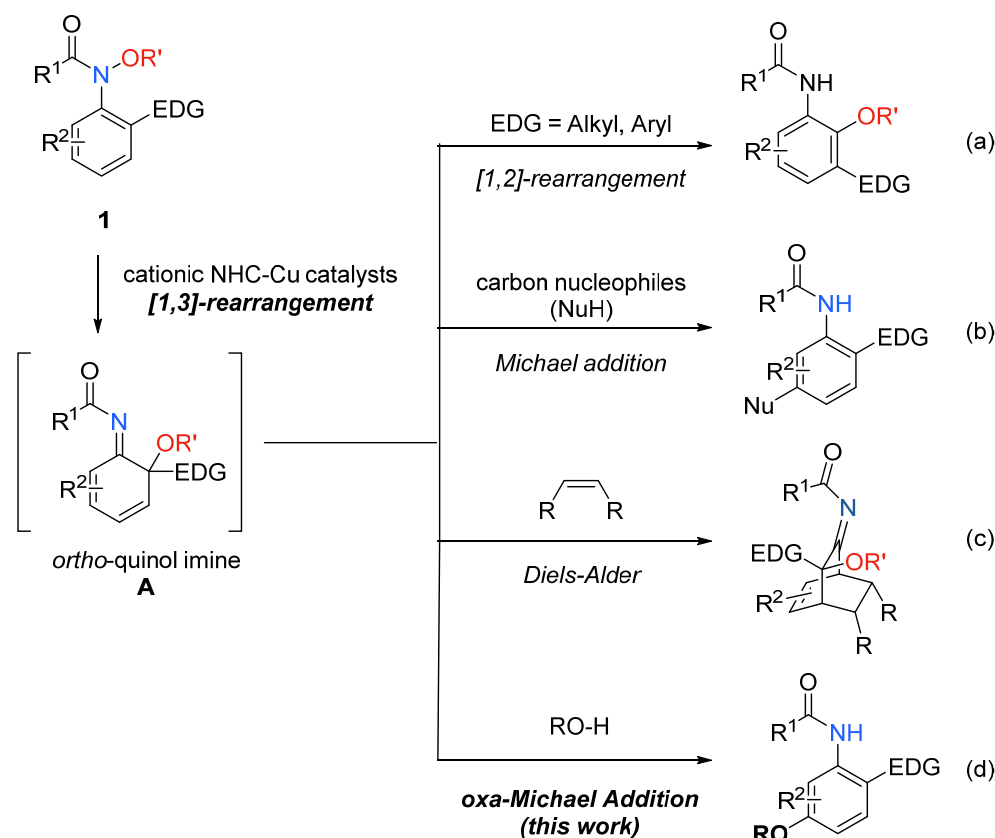
Figure 3. Cu-catalyzed [1,3]-alkoxy rearrangement: (**a**) domino [1,3]/[1,2] rearrangement, (**b**) [1,3]-rearrangement—Michael addition, (**c**) [1,3]-rearrangement—Diels-Alder reaction, and (**d**) [1,3]-rearrangement—oxa-Michael addition (this work).
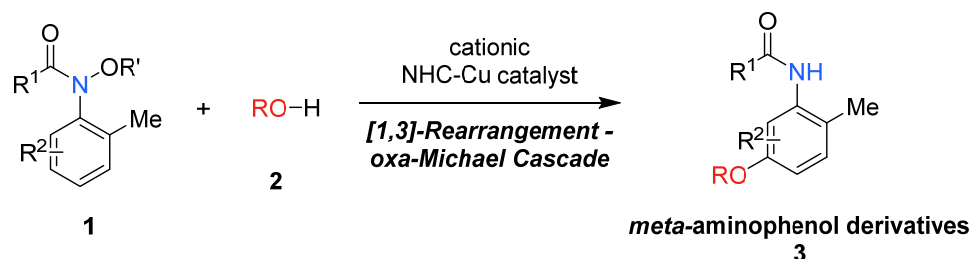

Figure 4. Cu-catalyzed [1,3]-rearrangement—oxa-Michael addition cascade reaction.

2. Results and Discussion

Initially, the reaction of *N*-methoxy-2-methylaniline **1a** having a *p*-trifluoromethylbenzoyl group on the nitrogen atom and one equivalent of methanol **2a** in the presence of catalytic amounts of IPrCuBr [IPr: *N*,*N*′-bis(2,6-diisopropylphenyl)-imidazol-2-ylidene, 10 mol%] and AgSbF$_6$ (10 mol%) in chlorobenzene at 70 °C afforded a mixture of the following four regioisomers: desired 6-methyl-3-anisidine **3aa**; 2-methyl-3-anisidine **4aa**, which was derived from the oxa-Michael addition to the meta position next to the *ortho*-methyl group; 3-methyl-2-anisidine **5a**, which was derived from domino [1,3]/[1,2]-rearrangement reactions [25]; and 6-methyl-2-anisidine **6a**, which was derived from the [1,3]-rearrangement reactions of the methoxy group to the unsubstituted ortho position (namely, [1,3]′-rearrangement) to generate *ortho*-quinol imine intermediate **7a′** (Scheme 1). Attempts to optimize the reaction conditions to selectively synthesize **3aa** were unsuccessful.
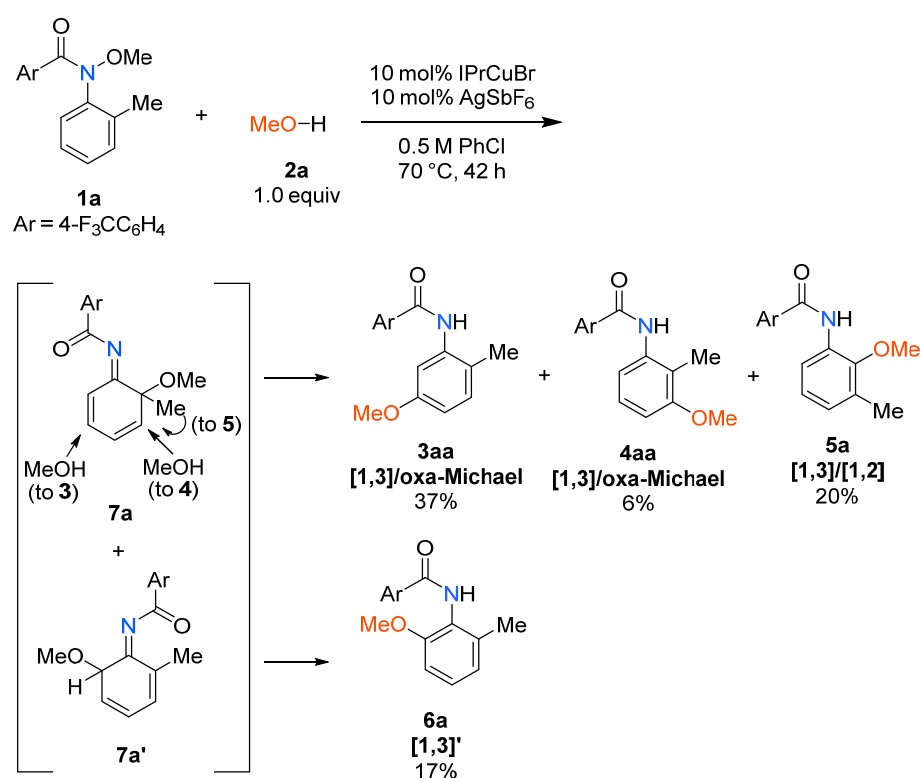
**Scheme 1.** Cu-catalyzed reaction of **1a** and methanol **2a**.

To reduce the number of regioisomers prior to the optimization of reaction conditions, we preliminary screened several starting materials **1**. To our delight, the reaction of substrate **1b** having a fluorine atom at the para position of the aniline ring at 70 °C generated two regioisomers, **3ba** and **6b**. Among the NHC ligands examined, IPr exhibited the best reactivity and product selectivity (Table 1, entry 1), whereas the use of IMes [1,3-Bis(2,4,6-trimethylphenyl)-1,3-dihydro-2*H*-imidazol-2-ylidene] and SIPr [1,3-bis(2,6-diisopropylphenyl)imidazolidine] resulted in low catalytic activity (entries 2 and 3). The reactivity was significantly affected by counteranions; less coordinative counteranions such as hexafluoroantimonate were effective for the present transformations. On the other hand, when AgBF$_4$ and AgNTf$_2$ were used instead of AgSbF$_6$, **3ba** was formed in low chemical yields along with a considerable amount of recovered **1b** (entries 4 and 5). The reaction in 1,2-dichloroethane (DCE) proceeded quickly to afford product **3ba** in the best yield among the solvents examined (entries 6–9). Neither the chemical yield nor the product selectivity was improved when the temperature of the reaction of **1b** and **2a** was changed from 70 °C to 60 °C and 80 °C, respectively (entries 10 and 11). The reaction in the absence of either Cu or Ag did not yield desired product **3ba**; *N*-methoxyaniline **1b** was quantitatively recovered (entries 12 and 13).

The protecting group on the nitrogen atom significantly affected the product selectivity (Table 2, entries 1–4); desired *meta*-anisidines **3** were obtained with better product selectivity with carbamate-type protecting groups (entries 2–4) than with the amide-type protecting groups (Table 1 entry 6, and Table 2, entry 1). The use of one equivalent of methanol **2a** was effective, whereas the use of a large excess (five equivalents) of methanol **2a** diminished the catalytic activity (entry 2 versus entry 6). It should be noted that the reaction using half an equivalent of methanol at 80 °C afforded **3da** in the 71% yield, suggesting that the methoxy group eliminated from substrate **1d** participated in the reaction as a nucleophile (entry 8). Finally, the chemical yield was improved by increasing the scale from 0.2 mmol to 0.5 mmol (entry 9, Appendix A).

Table 1. Optimization of reaction conditions.
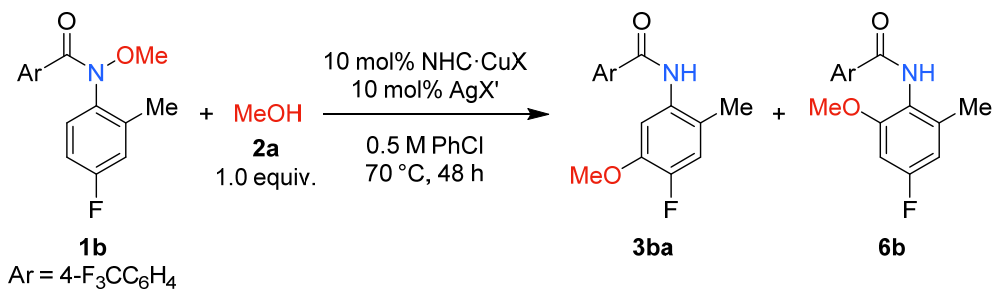
Entry	NHC·CuX	AgX′	Solvent	Temp. (°C)	3ba (%) [a]	6b (%) [a]	1b (%) [a]
1	IPrCuBr	AgSbF$_6$	PhCl	70	70	28	<1
2	IMesCuCl	AgSbF$_6$	PhCl	70	21	3	76
3	SIPrCuCl	AgSbF$_6$	PhCl	70	13	5	47
4	IPrCuBr	AgBF$_4$	PhCl	70	43	13	37
5	IPrCuBr	AgNTf$_2$	PhCl	70	<10	<15	- [b]
6	IPrCuBr	AgSbF$_6$	DCE	70 [c]	76	22	<2
7	IPrCuBr	AgSbF$_6$	toluene	70	63	18	11
8	IPrCuBr	AgSbF$_6$	1,4-dioxane	70	59	19	7
9	IPrCuBr	AgSbF$_6$	EtOAc	70	29	12	38
10	IPrCuBr	AgSbF$_6$	DCE	60 [d]	<78	18	3
11	IPrCuBr	AgSbF$_6$	DCE	80 [e]	75	22	6
12	IPrCuBr	-	DCE	70	<1	<1	99
13	-	AgSbF$_6$	DCE	70	<1	<1	92

[a] ^{1}H NMR yields using CH$_2$Br$_2$ as the internal standard. [b] The yield was not determined, but a considerable amount of **1b** was recovered; [c] 17 h; [d] 40 h; [e] 10 h.

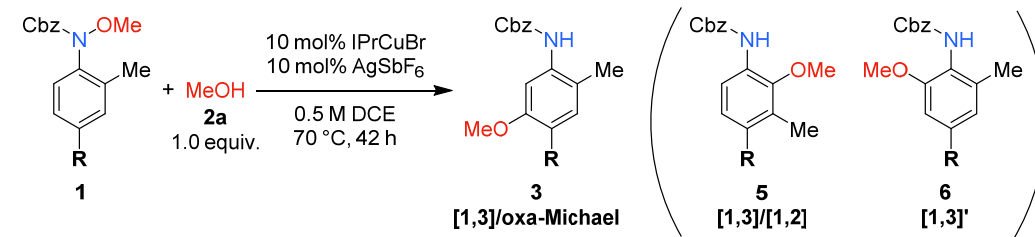**Table 2.** Optimization of the protecting group of **1** and the molar amount of methanol **2a**.
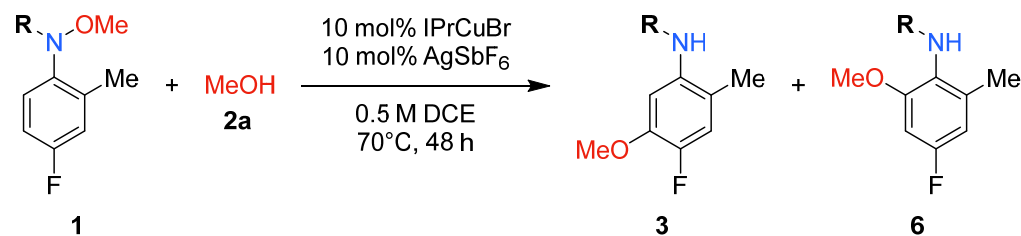
Entry	1	R	2a (Equiv)	3 (%) [a]	6 (%) [a]	1 (%) [a]
1 [b]	1c	Bz	1	3ca (73)	6c (12)	<1
2	1d	Cbz	1	3da (72)	<1	<1
3	1e	Troc	1	3ea (54)	<1	27
4	1f	Alloc	1	3fa (26)	6f (6)	32
5	1d	Cbz	2	3da (48)	6d (4)	46
6	1d	Cbz	5	3da (18)	6d (3)	29
7	1d	Cbz	0.5	3da (50)	6d (3)	<31
8 [d]	1d	Cbz	0.5	3da (71)	6d (9)	<11
9 [e]	1d	Cbz	1	3da (85) [c]	<1	<1

[a] ^{1}H NMR yields using CH$_2$Br$_2$ as the internal standard. The reactions were conducted on a 0.2 mmol scale; [b] 17 h. [c] Isolated yield. [d] At 80 °C. [e] The reaction was conducted at a 0.5 mmol scale.

The optimized conditions (Table 2, entry 9) were applied to the reactions of various *N*-methoxyanilines **1**, as summarized in Table 3. The reactions of substrates **1g** and **1h**, having a methyl and a phenyl group, respectively, at the para position, proceeded at 70 °C, affording corresponding *meta*-anisidines **3ga** and **3ha** in good yields (entries 1 and 2). Substrate **1j**, having a bromo group, was converted into desired product **3ja** when the loading amount of the Cu catalyst was increased (20 mol%, entry 7). The chemical

yield of **3ia**, which has a chloro group at the para position, was slightly improved when the reaction was performed at 90 °C using chlorobenzene instead of DCE as the solvent (entries 3–5). An iodo group (**1k**) was tolerated under the present reaction conditions, affording multi-substituted *meta*-aminophenol derivative **3ka** in an acceptable yield (entry 8). 3-Anisidine **3la**, which has an alkynyl group at the para position of the nitrogen atom, could also be generated (entry 9). In contrast, substrate **1m** having a methoxycarbonyl group at the para position, exclusively afforded domino-rearrangement byproduct **5m** (entry 10). The reaction of *N*-ethoxyaniline **1n** and ethanol **2b** afforded corresponding 3-ethoxyaniline **3nb** in a good yield (Scheme 2).

Table 3. Cu-catalyzed reactions of *N*-methoxyanilines **1g-m** and methanol **2a** [a].

Entry	1	R	Temp (°C)	3 (%) [b]	1 (%) [c]	Byproduct (%) [c]
1 [d,e]	**1g**	Me	70	**3ga** (64)	<1	**5g** (<3)
2 [e]	**1h**	Ph	70	**3ha** (45)	<1	**5h** (28), **6h** (27)
3	**1i**	Cl	70	**3ia** (23)	36	
4 [f]	**1i**	Cl	70	**3ia** (30)	19	
5 [e,f,g]	**1i**	Cl	90 [c]	**3ia** (61)	<1	
6	**1j**	Br	70	**3ja** (40)	32	
7 [f]	**1j**	Br	70	**3ja** (60)	<1	
8 [f]	**1k**	I	70	**3ka** (42)	6	**5k** (8)
9 [g,h]	**1l**	-C≡CPh	90	**3la** (28)	<1	
10 [g,i]	**1m**	CO$_2$Me	90	<1	9	**5m** (80)

[a] The reaction of **1** (0.5 mmol) and **2a** (0.5 mmol) was carried out in the presence of IPrCuBr (10 mol%) and AgSbF$_6$ (10 mol%) in DCE at 70 °C for 18 h. [b] Isolated yields. [c] ^{1}H NMR yields using CH$_2$Br$_2$ as the internal standard. [d] The reaction was conducted at a 2.0 mmol scale; [e] 18 h; [f] 20% IPrCuBr and 20 mol% AgSbF$_6$ were used. [g] Chlorobenzene was used, instead of DCE; [h] 48 h; [i] 24 h.
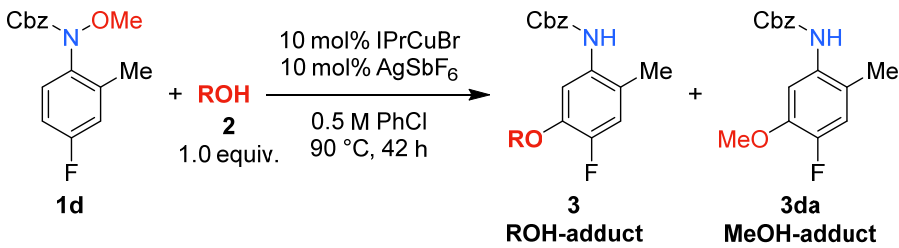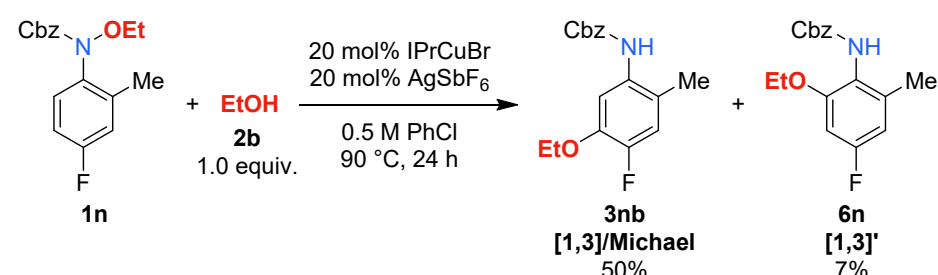

Scheme 2. Cu-catalyzed reaction of *N*-ethoxyaniline **1n** and ethanol **2b**.

The reaction of *N*-methoxyaniline **1d** and one equivalent of 2-phenethyl alcohol **2c** afforded 3-phenylethoxyaniline **3dc** in a 51% yield, along with **3da**, which was produced through the oxa-Michael addition of methanol derived from **1d**, in a 14% yield (Table 4, entry 1). The use of two equivalents of **2c** did not improve the product selectivity (entry 2). The reaction of **1d** and allyl alcohol **2d** also afforded 3-allyloxyaniline **3dd** as the major product (entry 3). These results suggest that substrates **1** react more preferentially with external alcohols **2c** and **2d** than with methanol **2a** derived from **1**, although the product selectivity depends on the structure of **2**. When *tert*-butanol (**2e**) and phenol (**2f**) were

employed as an alcohol nucleophile, the reactions gave a mixture of unidentified products (entries 4 and 5).

Table 4. Cu-catalyzed reactions of *N*-methoxyanilines **1d** and alcohols **2**.

Entry	2	ROH	3 (%) [a]	3da (%) [a]
1	2c	PhCH$_2$CH$_2$OH	3dc (51)	14
2	2c [b]	PhCH$_2$CH$_2$OH	3dc (51)	7
3	2d	H$_2$C=CHCH$_2$OH	3dd (35)	23
4	2e	*t*BuOH	- [c]	- [c]
5	2f	PhOH	- [c]	- [c]

[a] The reaction of **1d** (0.5 mmol) and **2** (0.5 mmol) was carried out in the presence of IPrCuBr (10 mol%) and AgSbF$_6$ (10 mol%) in PhCl at 90 °C for 42 h. [b] Two equivalents of **2c** were used. [c] A mixture of unidentified products was obtained.

A proposed mechanism for the Cu-catalyzed reactions of *N*-methoxyanilines **1** and alcohol nucleophiles **2** is illustrated in Figure 5a. The cationic copper catalyst coordinates to **1** to form chelate complex **8**, and this is followed by an oxidative addition of the N–O bond to the Cu(I) catalyst to form Cu(III) complex **9** [29]. Because of the contribution of canonical form **9′**, a C–O bond is formed at the methyl-substituted ortho position, generating *ortho*-quinol imine intermediates **10** that coordinate to the cationic Cu catalyst. Electrophilically activated *ortho*-quinol imine intermediates **10** undergo nucleophilic addition of **2** to form Cu enamide species **11**. Finally, proton transfer and elimination of methanol **2a** give products **3** along with the regenerated cationic Cu catalyst. Byproducts **5** are formed via a Cu-catalyzed [1,2]-rearrangement of *ortho*-quinol imine intermediates **12** [25]. The product selectivity of the present reaction system was greatly influenced by the para substituent; a fluorine atom (**1d**) was effective in suppressing the formation of the domino [1,3]/[1,2]-rearrangement product (**5**, Table 2, entry 9). This is possibly because the mesomeric electron-donating effect of the fluorine atom increases the electron density of the carbon next to the quaternary carbon in *ortho*-quinol imine intermediates **10d**/**10d′**, decelerating the [1,2]-rearrangement of the methyl group (Figure 5(bi)). In contrast, when an ester group was present, the selective formation of the domino rearrangement product (**5m**) occurred even in the presence of methanol (Table 3, entry 10), presumably because of the undesired [1,2]-rearrangement reaction facilitated by the electron-withdrawing effect (Figure 5(bii)). In addition, because substrate **1m** reacted with stronger carbon nucleophiles, such as 1,3,5-trimethoxybenzene, via [1,3]-rearrangement/Michael addition [26], the low nucleophilicity of alcohols **2** also causes the selective formation of byproduct **5m**. Our preliminary DFT calculations for the [1,2]-rearrangement of *para*-substituted *ortho*-quinol imine intermediates **10** were in good agreement with these experimental results (Figure 5c). The reaction of *N*-methoxyaniline **1d** and alcohol **2c** afforded **3dc** (51%) in a higher yield than **3da** (14%) derived from the reaction of **1d** and generated methanol **2a** (Table 4, entry 1). Because the product selectivity is dependent on the structure of external alcohols **2c** and **2d**, the elimination of methanol **2a** from enamide intermediates **11** may be mediated by external alcohol **2**, affecting the concentration of methanol **2a**. Further investigations to understand the reactivity of key intermediates **10** are under way in our laboratory.
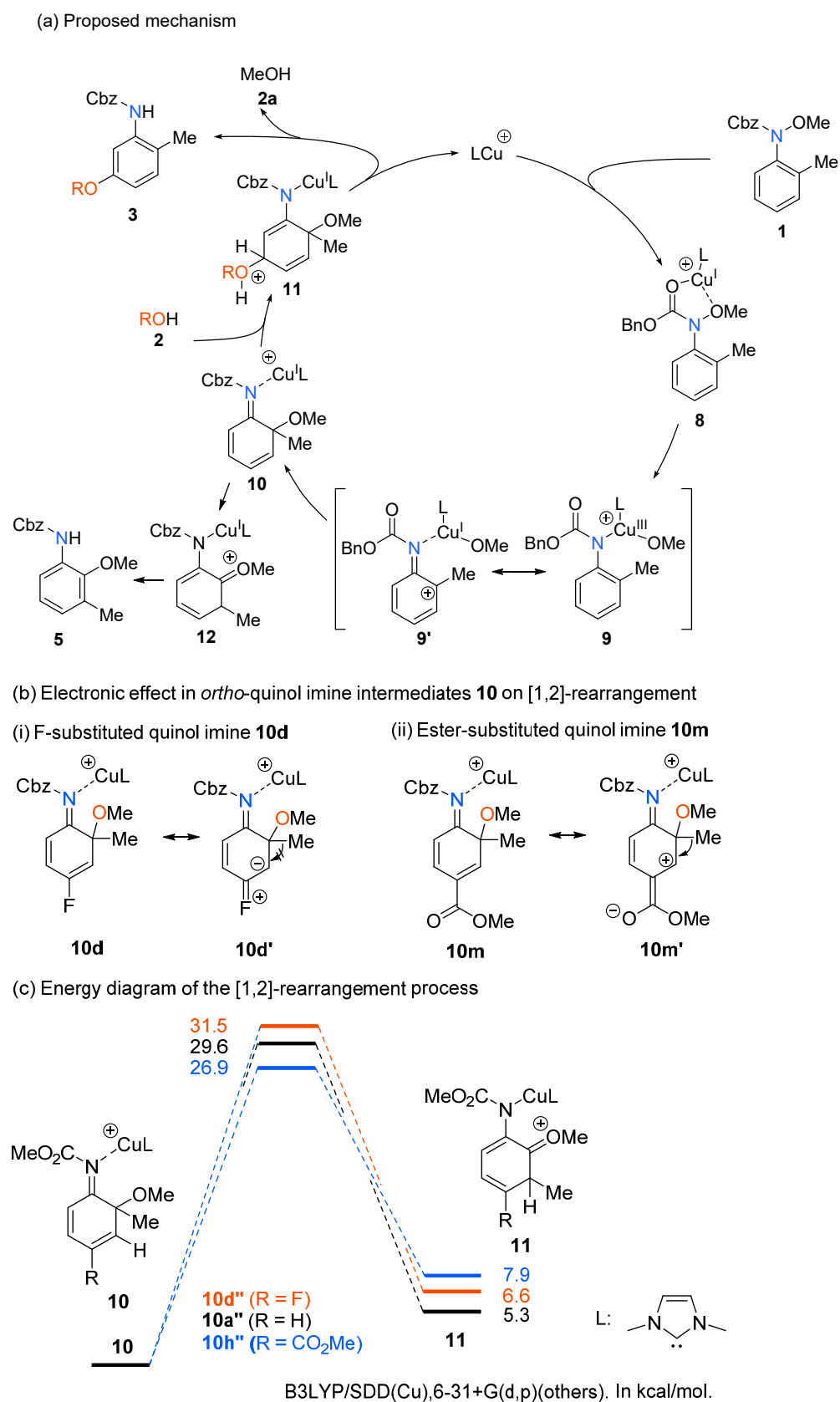
(a) Proposed mechanism

(b) Electronic effect in *ortho*-quinol imine intermediates **10** on [1,2]-rearrangement

(i) F-substituted quinol imine **10d**

(ii) Ester-substituted quinol imine **10m**

(c) Energy diagram of the [1,2]-rearrangement process

B3LYP/SDD(Cu),6-31+G(d,p)(others). In kcal/mol.

Figure 5. Mechanistic studies.

3. Materials and Methods

The general procedure for the Cu-catalyzed reactions of *N*-methoxyaniline **1d** and methanol **2a** is as follows: DCE (1.0 mL) and methanol **2a** (20.3 μL, 0.5 mmol) were added to a mixture of IPrCuBr (26.6 mg, 0.05 mmol), $AgSbF_6$ (24.0 mg, 0.05 mmol), and **1d** (144.8 mg, 0.5 mmol) under an argon atmosphere, and the mixture was stirred at 70 °C for 48 h. After complete consumption of **1d**, as monitored via TLC, the mixture was passed through a pad of silica gel with ethyl acetate (50 mL). The solvents were removed in vacuo, and the crude product was purified via silica gel column chromatography using hexane/ethyl acetate (20/1) as an eluent to afford **3da** (123.3 mg, 0.426 mmol, 85% yield) in an analytically pure form (Supplementary Materials).

4. Conclusions

In conclusion, we have developed a new approach to prepare *meta*-aminophenol derivatives via Cu-catalyzed cascade reactions involving [1,3]-rearrangement, oxa-Michael addition, and aromatization in an efficient manner. Because a variety of functional groups are tolerated in this transformation, the present method is potentially useful for synthesizing a new class of *meta*-aminophenol derivatives.

Appendix A

It is assumed that the larger reaction scale reduces influence of trace water on the reaction system, which can cause deactivation of the Cu catalysts and byproduct formation.

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