CHEMISTRY

Synthesis of medicinally relevant oxalylamines via copper/Lewis acid synergistic catalysis

Ziying Wu, Miao Hu, Yangbin Jin, Jianxiao Li, Wanqing Wu*, Huanfeng Jiang*

Allylamines have long been recognized as valuable synthons because of their excellent reactivity in organic synthesis. Here, an efficient amination reaction of allenyl ethers via copper/Lewis acid synergistic catalysis has been established, providing straightforward access to diverse functionalized Z-oxalylamines and E-halogenated oxalylamines in good to excellent yields with high regio- and stereoselectivities. The developed method tolerates more than 100 examples that include late-stage functionalization of bioactive molecules, and features gram-scale synthesis of oxalylamines with high turnover number (TON > 1000) under mild and simple conditions. The applicability of the protocol is further demonstrated with the construction of drug molecules.

INTRODUCTION

Allylamines, especially those with easy-to-transform functional groups, are an indispensable class of building blocks in the field of organic synthesis and the pharmaceutical industry (1). Typically, they are also the versatile synthetic intermediates in the atomic economical construction of alkaloids, amino acids, and complex natural products (2–4). A wide range of drug molecules (5–7) could be obtained by the derivatization of allylamines (Fig. 1A). In recent years, a variety of synthetic methods for accessing allylamine derivatives have been developed (8–14). Among the myriad strategies, the notable way to establish versatile allylamine scaffolds is based on the aminative functionalization of allenes (15–18).

Allenes are a class of unsaturated hydrocarbons with unique structures, which have high reactivity and multiple reaction sites (19–22). The introduction of amines with high regio- and stereoselectivity into the carbon-carbon double bonds of allenes is a fundamental organic transformation (23). To achieve regioselective amination of allenes, some strategies have been proposed. Among them, alkoxyallenes were used as the reaction substrates, taking advantage of their electronic bias to control the regioselectivity, and the aminative functionalization of alkoxyallenes usually generates the N,O-acetal products due to the positive charge formed at α-position stabilized by alkoxy group (Fig. 1B) (24–27). Recently, a substrate-directed strategy has come out as an attractive method to promote the metal-catalyzed regioselective functionalization of allenes. Various directing groups (DGs), such as amide, azole, and allylic, have been introduced to regulate the regioselective amination of allenes. However, E-allylamines are generally obtained, while thermodynamically unstable Z-allylamines are difficult to be constructed in most cases (Fig. 1C) (28, 29). Despite extensive efforts dedicated to developing efficient methods for aminative functionalization of allenes, there are still great challenges owing to regio- and stereocontrol as well as reactivity issues: (i) The unique accumulated diene structural units have greatly limited the selective activation of the two carbon-carbon double bonds of allenes (30). (ii) Efficient selective synthesis of Z-allylamines remains a challenging task for their thermodynamic instability (31–34). (iii) Transition metal catalysts might be poisoned or deactivated because of the high affinity of amines, which are prone to be oxidized under the oxidation reaction conditions (35). Therefore, the aminofunctionalization reactions are usually limited by the protection (and subsequently deprotection) of the amines (36).

To address these challenges, a strategy of copper/Lewis acid synergistic catalysis is proposed, which is able to activate both substrates to drive the bond formation reaction simultaneously and individually (37–39). Lewis acid is known to have an empty orbital, which can coordinate with a lone pair of electrons on the oxygen atom. We envisioned that merging an oxygen atom in alkoxyallene with Lewis acid might effectively tune the selectivity of the accumulated double bonds (40–42). Meanwhile, the synergy effect of copper and Lewis acid would ensure the control of the configuration over the activated intermediate (43). Here, a diverse collection of medicinally relevant oxalylamines via copper/Lewis acid synergistic catalysis is disclosed (Fig. 1D). A wide range of Z-oxalylamines and E-halogenated oxalylamines could be successfully synthesized with high yields and excellent regio- and stereoselectivities. An exciting opportunity offered by the strategy is that drug molecules could be obtained via an operationally simple reduction of the Z-oxalylamines.

RESULTS

Optimization studies for the aminative functionalization of allenyl ethers

To verify this strategy, phenyl 1,2-propadienyl ether (1a) and N,2-dimethylaniline (2a) were used as the model substrates (Table 1). First, in the presence of Cu(OAc)$_2$ as a catalyst and AgF as Lewis acid in CH$_2$Cl$_2$ at 50°C for 6 hours, the hydroamination product Z-3a was afforded in 24% yield (entry 1). To our delight, different Lewis acids were amenable for this transformation and ZnCl$_2$ served as the most effective additive, with Z-3a obtained in 98% nuclear magnetic resonance (NMR) yield and 93% isolated yield (entries 2 to 5). Studies of the copper salts indicated that Cu(OAc)$_2$ was the most reactive and selective catalyst for direct addition to forming oxalylamine Z-3a. The amounts of Cu(OAc)$_2$ and ZnCl$_2$ could reduce to 5 mole percent (mol %) loading without decreasing the yield (entry 5). Control experiments excluding additives or copper salts gave no corresponding product, demonstrating that Lewis acid and copper catalyst were indispensable for the success of this hydroamination

Key Laboratory of Functional Molecular Engineering of Guangdong Province, School of Chemistry and Chemical Engineering, South China University of Technology, Guangzhou 510640, China.
*Corresponding author. Email: cewuwq@scut.edu.cn (W.W.); jianghf@scut.edu.cn (H.J.)
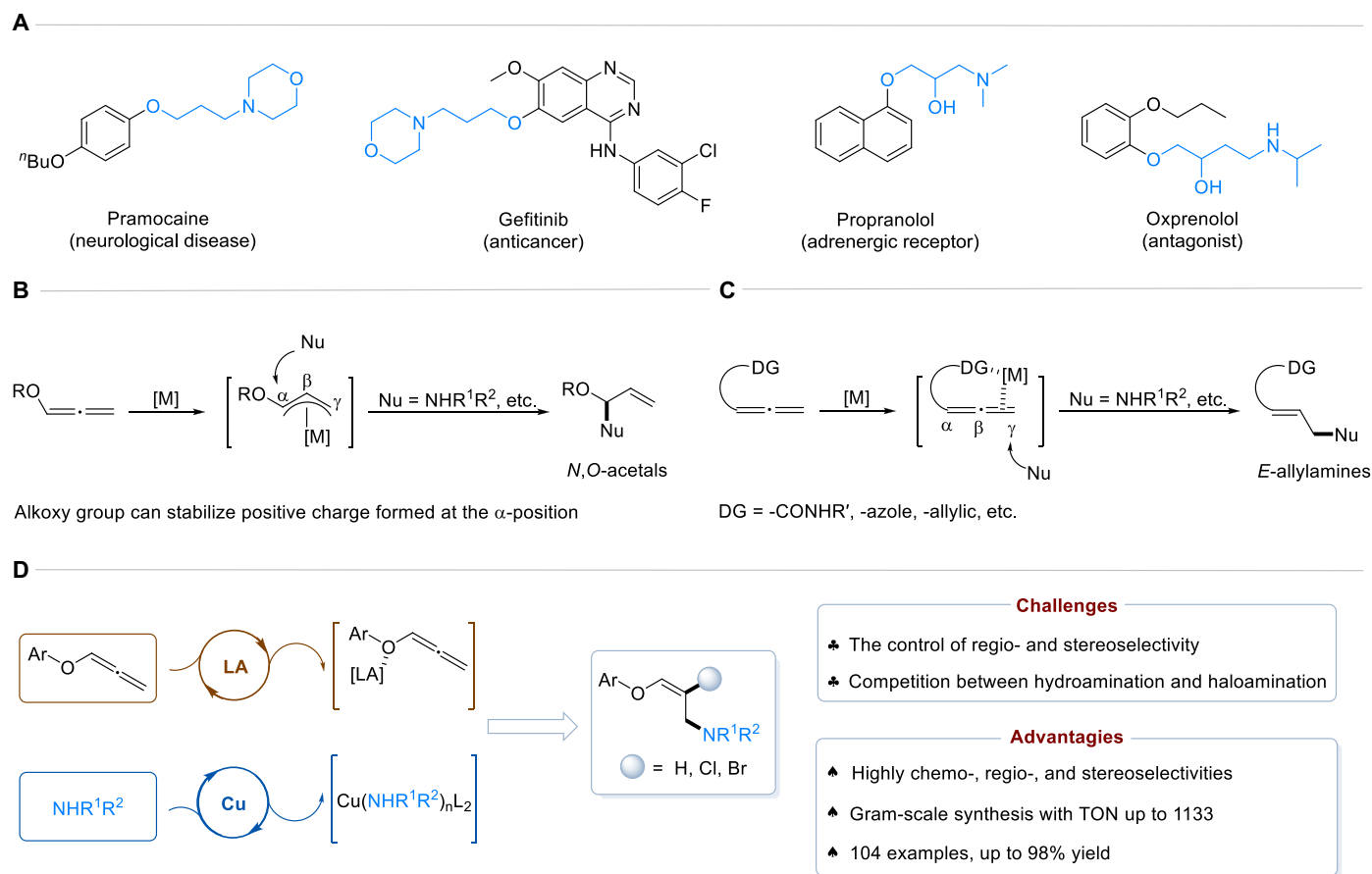
Fig. 1. Examples of biologically active molecules and strategies to obtain allylamine derivatives. (**A**) Examples of biologically active molecules. (**B**) Hydroamination of alkoxyallenes. (**C**) Hydroamination of allenes with directing group. (**D**) Our strategy: Copper/Lewis acid synergistic catalysis.

reaction (entries 6 and 7). We believed that CuX_2 could work as both the catalyst and Lewis acid, playing the role of halogen source to realize the aminative difunctionalization of allenes. As expected, the desired chloraminated product E-**4a** was obtained in 24% NMR yield by using 60 mol % of $CuCl_2$ under the oxygen (1 atm) atmosphere at 40°C for 6 hours (entry 8). Further solvent screening revealed that the nonpolar solvents exhibited much higher reactivity than polar solvents, and dioxane was found to be the optimal medium to deliver E-**4a** in 86% NMR yield with no detected alternative regio- and stereoisomers (entries 9 to 11). Further increasing the amount of $CuCl_2$ has no effect on chloramination reaction (entry 12). However, only a trace amount of E-**4a** was observed under N_2 atmosphere, indicating that O_2 played a vital role in the chloramination product formation step (entry 13). More detailed reaction conditions were displayed in the Supplementary Materials.

Substrate scope of hydroamination reactions
With the optimized reaction conditions in hand, the generality of hydroamination reaction was explored and the results were summarized in Fig. 2. Substituents on aromatic secondary amines were initially surveyed. Reactions of substrates bearing electron-donating and electron-withdrawing groups on the benzene ring proceeded well to afford the corresponding products Z-**3a** to Z-**3o** in moderate to good yields (32 to 93%). However, electron-deficient N-methyl aromatic amines exhibited lower reactivities (57% for E-**3m**, 44%

for Z-**3n**, and 32% for Z-**3o**, respectively). It was noteworthy that the configuration of the major product for the substrate bearing CN group was found to be reversed (Z:E = 1:12). The molecular structure and the relative stereochemistry of Z-**3o** were unambiguously confirmed by x-ray crystallographic analysis (44). Furthermore, a naphthyl-substituted amine and cyclic aromatic secondary amines, including carbazole and 1,2,3,4-tetrahydroquinoline, could be accommodated well to deliver the hydroamination products Z-**3p** to Z-**3r** in 56 to 87% yields. The conversions of diversely substituted amines, such as N-ethylaniline, N-allyl aniline, N-benzylaniline, and N-pentylaniline, proceeded well to produce the desired products Z-**3s** to Z-**3v** in satisfactory yields (81 to 90%). However, the hydroamination of aromatic primary amines gave the corresponding products (Z-**3w** to Z-**3z**) a slightly lower yield than those of secondary amines.

Then, a range of aliphatic secondary amines, including acyclic and cyclic secondary amines, was examined. Pleasingly, the reactivity of the system for acyclic amines enabled the hydroamination of alkyl chain amines with different functional groups (thienyl, naphthylmethyl, hydroxyl, amino acid ester, etc.), which provided the desired hydroamination products (Z-**3aa** to Z-**3ag**) in 40 to 82% yields with moderate to excellent stereoselectivities. Moreover, the reactivity of different cyclic amines was investigated. The hydroamination of N-heterocycles, which are commonly used for drug synthesis, afforded the desired products containing cyclohexylamine (**2ah**), piperidine (**2ai** and **2aj**), piperazine (**2ak-2am**), morpholine (**2an**), and thiomorpholine (**2ao**)

Table 1. Optimization studies for the aminative functionalization of allenyl ethers. Exploration of catalyst, Lewis acid, and solvent effects on the aminative functionalization of allenyl ether **1a**. DCE, dichloroethane; DMSO, dimethyl sulfoxide; ND, not determined.
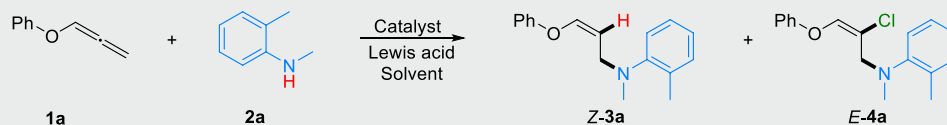
Entry	Catalyst	Lewis acid	Solvent	Yield of Z-3a (%)*	Yield of E-4a (%)†
1‡	Cu(OAc)$_2$	AgF	CH$_2$Cl$_2$	24	ND
2‡	Cu(OAc)$_2$	Fe(OTf)$_2$	CH$_2$Cl$_2$	42	ND
3‡	Cu(OAc)$_2$	InBr$_3$	CH$_2$Cl$_2$	74	ND
4‡	Cu(OAc)$_2$	CuCl$_2$	CH$_2$Cl$_2$	88	12
5‡,§	Cu(OAc)$_2$	ZnCl$_2$	CH$_2$Cl$_2$	98 (93)	ND
6‡	–	ZnCl$_2$	CH$_2$Cl$_2$	ND	ND
7‡	Cu(OAc)$_2$	–	CH$_2$Cl$_2$	Trace	ND
8‖	–	CuCl$_2$	CH$_2$Cl$_2$	18	24
9‖	–	CuCl$_2$	DCE	10	58
10‖	–	CuCl$_2$	DMSO	ND	ND
11‖	–	CuCl$_2$	Dioxane	10	86 (82)
12‖,¶	–	CuCl$_2$	Dioxane	10	85
13‖,#	–	CuCl$_2$	Dioxane	Trace	Trace

*The Z-type to E-type geometric ratio (Z/E) and yield of Z-**3a** were determined by ^{1}H NMR using CH$_2$BrCl as the internal standard analysis of the crude mixtures. The isolated yield of Z-**3a** was given in parentheses. Z/E > 20:1 unless otherwise noted. †The E-type to Z-type geometric ratio (E/Z) was determined by GC-MS analysis of the crude mixtures. Yield of E-**4a** was determined by ^{1}H NMR using CH$_2$BrCl as the internal standard analysis of the crude mixtures. The isolated yield of E-**4a** was given in parentheses. E/Z > 20:1 unless otherwise noted. ‡Condition A: All reactions were performed with **1a** (0.30 mmol), **2a** (0.20 mmol), catalyst (10 mol %), Lewis acid (10 mol %), and solvent (1.0 ml), 50°C, 6 hours. §Cu(OAc)$_2$ (5 mol %) and ZnCl$_2$ (5 mol %) were used. ‖Condition B: All reactions were performed with **1a** (0.30 mmol), **2a** (0.20 mmol), CuCl$_2$ (60 mol %), solvent (1.0 ml), and O$_2$ (1 atm), 40°C. ¶CuCl$_2$ (1 equiv) was used. #Under N$_2$ atmosphere.

in good to high yields with moderate stereoselectivities. Gratifyingly, this process was also compatible with the bridged cyclic amines, which successfully transformed to the desired products (Z-**3ap** to Z-**3ar**) in moderate to excellent isolated yields (60 to 86%) with retention of stereochemistry. Notably, evaluation of alkylamines bearing two N-H sites with the same reactivity indicated that they were all suitable for this transformation (Z-**3as** and Z-**3at**). However, the tightly binding primary aliphatic amines could not transform to the target products in this system.

The range of oxygen-substituted allenes (**1**) for hydroamination was subsequently probed. Various functional groups such as -X (**1au**-**1aw**, **1aae**), which could serve as handles for further functionalization through cross-coupling, -Me (**1ax** and **1aab**), -OMe (**1ay**), -CN (**1az**), -CF$_3$ (**1aaa**), -NHCOCH$_3$ (**1aac**), and -Ph (**1aad**) were used and successfully converted into the desired products in satisfying yields (80 to 95%). A notable feature of the reaction was that the electronic effects had little influence on the reaction conversion. The amination was also suitable for the disubstituted allene ethers. Both 3,4- (**1aaf**) and 2,6- (**1aag**) as well as 3,5- (**1aah**) disubstituted allene ethers and even a naphthyloxy-allene (**1aai**) could transform to the Z-oxalylamine derivatives in high yields with moderate to excellent stereoselectivities. Specifically, when 1-(buta-2,3-dien-2-yloxy)-2-iodobenzene was used to react with N,2-dimethylaniline or diethylamine under the standard conditions, highly substituted allylamines could be obtained. In addition, the configurations of

Z-**3aaj** and Z-**3aak** were confirmed by nuclear Overhauser effect spectroscopy experiments (see the Supplementary Materials for details).

Substrate scope of chloramination reactions

The scope of the aminochlorination reaction was then evaluated (Fig. 3). A broad range of N-methylanilines with different functional groups such as methyl, methoxyl, chloro, bromo, fluoro, trifluoromethyl, carbonyl at ortho-, meta-, and para-positions of the aromatic ring, as well as naphthyl was well tolerated in this transformation, and the desired products (E-**4a** to E-**4m**) were obtained in moderate to high yields. Moreover, reactions of aromatic secondary amines with ethyl (**2n**), allyl (**2o**), and benzyl (**2p**) substituents at the amino position afforded the desired products in synthetically useful yields. However, the aniline partners showed comparatively lower reactivity (40% for E-**4q** and 45% for E-**4r**), likely due to the high affinity of primary amines. Overall, oxygen-substituted allene (**1**) bearing various electron-deficient or electron-rich functionalities on the aryl ring also worked well, giving the desired chloramination products (E-**4s** to E-**4ad**) in 52 to 90% yields with high stereoselectivities (E/Z > 20:1). Among them, phenyl allene ether derivatives with disubstituted groups on benzene ring underwent chloramination to afford the corresponding products E-**4ae** to E-**4ag** in 80 to 84% yields. In addition, naphthyloxy-allene (**1ah**) was found to participate readily in this hydroamination reaction with moderate yield.
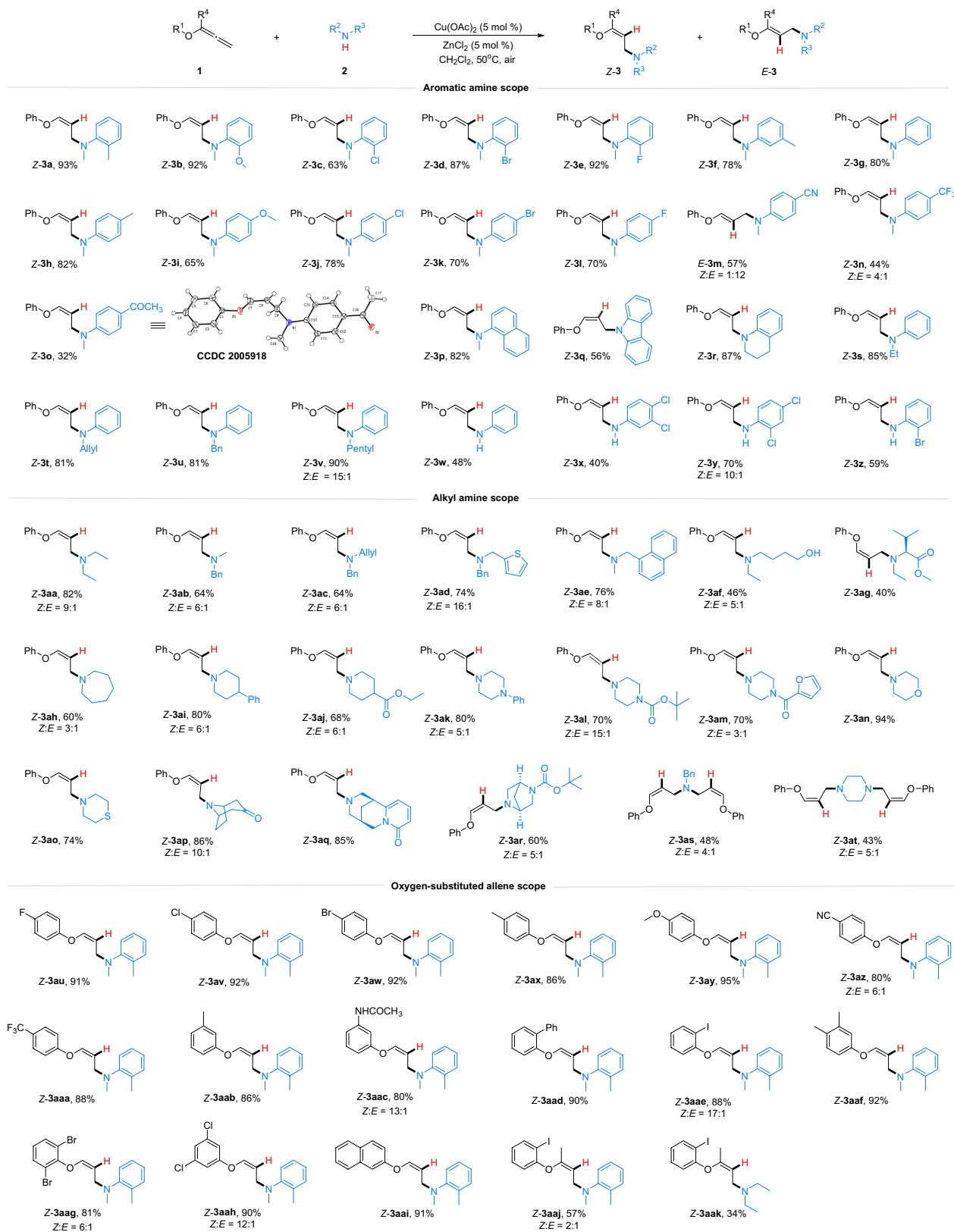
Fig. 2. Substrate scope of hydroamination reactions. Condition A: **1** (0.3 mmol), **2** (0.2 mmol), Cu(OAc)$_2$ (5 mol %), ZnCl$_2$ (5 mol %), and CH$_2$Cl$_2$ (1.0 ml), 50°C, 6 hours. All yields (given as a percentage) were isolated unless otherwise noted. The Z-type to E-type geometric ratio (Z/E) was determined by ^{1}H NMR using CH$_2$BrCl as the internal standard analysis of the crude mixtures. Z/E > 20:1 unless otherwise noted.
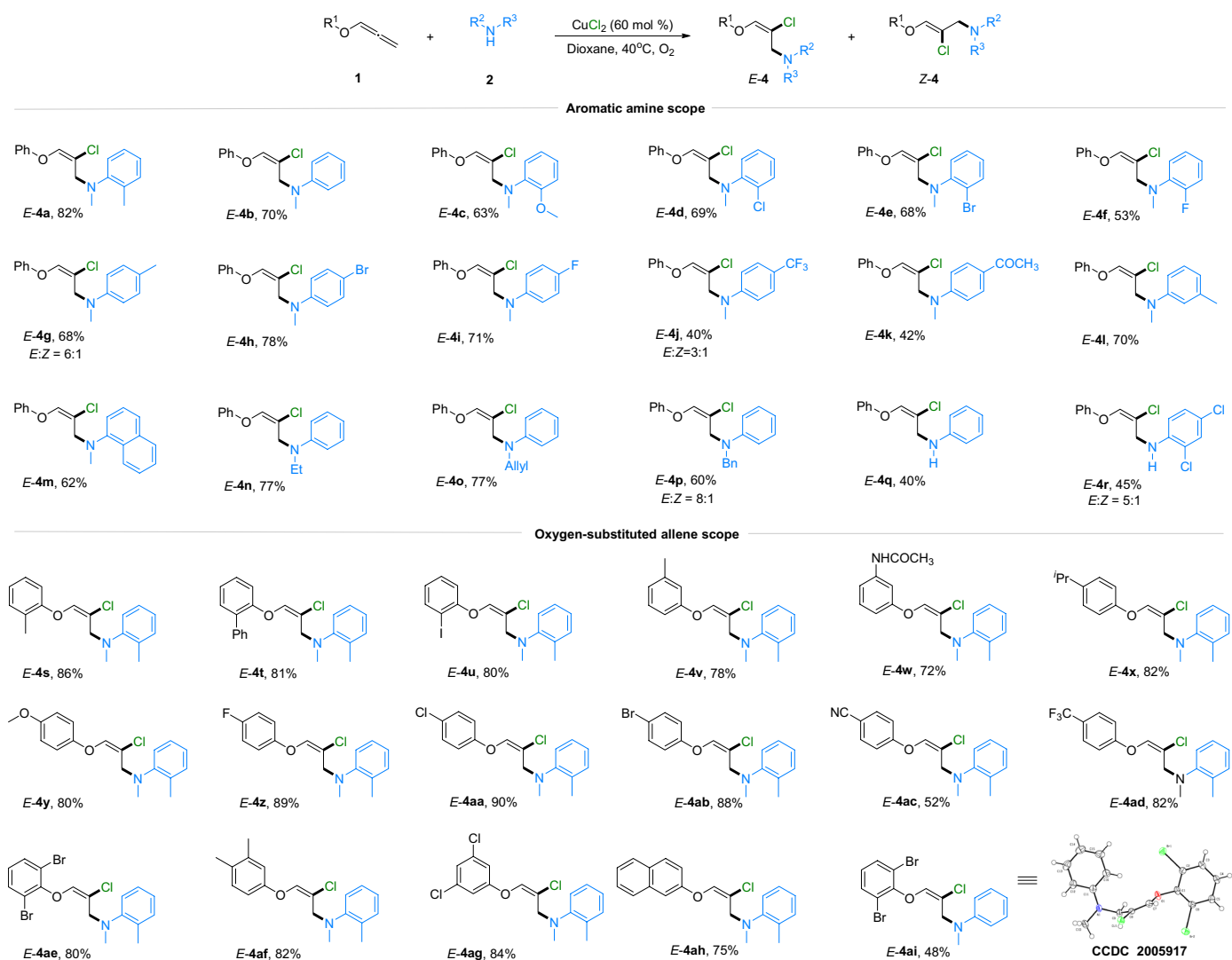
Fig. 3. Substrate scope of chloramination reactions. Condition B: **1** (0.3 mmol), **2** (0.2 mmol), CuCl$_2$ (60 mol %), dioxane (1.0 ml), and O$_2$ (1 atm), 40°C, 6 hours. All yields (given as a percentage) were isolated unless otherwise noted. The *E*-type to *Z*-type geometric ratio (*E/Z*) was determined by gas chromatography–mass spectrometry (GC-MS) analysis of the crude mixtures. *E/Z* > 20:1 unless otherwise noted.

The molecular structure and the relative stereochemistry of *E*-**4ai** were unequivocally confirmed by x-ray crystallographic analysis (*45*).

DISCUSSION

Synthetic utilities

To highlight the practicality and synthetic value of this copper/Lewis acid catalyzed aminative functionalization of alkoxyallenes, the reaction was applied for the further transformations to deliver more complex and useful compounds. As delineated in Fig. 4A, the late-stage functionalization of bioactive molecules could manifest the utility of this transformation. Under the hydroamination reaction conditions, a series of bioactive molecules such as aminoglutethimide, atomoxetine (a selective norepinephrine reuptake inhibitor) (*46*), desipramine, and ibrutinib intermediate could transform to the *Z*-oxalylamine derivatives (*Z*-**3aal** to *Z*-**3aao**) in moderate to good yields without a loss

of optical purity. In addition, gram-scale (10 mmol) experiments were successfully conducted to confirm the efficiency of the amination functionalization of alkoxyallenes (Fig. 4B). The desired hydroamination products *Z*-**3a** and *Z*-**3aj** and chloramination product *E*-**4a** could all be obtained with high yields and moderate to excellent steoroselectivities. Noteworthily, when reducing the loading of Cu(OAc)$_2$ and ZnCl$_2$ to 0.06 mol %, the desired product *Z*-**3a** was formed in 68% yield with high turnover number (TON = 1133). Besides, cross-coupling reaction was achieved with *E*-**4a** and phenyl magnesium bromide, as C—C bond formation occurred at the position of alkenyl chloride, leading to the useful phenyl-substituted oxalylamine (**6**). Moreover, the chloramination reaction could be extended to different halogen sources. For instance, under the conditions of 60 mol % of CuBr$_2$, the bromination reaction proceeded smoothly to deliver the brominated oxalylamine *E*-**4aj** in 62% yield with *E/Z* ratio equaling to 13:1 (Fig. 4B) (*47*). Given the functionary of this method, the intermediate
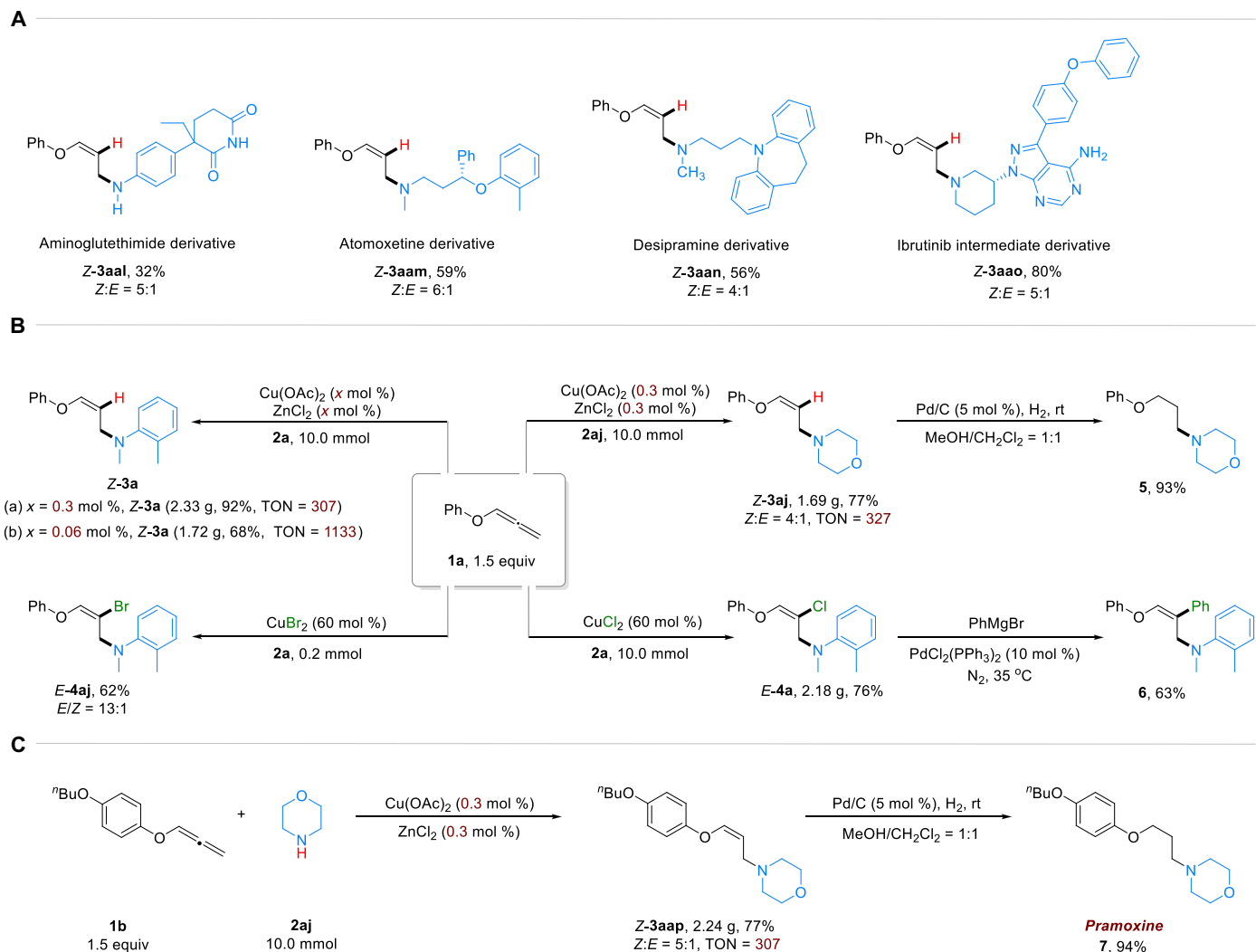
Fig. 4. Synthetic utility. (**A**) Late-stage hydroamination of bioactive molecules. (**B**) Gram-scale reactions and further decorations. (**C**) Synthesis of pramoxine.

Z-**3aap** of drug molecule could be constructed in gram scale. In the presence of Pd/C (5 mol %) as the catalyst, the drug molecule pramoxine (**7**) could be isolated in 94% yield under H_2 atmosphere (Fig. 4C) (*48*).

Mechanistic studies

To gain more insight into the mechanism of the amination process, a series of control experiments were conducted. First, a deuterium-labeling study was performed under the deuteration reaction condition A′. Applying deuterated diethylamine *d*-**2ab** as the amine source, the corresponding deuterated product Z-*d*-**3ab** was obtained with a separated yield of 80% and a deuteration rate of 82%, showing that amine served as a hydrogen atom donor (Fig. 5A). Moreover, the D_2O labeling experiment proved that amine and D_2O might undergo proton exchange in the hydroamination reaction (see the Supplementary Materials for details). Then, several radical trapping agents, such as 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), 2,6-*di-tert*-butyl-4-methylphenol (BHT), and 1,1-diphenylethylene, were used to perform the radical trapping experiments. The NMR yield of the products (Z-**3a** and E-**4a**) showed that no reactions were inhibited

except that TEMPO reduced the yield of the chloramination for its strong oxidation ability. These observations indicated that the free-radical process should not be involved (Fig. 5B). The addition of phenyl allene (**1a′**), nitrogen-substituted allene (**1a″**), or sulfur-substituted allene (**1a‴**) instead of alkoxyallene under the conditions A or B failed to mediate the desired hydroamination or chloramination products (Fig. 5C), which suggested that the coordination between oxygen atom and Lewis acid was important in the aminative functionalization of alkoxyallenes. Furthermore, no chloramination product E-**4a** was formed in the intermediate experiment when using Z-**3a** as the substrate, demonstrating that the hydroamination and chloramination reaction might go through different pathways (Fig. 5D). Kinetic analysis experiments for hydroamination were conducted under the most suitable reaction conditions (Fig. 5E). The rate data indicated a first-order dependence only on the concentration of Cu catalyst, which revealed that hydrolysis should be the rate-determining step (*49*, *50*).

On the basis of the above investigations and previous literatures (*28*, *29*, *51*), a mechanism is proposed in Fig. 5F. Initially, coordination of Cu(II) to the amine substrate **2** generates the intermediate **Int-I**.
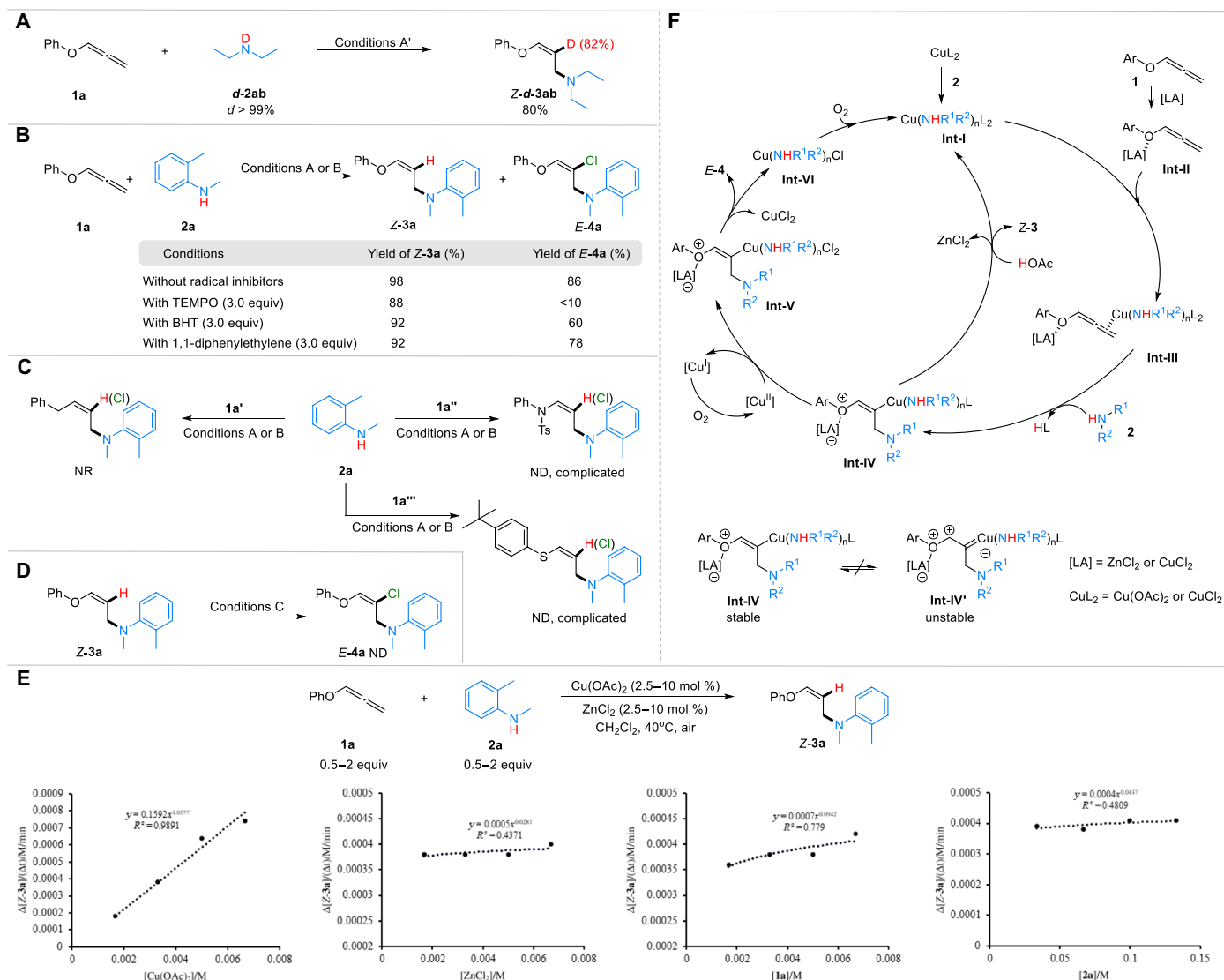
Fig. 5. Mechanistic studies. (A) Deuterium-labeling study. **(B)** Radical trapping experiment. **(C)** Control experiment. **(D)** Intermediate experiment. **(E)** Determination of the order. **(F)** Proposed mechanism. Condition A′: **1a** (0.3 mmol), *d*-**2ab** (0.2 mmol), Cu(OAc)₂ (5 mol %), ZnCl₂ (5 mol %), and dry CH₂Cl₂ (1.0 ml), 50°C, 6 hours. Condition A: **1** (0.3 mmol), **2a** (0.2 mmol), Cu(OAc)₂ (5 mol %), ZnCl₂ (5 mol %), and CH₂Cl₂ (1.0 ml), 50°C, 6 hours. Condition B: **1** (0.3 mmol), **2a** (0.2 mmol), CuCl₂ (60 mol %), dioxane (1.0 ml), and O₂ (1 atm), 40°C, 6 hours. Condition C: *Z*-**3a** (0.3 mmol), CuCl₂ (60 mol %), dioxane (1.0 ml), and O₂ (1 atm), 40°C, 6 hours. **1a′**: Buta-2,3-dien-1-ylbenzene. **1a″**: 4-Methyl-*N*-phenyl-*N*-(propa-1,2-dien-1-yl)benzenesulfonamide. **1a‴**: 1-*tert*-Butyl-4-(propa-1,2-dienylthio)benzene.

At the same time, **Int-II** is formed by coordination of Lewis acid (ZnCl₂ or CuCl₂) with alkoxyallene **1**. Subsequently, a nucleophilic attack of amine **2** to Cu(II)/allene complex **Int-III** gives an *E*-alkenylcopper **Int-IV** exclusively, which improves the regioselectivity of the reaction. The isomerization of **Int-IV** to **Int-IV′** could be inhibited by the coordination of Lewis acid and oxygen to enhance the stereoselectivity of this process (*43*). In the case of addition of Cu(OAc)₂ and ZnCl₂, intermediate **Int-IV** might undergo hydrolysis to deliver the hydroamination product *Z*-**3**. Alternatively, in the case of addition of CuCl₂, the resulting alkenyl Cu^II species **Int-IV** is oxidized by another equivalent of [Cu^II] to yield an alkenyl Cu^III intermediate **Int-V** that can undergo facile C—Cl bond formation through reductive

elimination. Last, rapid aerobic oxidation of [Cu^I] regenerates [Cu^II] to complete the catalytic cycle.

In conclusion, by using a strategy of synergistic catalysis, we have realized a copper/Lewis acid–catalyzed intermolecular hydroamination of alkoxyallenes to produce *Z*-oxalylamines. The intermolecular aminohalogenation reactions have been developed in succession to obtain a series of *E*-halogenated oxalylamines by using CuX₂ as the transition metal catalyst and Lewis acid as well as halogen sources. This protocol was performed under mild reaction conditions and compatible with a wide scope of alkoxyallenes and amines, simultaneously with high atom economy. The advantages of gram-scale reactions, late-stage functionalization of bioactive molecules, and the synthesis

of drug molecules all showcased the potential of this strategy to be widely used.

MATERIALS AND METHODS
General procedure A: Hydroamination of allenyl ethers
The mixture of oxygen-substituted allene **1** (0.3 mmol), amine **2** (0.2 mmol), $Cu(OAc)_2$ (5 mol %), and $ZnCl_2$ (5 mol %) in CH_2Cl_2 (1.0 ml) was added to a 10-ml dried reaction tube successively. The mixture was stirred at 50°C for 6 hours under air atmosphere. After the reaction was completed, the mixture was cooled to room temperature, diluted with H_2O (15 ml), and extracted with CH_2Cl_2 (10 ml × 3). Combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuum. The resulting crude materials were purified by flash column chromatography on silica gel with petroleum ether/ethyl acetate (1:1 to 500:1) to give the desired products Z-**3** in 40 to 95% isolated yields with Z/E ratio from 3:1 to single Z configuration.

General procedure B: Chloramination of allenyl ethers
The mixture of amine **1** (0.2 mmol), oxygen-substituted allene **2** (0.3 mmol), and $CuCl_2$ (60 mol %) in 1,4-dioxane (1.0 ml) was added to a 25-ml dried reaction tube successively. The mixture was stirred at 40°C for 6 hours under O_2 atmosphere. After the reaction was completed, the mixture was cooled to room temperature, diluted with H_2O (15 ml), and extracted with EtOAc (10 ml × 3). Collected organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuum. The resulting crude materials were purified by flash column chromatography on silica gel with petroleum ether/ethyl acetate (50:1 to 200:1) to give the desired products E-**4** in 40 to 89% isolated yields with E/Z ratio from 3:1 to single E configuration.

General procedure for the preparation of allenyl ethers 1 (52)
Step 1
3-Bromopropyne (16 mmol) was added to a flask containing phenol (14 mmol) and K_2CO_3 (2.5 equiv) in N,N′-dimethylformamide (20 ml) at room temperature under Ar. After addition, stirring was continued for 12 hours. The mixture was treated with 10 ml of H_2O. The resulting mixture was extracted with Et_2O (30 ml × 4) and dried over anhydrous Na_2SO_4. After concentration, the residue was purified by flash column chromatography on silica gel (EtOAc/petroleum ether = 1:100) to give the corresponding alkyne.
Step 2
t-BuOK (0.5 equiv) was added to a solution of the above alkyne (4.0 mmol) in tetrahydrofuran (THF) (20 ml) at 0°C under Ar. The mixture was stirred at room temperature until completion of the reaction [thin-layer chromatography (TLC)]. The solution was filtered through Celite, and the solvent was concentrated under reduced pressure and purified by column chromatography to give the desired products **1** in 70 to 90% yields (petroleum ether). The spectral data of **1** were in accordance with the literature.

General procedure for the preparation of buta-2,3-dien-1-ylbenzene 1a′ (53)
Prop-2-yn-1-ylbenzene (5.0 mmol, 1.0 equiv) and dicyclohexylamine (9.0 mmol, 1.8 equiv) were added to a stirred solution of para-formaldehyde (12.5 mmol, 2.5 equiv) and CuI (2.5 mmol, 0.5 equiv) in dioxane (25 ml) under atmosphere of argon. The resulting mixture was then refluxed for 4 hours. After the reaction was completed as monitored by TLC, the mixture was cooled to room temperature and filtered. The filtrate was concentrated under reduced pressure and then diluted with water and ether, followed by the addition of 1 N HCl to pH 1 to 2. The resulting mixture was extracted three times with ether (30 ml × 3). The organic layer was then washed with brine and dried over Na_2SO_4, filtrated, and evaporated of the solvent. The residue was purified by flash chromatography with hexane to give the corresponding product **1a′** as a colorless oil in 70% yield (507.5 mg). The spectral data of **1a′** were in accordance with the literature.

General procedure for the preparation of 4-methyl-N-phenyl-N-(propa-1,2-dien-1-yl)benzenesulfonamide 1a″ (54)
t-BuOK (1.5 mmol) was added to a solution of 4-methyl-N-phenyl-N-(prop-2-yn-1-yl)benzenesulfonamide (5 mmol, 1 equiv) in anhydrous THF (15 ml) in three portions under an argon atmosphere at 0°C in an ice water bath. The reaction mixture was allowed to stir at room temperature for 2 hours. The mixture was filtered through Celite, washed with EtOAc, and concentrated. The crude residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 30:1 to 20:1) to give **1a″** as a yellow solid in 87% yield (0.124 g). The spectral data of **1a″** were in accordance with the literature.

General procedure for the preparation of 1-tert-butyl-4-(propa-1,2-dienylthio)benzene 1a‴ (55)
Step 1
A solution of sodium thiosulfate pentahydrate (2.7 g, 9.0 mmol) and benzyltriethylammonium chloride (0.2 g, 0.9 mmol) in water (2.0 ml) was added to a solution of propargyl bromide (0.96 ml, 9.0 mmol) in chloroform (8.0 ml), and the reaction mixture was heated at 60°C with vigorous stirring for 4 hours. The reaction mixture was then evaporated to dryness, and the residue was extracted with MeOH (50 ml × 2). The combined methanol extract was evaporated, and the residue was washed with CH_2Cl_2 to remove the catalyst and the remaining propargyl bromide. The resulting solid was dried in vacuum to give sodium propargylthiosulfate (1.22 g, 78%) as a white-cream solid.
Step 2
The p-tert-butylthiophenol (1.61 mmol) was added under stirring to an aqueous solution (5.0 ml) of KOH (0.10 g, 1.78 mmol), and the reaction mixture was heated to reflux for 1 hour. After cooling to 0°C, an aqueous solution (5.0 ml) of sodium propargylthiosulfate (0.56 g, 3.22 mmol) was added. The resulting mixture was further stirred at room temperature for 1 hour, diluted with diethyl ether (50 ml), washed with 10% KOH (15 ml) and H_2O (15 ml), dried over $MgSO_4$, and evaporated to give the crude product 1-tert-butyl-4-(prop-2-ynyldithio)benzene.
Step 3
Triphenylphosphine (0.26 g, 1.0 mmol) was added to a solution of the 1-tert-butyl-4-(prop-2-ynyldithio)benzene (0.5 mmol) in benzene (10.0 ml), and the reaction mixture was heated at 60°C. After completing the reaction (TLC), benzene was evaporated to give the crude reaction mixture as a viscous oil, from which the pure sulfides **1a‴** (yellow oil, 57%) was separated by column chromatography on silica gel with hexane as eluent.

SUPPLEMENTARY MATERIALS

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