JOC The Journal of Organic Chemistry

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One-Pot Tandem Access to Phenothiazine Derivatives from Acetanilide and 2-Bromothiophenol *via* Rhodium-Catalyzed C−H Thiolation and Copper-Catalyzed C−N Amination

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Cite This: *J. Org. Chem.* 2021, 86, 6622−6632 Read Online

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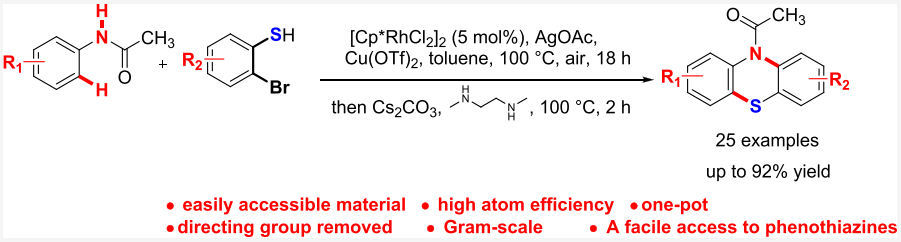


ABSTRACT: A one-pot and step economic reaction involving Rh(III)-catalyzed C−H thiolation and relay Cu(II)-catalyzed C−N amination of acetanilide and 2-bromothiophenol is reported here, with several valuable phenothiazine products obtained. This synthesis protocol proceeds from easily starting materials, demonstrating high atom economy, broad substrate scope, and good yield. Furthermore, the directing group can be easily eliminated, and chlorpromazine is provided in a large scale; thus this synthesis protocol could be utilized to construct phenothiazine scaffolds.

INTRODUCTION

Aryl sulfides are potential biologically active and pharmacologically active compounds, and they have been widely utilized in pharmaceuticals, materials science, and organic synthesis.[1] Among the aryl sulfide units, phenothiazines are of great importance and have gained lots of interest. Several phenothiazine derivatives have been launched to the market or in clinical trials, such as promazine, chlorpromazine, and triflupromazine (Figure 1). Phenothiazines were described and introduced as antipsychotic drugs and antagonists of central dopamine receptors.[2] Meanwhile, there are also tremendous phenothiazine derivatives possessing antimalarial, antiviral, antitumor, anti-inflammatory activities, *etc.*[3,4]

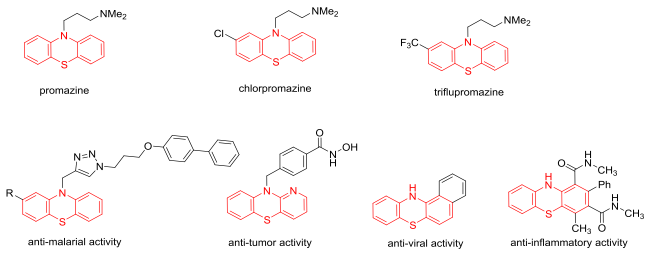


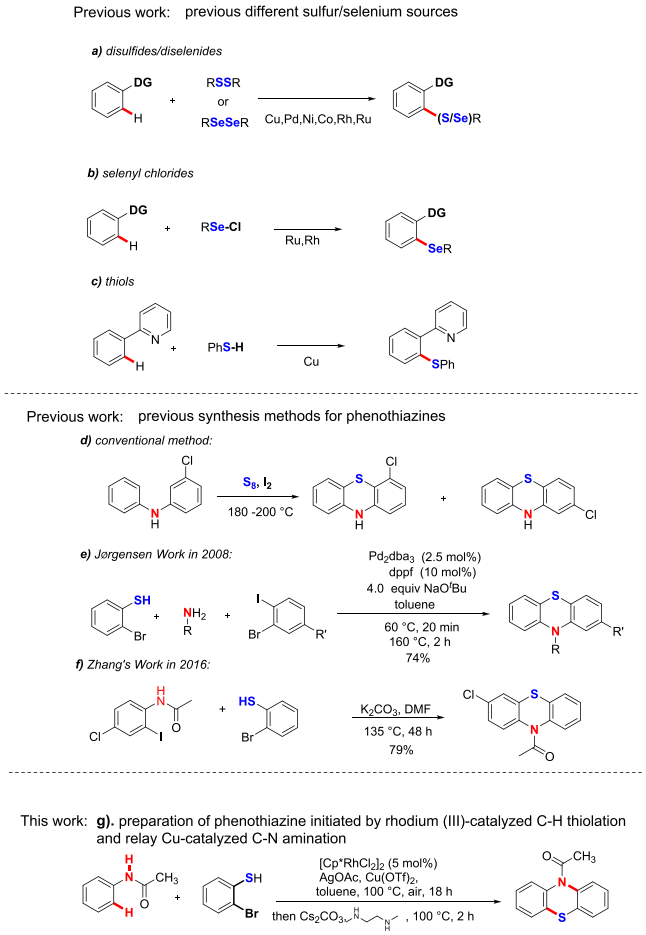
Figure 1. Representative compounds containing phenothiazine moieties.

In the past two decades, transition-metal-catalyzed carbon−hydrogen (C−H) bond functionalization is considered as a powerful strategy for the construction of carbon−carbon (C−C) and carbon−heteroatom (C−N, C−O, and C−S) bonds because of its remarkable atom economy and environmental sustainability.[5,6] Various synthesis methods for sulfenylation/selenylation *via* transition-metal-catalyzed C−H bond functionalization have been reported.[7] For example, diaryl sulfide and diaryl selenide scaffolds are essential reagents to accomplish sulfenylation/selenylation transformation under various catalysts, such as Pd, Co, Ni, Rh, Ru, *etc.* (Scheme 1a).[8] However, this protocol removes half of the diverse disulfide substituents that were difficult to synthesize, leading to lower atom economy and poorer applicability. Subsequently, encouraged by Glorius et al. and Yu et al.'s work on Rh(III)-catalyzed amination of arenes and electrophilic *N*-choloramine substrates,[9] some researchers are focusing on selenylation employing selenenyl chlorides as electrophilic selenium sources (Scheme 1b).[10] Though these are representative pioneering work in the transition-metal-catalyzed C−H selenylation, the lower atom economy of these synthesis methodologies greatly restricts their further application. As an excellent nucleophilic reagent, thiols are also widely employed to construct the C−S

Received: February 18, 2021
Published: April 21, 2021

https://doi.org/10.1021/acs.joc.1c00403
J. Org. Chem. 2021, 86, 6622−6632

Scheme 1. (a−g) Transition-Metal-Catalyzed C−H Thiolation/Selenylation Reactions



bond with great atom economy. Yu et al. reported a copper-catalyzed thiolation of 2-phenylpyridine with thiols under an oxygen atmosphere, resulting in only 40% yield due to the weak catalytic ability of Cu(II) (Scheme 1c).[11] Recently, Rh(III) catalysts have been extensively employed as useful and efficient catalysts for the activation of C−H bonds and the construction of C−S bonds.,[7a12] However, there is no research reported on thiols forming C−S bonds through Rh(III)-catalyzed C−H thiolation with weakly directing groups.

Due to the promising activities of substituted phenothiazines, many synthetic methodologies had been developed to yield phenothiazine scaffolds, including cyclization of acyclic precursors, transition-metal-catalyzed coupling reactions, and other methods.[13] The traditional method for synthesizing phenothiazines was oxidative cyclization of diarylamines and sulfur with iodine as a catalyst at 180 °C for 30 min (Scheme 1d).[13a] However, high temperatures made the reaction proceed with no regioselectivity, yielding two regioisomers at a 1:1 ratio. Isolation of these two regioisomers was difficult owing to the high structural similarity of isomers, and the yield of regioisomers was very low. Recently, the transition-metal-catalyzed coupling reaction had been developed significantly. In 2008, Jørgensen et al. reported a three-component reaction to obtain the target phenothiazine scaffold by palladium-catalyzed coupling annulation (Scheme 1e).[14] However, this synthetic protocol was limited by its unavailability of substituted 1-bromo-2-iodobenzenes, which resulted in a narrow substrate scope, deficiency of atom economy, and high reaction temperature. Subsequently, Zhang's research group reported a metal-free synthetic method by using *N*-acetylanilines and 2-bromothiophenols (Scheme 1f).[15] Though the synthesis route was metal-free, the desired product can be obtained in a moderate yield by stirring the reaction at 135 °C for 48 h. Hence, a kind of novel synthetic method to prepare phenothiazine scaffolds with high atom efficiency, low reaction temperature, and short reaction time is highly desirable.

Acetanilide is widely used in organic synthesis and medicinal chemistry. Several transition-metal-catalyzed C−H functionalization with acetanilide had been reported, involving C−C, C−O, and C−N bond formation because of the weakly directing group on acetanilide.[16] Among these research studies, Ackermann et al. reported Ru-catalyzed C−H chalcogenations of anilides with diselenides and disulfides;[16f] however, the sulfur-containing heterocycles involving phenothiazine had not been synthesized. Herein, we first report an efficient one-pot tandem Rh (III)-catalyzed C−H thiolation and relay Cu(II)-catalyzed C−N amination of acetanilide and 2-bromothiophenol under mild conditions. Several phenothiazine products could be obtained from these consecutive reactions. This method has features of good atom economy, broad substrate scope, and good yield, and it can be ultimately developed as a facile synthesis method of phenothiazine derivatives.

RESULTS AND DISCUSSION

We commenced our study by optimizing phenothiazine synthesis conditions (Table 1 and Supporting Information). Initially, acetanilide **1a** was treated with 2-bromothiophenol **2a** in the presence of $[RuCl_2(p\text{-cymene})]_2$, Ag_2CO_3, AgOTf, and toluene at 100 °C under an air atmosphere for 18 h, and then N^1,N^2-dimethylethane-1,2-diamine and Cs_2CO_3 were added into the reaction mixture and stirred for another 2 h. Fortunately, the desired phenothiazine product **4a** can be obtained with 42% yield, which involved a consecutive reaction involving C−H thiolation and relay C−N amination (entry 1). To enhance the reaction efficiency, various catalysts, oxidants, additives, and solvents were screened. Then, different catalysts such as Rh, Pd, and Cu were investigated, and as a result, the yield of **4a** was promoted to 54% when rhodium(III) was used as a catalyst (entries 2−4). Considering additives with hydrogen-extracted acid radical anions, the yields of **4a** were gained as 47, 35, 12, and 65% when AgOTf, HOTf, $AgSbF_6$, and $Cu(OTf)_2$, respectively, were used as additives (entries 5−8). Thus, $Cu(OTf)_2$ was selected as the best additive for C−S bond formation. In the catalytic cycle, the $Cu(OTf)_2$ additive deprived the chloride ligand from the $[Cp^*RhCl_2]_2$ catalyst complex to generate the cationic rhodium species. Most importantly, $Cu(OTf)_2$ was also identified as the catalyst for the relay C−N annulation. Once in the scenario of absence of N^1,N^2-dimethylethane-1,2-diamine and Cs_2CO_3, the reaction ceased at the initial Rh(III)-catalyzed C−H thiolation phase and there was no annulation product detected (entries 9 and 10). When Cs_2CO_3 was replaced by Li_2CO_3, the yield of **4a** was decreased to 32% (entries 11 *vs* 8). To further simplify the reaction conditions, silver salt Ag_2CO_3 was replaced by Li_2CO_3; however, the C−H thiolation reaction did not occur (entry 12), indicating that the silver salt acted as an oxidant only, which oxidized the rhodium catalyst to participate in the catalytic cycle. The above results also proved that Cs_2CO_3 was the best base for C−N amination to promote the release of protons, and N^1,N^2-dimethylethane-1,2-diamine performed as

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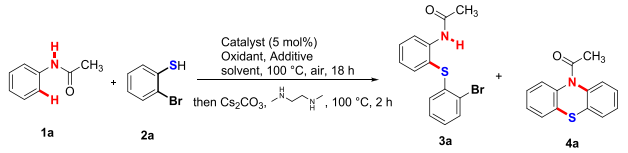
J. Org. Chem. 2021, 86, 6622−6632

Table 1. Screening the Reaction Conditions[a]



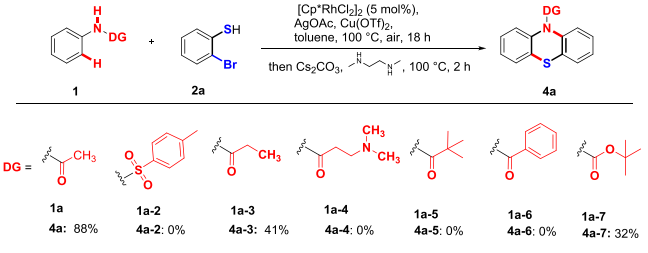
entry	catalyst	oxidant	additive	solvent	**4a** yield (%)[b]
1	$[RuCl_2(p\text{-cymene})]_2$	Ag_2CO_3	AgOTf	toluene	42
2	$[Cp^*RhCl_2]_2$	Ag_2CO_3	AgOTf	toluene	54
3	$Pd(OAc)_2$	Ag_2CO_3	AgOTf	toluene	0
4	$Cu(OAc)_2$	Ag_2CO_3	AgOTf	toluene	0
5	$[Cp^*RhCl_2]_2$	Ag_2CO_3	HOTf	toluene	47
6	$[Cp^*RhCl_2]_2$	Ag_2CO_3	NaOTf	toluene	35
7	$[Cp^*RhCl_2]_2$	Ag_2CO_3	$AgSbF_6$	toluene	12
8	$[Cp^*RhCl_2]_2$	Ag_2CO_3	$Cu(OTf)_2$	toluene	65
9[c]	$[Cp^*RhCl_2]_2$	Ag_2CO_3	$Cu(OTf)_2$	toluene	0
10[d]	$[Cp^*RhCl_2]_2$	Ag_2CO_3	$Cu(OTf)_2$	toluene	0
11[e]	$[Cp^*RhCl_2]_2$	Ag_2CO_3	$Cu(OTf)_2$	toluene	32
12	$[Cp^*RhCl_2]_2$	Li_2CO_3	$Cu(OTf)_2$	toluene	0
13	$[Cp^*RhCl_2]_2$	Ag_2O	$Cu(OTf)_2$	toluene	26
14	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2$	$Cu(OTf)_2$	toluene	10
15	$[Cp^*RhCl_2]_2$	AgOAc	$Cu(OTf)_2$	toluene	70
16	$[Cp^*RhCl_2]_2$	AgOAc[f]	$Cu(OTf)_2$	toluene	88
17	$[Cp^*RhCl_2]_2$	AgOAc	$Cu(OTf)_2$	DMF	0
18	$[Cp^*RhCl_2]_2$	AgOAc	$Cu(OTf)_2$	dioxane	35
19	$[Cp^*RhCl_2]_2$	AgOAc	$Cu(OTf)_2$	EtOAc	22
20	$[Cp^*RhCl_2]_2$	AgOAc	$Cu(OTf)_2$	acetone	31
21	$[Cp^*RhCl_2]_2$	AgOAc	$Cu(OTf)_2$	CCl_4	25
22	$[Cp^*RhCl_2]_2$	AgOAc	$Cu(OTf)_2$	THF	0
23	$[Cp^*RhCl_2]_2$	AgOAc	$Cu(OTf)_2$	DMSO	0
24		AgOAc	$Cu(OTf)_2$	toluene	0
25	$[Cp^*RhCl_2]_2$	AgOAc		toluene	0

[a]Reaction conditions: acetanilide **1a** (0.30 mmol, 1.0 equiv), 2-bromothiophenol **2a** (0.30 mmol, 1.0 equiv), catalyst (0.015 mmol, 5 mol %), oxidant (0.60 mmol, 2.0 equiv), additive (0.06 mmol), and solvent (2 mL); the reaction mixture was stirred in a sealed tube at 100 °C for 18 h, and then N^1,N^2-dimethylethane-1,2-diamine (0.60 mmol) and Cs_2CO_3 (0.36 mmol) were added into the mixture and stirred for another 2 h. [b]Isolated yield. [c]Standard reaction conditions without N^1,N^2-dimethylethane-1,2-diamine. [d]Standard reaction conditions without Cs_2CO_3. [e]Cs_2CO_3 was replaced by Li_2CO_3; Li_2CO_3 (0.36 mmol) was added into the mixture. [f]AgOAc (3.0 equiv) was added.

a ligand and coordinated with copper salt to provide a five-membered copper metallacycle. In order to improve the reactivity, different oxidant species such as Ag_2O, $Cu(OAc)_2$, and AgOAc were investigated (entries 13−15); as a result, AgOAc was considered as the best oxidant in terms of the yield of **4a**. Moreover, when AgOAc was added in 3.0 equiv, the yield of **4a** went up to 88% (entry 16). On the contrary, other solvents such as DMF, dioxane, EtOAc, acetone, CCl_4, THF, and DMSO led to a dramatic decrease in the yield, and product **4a** could not even be found, indicating that toluene was the best solvent for this synthesis protocol (entries 17−23). Finally, several control experiments were carried out to reveal that $[Cp^*RhCl_2]_2$ and $Cu(OTf)_2$ were indispensable for the synthesis protocol, and this one-pot transformation could not be accomplished through a catalyst-free process (entries 24 and 25). In summary, in the initial C−H thiolation, AgOAc and $Cu(OTf)_2$ performed as an oxidant and additive, respectively. Additionally, $Cu(OTf)_2$ as a catalyst and N^1,N^2-dimethylethane-1,2-diamine as a ligand, along with Cs_2CO_3 as a base, participated in the relay C−N annulation.

With the optimized reaction conditions, various *N*-phenylacetamide derivatives containing different directing groups were investigated (Scheme 2). It was noteworthy that the target phenothiazine products could be obtained in 88% yield

Scheme 2. Substrate Scope of Directing Groups[a,b]



[a]Reaction conditions: *N*-phenylacetamide (1.20 mmol), 2-bromothiophenol (1.20 mmol), $[Cp^*RhCl_2]_2$ (0.060 mmol, 5 mol %), AgOAc (3.60 mmol), $Cu(OTf)_2$ (0.24 mmol), and toluene (8 mL); the reaction mixture was stirred in a sealed tube at 100 °C for 18 h. Then, N^1,N^2-dimethylethane-1,2-diamine(2.40 mmol) and Cs_2CO_3 (1.44 mmol) were added into the reaction mixture and stirred for another 2 h. [b]Isolated yields of phenothiazine derivatives.

by an acetyl substitution directing group. Once the acetyl group was extended to propionyl (**1a-3**), the yield of product **4a-3** was decreased sharply to 41%. Meanwhile, when *N*-phenylacetamide bore a strong electron-withdrawing sulfonyl group (**1a-2**) and benzoyl group (**1a-6**), the reaction proceeded difficultly. In addition, owing to steric hindrance,

https://doi.org/10.1021/acs.joc.1c00403
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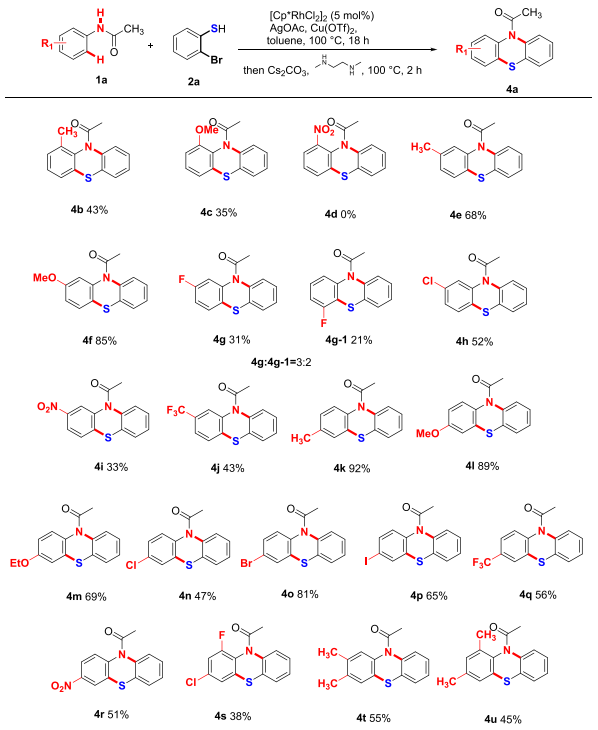
the transformation was not tolerated with bulkier substituents involving 4-(dimethylamino)butanyl (**1a-4**) and *tert*-butyryl (**1a-5**). Also, the yield of **4a-7** was decreased to 32% (**4a** *vs* **4a-7**) when *tert*-butoxycarbonyl (Boc) was explored as a directing group (**1a-7**). These results indicated that the directing group was critical to the consecutive C−S formation and the relay C−N cyclization process, and the one-pot reaction could be accomplished to obtain phenothiazine derivatives with only the acetyl and Boc group as a directing group.

To further investigate the substrate scope, the effects of different substituents of *N*-phenylacetamide **1a** were studied (Scheme 3). The *ortho*-position substituted compounds could

Scheme 3. Substrate Scope of *N*-phenylacetamide[a,b]

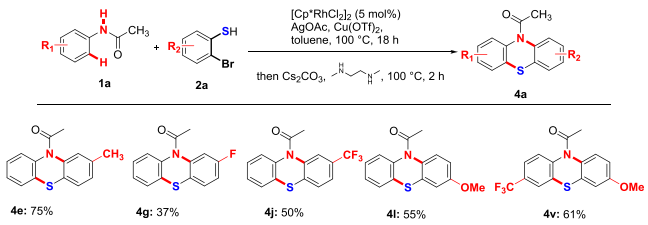


[a]Reaction conditions: *N*-phenylacetamide (1.20 mmol), 2-bromothiophenol (1.20 mmol), $[Cp^*RhCl_2]_2$ (0.060 mmol,5 mol %), AgOAc (3.60 mmol), $Cu(OTf)_2$ (0.24 mmol), and toluene (8 mL), reactions run in a sealed tube at 100 °C for 18 h. Then, N^1,N^2-dimethylethane-1,2-diamine(2.40 mmol) and Cs_2CO_3 (1.44 mmol) were added into the reaction mixture and stirred for another 2 h. [b]Isolated yields of phenothiazine derivatives.

transform to the corresponding phenothiazine product only when the reagents contain electron-donating groups. The phenothiazine products **4b** bearing *o*-CH_3 and **4c** bearing *o*-OCH_3 could provide 43 and 35% yields, respectively. However, the *o*-NO_2-substituted substrate might hinder C−H thiolation and no desired product **4d** could be found. Subsequently, the reactivity of this transformation for *meta*-substituents was observed. The reaction efficiency showed the same trend as that of *ortho*-substituents. The compounds replaced by electron-withdrawing groups, namely, *m*-F (**4g**: 31%; **4g-1**: 21%), *m*-Cl (**4h**: 52%), *m*-NO_2 (**4i**: 33%), and *m*-CF_3 (**4j**: 43%), gave a relatively lower yield than electron-rich substituents, *m*-OCH_3 (**4f**: 85%) and *m*-CH_3 (**4e**: 68%). The reaction efficiency was most affected by the strong electron-withdrawing group, and the *m*-NO_2 precursor generated the desired product **4i** with a poor yield of 33%. Meanwhile, as the regioselectivity was deficient for the direct thiolation of C−H bonds, the C−H activation did not proceed selectively at C_2 or C_4 positions, which resulted in two isomers (**4g**: 31% and **4g-1**: 21%). Although the rhodium(III)-catalyzed C−H thiolation proceeded selectively, the products **4e**, **4f**, **4i**, and **4j** did not have regiomeric mixtures because of the large steric hindrance in substituted groups. Meanwhile, as the other regiomeric mixture was in trace, the regioselectivity of **4h** was excellent. The electron-rich substituents at the *para*-position were also tolerated for this reaction, and the substrates bearing *p*-CH_3, *p*-OCH_3, and *p*-OCH_2CH_3 were transformed well into the phenothiazine products **4k**, **4l**, and **4m** in good to moderate yield (**4k**: 92%; **4l**: 89%; **4m**: 69%). With the same electron-donating groups, the yield of *para*-substituted compounds (**4k**: 92%; **4l**: 89%) was much higher than that of the corresponding *ortho*-substituted substrates (**4b**: 43%; **4c**: 35%) or *meta*-substituted substrates (**4e**: 68%; **4f**: 85%). It was also noticed that compounds containing electron-deficient groups at the *para*-position reduced the reaction activities, and the yields of corresponding products **4n** (47%), **4q** (56%), and **4r** (51%) were decreased. When chlorine was replaced by bromine and iodine, the reaction efficiency was improved and the yield of phenothiazine products **4o** (81%) and **4p** (65%) increased. Therefore, the electronic effects of phenyl had a significant effect on this consecutive C−S formation and relay C−N amination. Furthermore, the combination between disubstituted substrates and various substituents decreased their yields (**4s**: 38%, **4t**: 55%, **4u**: 45%), which indicated that the yield of this synthesis protocol was hindered by the aromatic ring. In conclusion, the *N*-phenylacetamide substrates bearing small electron-donating groups were favorable for the phenothiazine preparation, but the bulkier substituents were not suitable.

2-Bromothiophenol also contributed greatly to this one-pot tandem C−H thiolation and C−N annulation. The effects of 2-bromothiophenol derivatives with various substituents were explored (Scheme 4). Interestingly, as for the different

Scheme 4. Substrate Scope of 2-Bromothiophenol[a,b]



[a]Reaction conditions: *N*-phenylacetamide (1.20 mmol), 2-bromothiophenol (1.20 mmol), $[Cp^*RhCl_2]_2$ (0.060 mmol,5 mol %), AgOAc (3.60 mmol), $Cu(OTf)_2$ (0.24 mmol), and toluene (8 mL), reactions run in a sealed tube at 100 °C for 18 h. Then, N^1,N^2-dimethylethane-1,2-diamine(2.40 mmol) and Cs_2CO_3 (1.44 mmol) were added into the reaction mixture and stirred for another 2 h. [b]Isolated yields of phenothiazine derivatives.

structures of 2-bromothiophenol derivatives, the same phenothiazine products **4e**, **4g**, **4j**, and **4l** as those of *N*-phenylacetamide substrates could be obtained. The structure modification of 2-bromothiolphenol substrates was beneficial to the selective C−H thiolation at the C_2 or C_4 position and prompted the yield of corresponding product **4g** (**4g**: 37%). However, the desired phenothiazine product **4l** had a relatively low yield (55%), and the trifluoromethyl group was also tolerated by this transformation (**4v**: 61%). In summary, the 2-

https://doi.org/10.1021/acs.joc.1c00403
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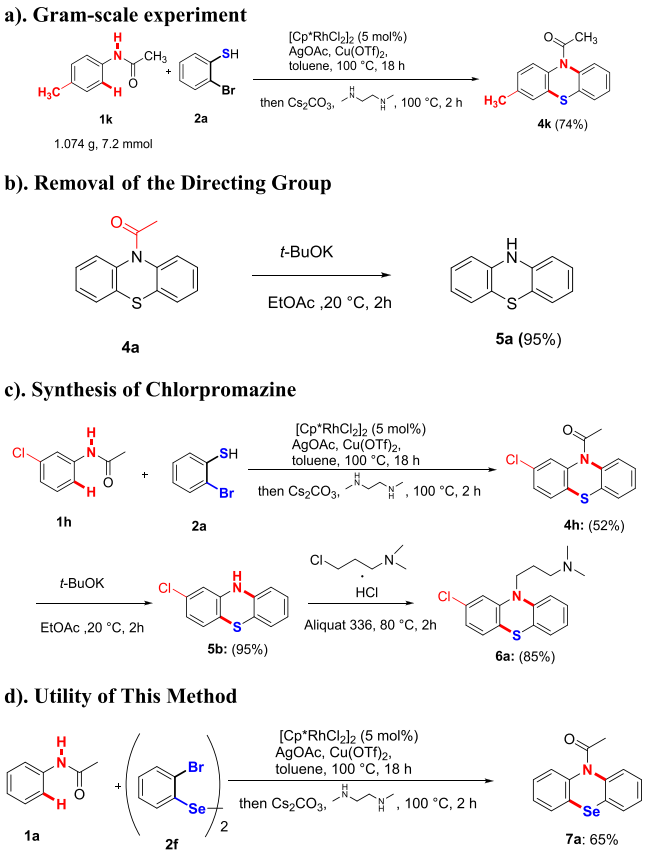
bromothiophenol derivatives exhibited the same trend as the *N*-phenylacetamide substrates where electron-rich groups were favorable for phenothiazine preparation.

To further evaluate the synthetic utilization and practicality of this methodology, a gram-scale synthesis was investigated under the standard reaction conditions (Scheme 5a). To our

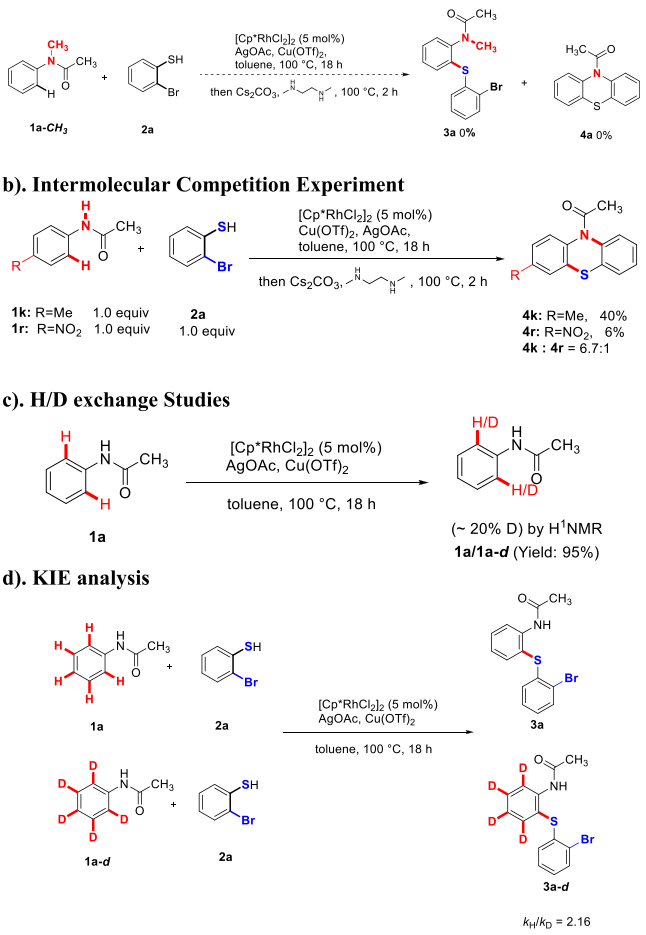
Scheme 5. (a–d) Further Studies of the Reaction



delight, while the reaction was scaled up to 7.2 mmol, the corresponding phenothiazine product **4k** was obtained in 74% yield, which proved that this protocol was practical. In addition, the directing group might limit the further structural modification of the substrate, and a method to remove the directing group became important for the applicability of this reaction. Interestingly, the acetyl directing group could be easily eliminated under mild conditions (Scheme 5b). Furthermore, chlorpromazine as a representative drug of phenothiazine could be acquired with high yield (Scheme 5c).[17] We also expanded the substrate scope to organo-selenium compounds, indicating that this approach was applicable to construct phenoselenazines (Scheme 5d).

To probe the reaction mechanism, we also carried out some control experiments. Once NH at *N*-phenylacetamide was replaced by *N*-methyl, the reaction did not transform smoothly (Scheme 6a). When employing *N*-Me acetanilide as a substrate, the conformation of *N*-Me acetanilide was changed, and thus it could not be employed as a directing group and the initial C–H thiolation reaction was ceased. This result indicated that C–H thiolation was triggered by a C–H activation progress, and the directing group was critical to the transformation. By conducting the intramolecular competition experiment, we found that the reaction ability of electron-

Scheme 6. (a–d) Control Experiments



withdrawing group **4r** (6%) was obviously weaker than the electron-donating group **4k** (40%) (Scheme 6b). Additionally, a H/D exchange study was also conducted. When the starting material **1a** was subjected to CH_3OD under the standard conditions, the resulting deuterium products **1a-*d*** were provided in 20% yield, and this revealed that C–H thiolation was reversible for the C–H activation (Scheme 6c). Finally, a kinetic isotopic effect (KIE) value (K_H/K_D) of 2.16 was observed, which demonstrated that the cleavage of the *ortho*-C–H bond of *N*-phenylacetamide was the rate-limiting step (Scheme 6d).

On the basis of the above experimental results and reported literature, we proposed a plausible mechanism for this one-pot reaction (Scheme 7).[18] Initially, the oxidant AgOAc and the additive $Cu(OTf)_2$ reacted with $[Cp^*RhCl_2]_2$ to provide the active cationic rhodium complex **I**. Subsequently, cationic rhodium complex **I** coordinated with amide of **1a** to generate a six-membered rhodium intermediate **II**, which then underwent metalation with **2a** to obtain metallacycle **III**. Then, the migratory insertion of **III** offers the intermediate **IV**, and as a result, the first C–H thiolation product **3a** was obtained after reductive elimination of intermediate **IV**, along with the remaining rhodium complex that was regenerated for the next catalytic cycle. The next step was that N^1,N^2-dimethylethane-1,2-diamine performed as a ligand and coordinated with the Cu(II) salt to generate a metallacycle **V**.[19] Then, the intermediate **V** attacked the NH of the amide, deprived a

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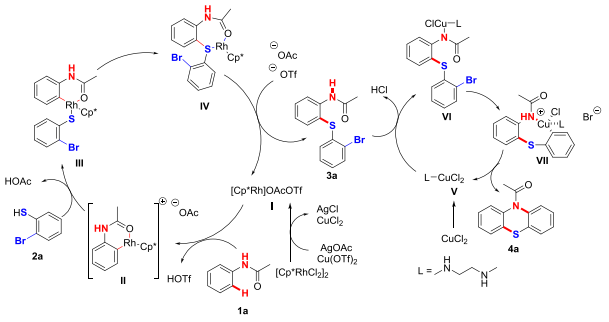
Scheme 7. Plausible Mechanism



hydrogen halide unit, and afforded the intermediate **VI**. Finally, with the elimination of the coupling intermediate **VII**, the target phenothiazine product **4a** was afforded in the presence of Cs_2CO_3 and the redundant Cu(II) complex was regenerated for the next catalytic cycle. Thus, $Cu(OTf)_2$ was not only selected as the additive for the initial C−H thiolation, but it could also be identified as the catalyst for the relay C−N annulation.

CONCLUSIONS

In conclusion, we first reported an efficient Rh(III)-catalyzed C−H thiolation of acetanilide and 2-bromothiophenol and relay Cu(II)-catalyzed C−N amination. Several phenothiazine products could be obtained from this one-pot tandem reaction. This synthesis protocol proceeds from easily accessible materials, demonstrating high atom economy, broad substrate scope, and good yield, and the directing group can be easily eliminated. Moreover, this method can be utilized for the synthesis of chlorpromazine in a large scale under convenient conditions. Therefore, this synthesis methodology has potential application in medicinal chemistry and organic synthesis.

EXPERIMENTAL SECTION

General Information. Reactions were run using standard tubes (10 and 100 mL). C−H activation was carried out in a sealed pressure tube purchased from Aladdin. Unless otherwise stated, all reactions and manipulations were performed under an atmosphere of air. Yields refer to isolated compounds, estimated to be >95% pure as determined by HPLC. All the solvents were used as received. All the chemicals were purchased from Shanghai Sun Chemical Technology Co., Ltd. and Shanghai Haohong Scientific Co., Ltd. For column chromatography, silica gel (80 Å) from HaiLang (Qingdao, China) was used. A series of ethyl acetate (EA)/light petroleum ether (PET) compositions were used to identify optimal detection for use with JiangYou (Yantai, China) TLC sheets (silica gel on aluminum foils with a fluorescence indicator (254 nm)). ^{1}H NMR, ^{13}C NMR, ^{19}F NMR spectroscopy, and high-resolution mass spectrometry (HRMS) were performed to characterize all isolated compounds. Furthermore, all the compounds were characterized using a melting point apparatus. Nuclear magnetic resonance spectra were recorded on a Bruker Avance III, 500 MHz instrument. All ^{1}H NMR experiments were reported in units of parts per million (ppm) and were measured relative to the signals for residual chloroform (7.28 ppm) or dimethyl sulfoxide (2.51 ppm) in the deuterated solvent, unless otherwise stated. All ^{13}C NMR spectra were reported in ppm relative to deuterated chloroform (77.01 ppm) or dimethyl sulfoxide (40.10 ppm), unless otherwise stated, and all were obtained with H decoupling. HRMS were measured using an ESI-QTOF mass spectrometer.

Experimental Procedure. 4-Methyl-*N*-phenylbenzenesulfonamide (**1a-2**),[20a] *N*-phenylpropionamide (**1a-3**),[20b] 3-(dimethylamino)-*N*-phenylpropanamide (**1a-4**),[20c] *N*-phenylpivalamide (**1a-5**),[20d] *N*-phenylbenzamide (**1a-6**),[20e] and substituted *o*-bromobenzenethiol (**2**)[21] were synthesized according to the previously reported procedures. *tert*-Butyl phenylcarbamate (**1a-7**) was purchased from Aladdin Biochemical Technology Co., Ltd. (Shanghai, China).

Synthesis of *N*-(Phenyl-d_5) Acetamide. A solution of acetyl chloride (0.4 mL, 0.432 g, 5.5 mmol) in DCM (1.5 mL) was slowly added at 0 °C to a colorless solution of benzen-d_5-amine (0.481 mL, 0.491 g, 5 mmol) and triethylamine (0.7 mL, 0.658 g, 6.5 mmol) in DCM (2.5 mL), which resulted in a white precipitate. After the reaction mixture was stirred for 4 h at room temperature, DCM was removed *in vacuo*. The resulting residue was purified by column chromatography (PET/EA = 4:1−1:1) to give the desired product. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.93 (s, 1H), 2.04 (s, 3H).

General Procedure for the Synthesis of Phenothiazine Derivatives 4a−4v (4a as an Example). *N*-Phenylacetamide **1** (1.20 mmol, 1.0 equiv), 2-bromothiophenol **2** (1.20 mmol, 1.0 equiv), $[Cp^*RhCl_2]_2$ (0.060 mmol), AgOAc (3.6 mmol, 3.0 equiv), $Cu(OTf)_2$ (0.24 mmol, 0.2 equiv), and toluene (8 mL) were added in a 10 mL vial, and the reaction mixture was stirred at 100 °C under air for 18 h. Then, N^1,N^2-dimethylethane-1,2-diamine (2.40 mmol, 2.0 equiv) and Cs_2CO_3 (1.44 mmol, 1.2 equiv) were added into the mixture, and the mixture was stirred at 100 °C for another 2 h. The mixture was cooled to room temperature and was filtered using celite, and the filtrate was extracted with ethyl acetate. The ethyl acetate layer was washed with brine, dried by anhydrous Na_2SO_4, and concentrated under vacuum to give the crude product. The crude product was then further purified by flash column chromatography on silica gel (PET/EA = 8:1).

Spectroscopic Data of All New Compounds. *1-(10H-Phenothiazin-10-yl)ethan-1-one (**4a**).* Compound **4a** was prepared from **1a** and **2a** following the general procedure. Purification by column chromatography on silica gel (PET/EA = 8:1) yielded **4a** (88%, 231 mg) as a white solid, mp: 200.1−202.3 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.63 (d, J = 7.9 Hz, 2H), 7.56 (dd, J = 7.8, 1.1 Hz, 2H), 7.42−7.39 (m, 2H), 7.33−7.30 (m, 2H), 2.13 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 168.9, 139.1, 132.4, 128.3, 127.9, 127.7, 127.4, 23.1. HRMS(ESI) m/z: [M + H]$^+$ calcd for $C_{14}H_{12}NOS$ 242.0640; Found 242.0629.

*1-(10H-Phenothiazin-10-yl)propan-1-one (**4a-3**).* Compound **4a-3** was prepared from **1a-3** and **2a** following the general procedure. Purification by column chromatography on silica gel (PET/EA = 8:1) yielded **4a-3** in 41% (125 mg) isolated yield as a purple oil. ^{1}H NMR (500 MHz, acetone): δ 7.64 (dd, J = 8.0, 1.2 Hz, 2H), 7.53 (dd, J = 7.8, 1.3 Hz, 2H), 7.40 (td, J = 7.7, 1.4 Hz, 2H), 7.31 (td, J = 7.6, 1.3 Hz, 2H), 2.49 (q, J = 7.3 Hz, 2H), 1.03 (t, J = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, acetone): δ 171.8, 139.3, 133.0, 127.74, 127.67, 127.1, 126.8, 27.4, 8.8. HRMS(ESI) m/z: [M + H]$^+$ calcd for $C_{15}H_{14}NOS$ 256.0796; Found 256.0801.

*tert-Butyl 10H-Phenothiazine-10-carboxylate (**4a-7**).* Compound **4a-7** was prepared from **1a-7** and **2a** following the general procedure. Purification by column chromatography on silica gel (PET/EA = 8:1) yielded **4a-7** as a white solid in 32% (115 mg) isolated yield. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.56 (d, J = 7.7 Hz, 2H), 7.45 (dd, J = 7.7, 0.7 Hz, 2H), 7.37−7.33 (m, 2H), 7.24 (t, J = 7.1 Hz, 2H), 1.43 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 151.9, 138.7, 131.6, 127.9, 127.8, 127.4, 126.8, 82.2, 28.1. HRMS(ESI) m/z: [M + H]$^+$ calcd for $C_{17}H_{18}NO_2S$ 300.1058; Found 300.1062.

*1-(1-Methyl-10H-phenothiazin-10-yl)ethan-1-one (**4b**).* Compound **4b** was prepared from **1b** and **2a** following the general procedure. Purification by column chromatography on silica gel (PET/EA = 8:1) yielded **4b** (132 mg, 43%) as a white solid. mp: 192.4−194.3 °C. ^{1}H NMR (500 MHz, DMSO-d_6):δ 7.78 (d, J = 7.7 Hz, 1H), 7.62 (d, J = 7.6 Hz, 1H), 7.46−7.42 (m, 1H), 7.40−7.33 (m, 2H), 7.25 (d, J = 7.1 Hz, 1H), 7.20 (t, J = 7.5 Hz, 1H), 2.32 (s, 3H), 2.04 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 168.4, 140.2, 138.2, 137.0, 134.5, 133.2, 129.5, 128.7, 128.2, 128.0, 127.9, 127.2, 125.8, 22.9, 18.6. HRMS(ESI) m/z: [M + H]$^+$ calcd for $C_{15}H_{14}NOS$ 256.0791; Found 256.0794.

https://doi.org/10.1021/acs.joc.1c00403
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*1-(1-Methoxy-10H-phenothiazin-10-yl)ethan-1-one (**4c**).* Compound **4c** was prepared from **1c** and **2a** following the general procedure. Purification by column chromatography on silica gel (PET/EA = 8:1) yielded **4c** (114 mg, 35%) as a white solid. mp: 164.7−166.3 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.54 (d, J = 4.0 Hz, 2H), 7.38−7.31 (m, 2H), 7.28 (d, J = 7.4 Hz, 1H), 7.18 (d, J = 7.7 Hz, 1H), 7.14 (d, J = 8.2 Hz, 1H), 3.92 (s, 3H), 1.99 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 169.4, 154.3, 139.2, 135.3, 132.2, 128.9, 128.5, 127.9, 127. 8, 127.3, 127.1, 120.6, 111.9, 56.5, 21.6. HRMS(ESI) m/z: [M + H]$^+$ calcd for $C_{15}H_{14}NO_2S$ 272.0745; Found 272.0748.

*1-(2-Methyl-10H-phenothiazin-10-yl)ethan-1-one (**4e**).* Compound **4e** was prepared from **1e** and **2a** following the general procedure. Meanwhile, **4e** was also prepared from **1a** and **2b** following the general procedure **4**. Purification by column chromatography on silica gel (PET/EA = 8:1) yielded **4e** (207 mg, 68% or 229 mg, 75%) as a yellow solid. mp: 198.9−200.1 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.61 (d, J = 7.9 Hz, 1H), 7.54 (d, J = 7.7 Hz, 1H), 7.46 (s, 1H), 7.42 (d, J = 8.0 Hz, 1H), 7.38 (t, J = 7.7, 1H), 7.29(t, J = 7.6, 1.2 Hz, 1H), 7.12 (d, J = 7.9 Hz, 1H), 2.33 (s, 3H), 2.12 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 168.9, 139.2, 139.1, 137.5, 132.8, 129.0, 128.3, 128.2, 128.1, 128.0, 127.9, 127.6, 127.3, 23.2, 21.0. HRMS(ESI) m/z: [M + H]$^+$ calcd for $C_{15}H_{14}NOS$ 256.0796; Found 256.0800.

*1-(2-Methoxy-10H-phenothiazin-10-yl)ethan-1-one (**4f**).* Compound **4f** was prepared from **1f** and **2a** following the general procedure. Purification by column chromatography on silica gel (PET/EA = 8:1) yielded **4f** (276 mg, 85%) as a white solid. mp: 180.1−182.2 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.60 (d, J = 7.9 Hz, 1H), 7.53 (d, J = 7.6 Hz, 1H), 7.44 (d, J = 8.7 Hz, 1H), 7.38 (t, J = 7.7 Hz, 1H), 7.30−7.27 (m, 2H), 6.92 (dd, J = 8.7, 2.6 Hz, 1H), 3.78 (s, 3H), 2.15 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 168.9, 159.3, 140.5, 139.2, 133.1, 128.8, 128.2, 127.9, 127.5, 127.3, 123.2, 113.8, 113.7, 56.1, 23.3. HRMS(ESI) m/z: [M + H]$^+$ calcd for $C_{15}H_{14}NO_2S$ 272.0745; Found 272.0750.

*1-(2-Fluoro-10H-phenothiazin-10-yl)ethan-1-one (**4g**).* Compound **4g** was prepared from **1g** and **2a** following the general procedure. Meanwhile, **4g** was also prepared from **1a** and **2e** following the general procedure **4**. Purification by column chromatography on silica gel (PET/EA = 8:1) yielded **4g** (96 mg, 31% or 115 mg, 37%) as a yellow solid. mp:216.3−217.6 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.62 (d, J = 7.9 Hz, 1H), 7.60−7.54 (m, 3H), 7.41 (t, J = 7.6 Hz, 1H), 7.32 (d, J = 15.0 Hz, 1H), 7.21−7.18 (m, 1H), 2.16 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 168.9, 161.5(d, $J_{C\text{-}F}$ = 242.6 Hz), 140.6, 138.7, 129.43, 129.35, 128.4, 127.9, 127.6, 115.5, 115.3, 114.9, 114.7, 23.2. ^{19}F NMR (471 MHz, DMSO-d_6): δ −114.74. HRMS(ESI) m/z: [M + H]$^+$ calcd for $C_{14}H_{11}FNOS$ 260.0540; Found 260.0543.

*1-(4-Fluoro-10H-phenothiazin-10-yl)ethan-1-one (**4g-1**).* Compound **4g-1** was prepared from **1g** and **2a** following the general procedure. Purification by column chromatography on silica gel (PET/EA = 8:1) yielded **4g-1** (65 mg, 21%) as a white solid. mp: 179.8−181.5 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.65 (d, J = 7.9 Hz, 1H), 7.62(d, J = 7.8 Hz, 1H), 7.51 (d, J = 7.9 Hz, 1H), 7.48−7.42(m, 2H), 7.34 (t, J = 7.5 Hz, 1H), 7.29 (t, J = 8.6 Hz, 1H), 2.15 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 169.0, 158.6(d, $J_{C\text{-}F}$ = 242.2 Hz), 141.0, 139.0, 128.8, 128.7, 128.6, 128.2, 128.1, 127.7, 124.0, 114.0, 113.8, 23.2. ^{19}F NMR (471 MHz, DMSO): δ −113.17. HRMS(ESI) m/z: [M + H]$^+$ calcd for $C_{14}H_{11}FNOS$ 260.0540; Found 260.0546.

*1-(2-Chloro-10H-phenothiazin-10-yl)ethan-1-one (**4h**).* Compound **4h** was prepared from **1h** and **2a** following the general procedure. Purification by column chromatography on silica gel (PET/EA = 8:1) yielded **4h** (172 mg, 52%) as a yellow solid. mp: 198.7−200.4 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.73(s, 1H), 7.63 (d, J = 7.9 Hz, 1H), 7.58−7.54 (m, 2H), 7.42 (td, J = 7.8, 1.3 Hz, 1H), 7.37 (dd, J = 8.4, 2.2 Hz, 1H), 7.32 (td, J = 7.7, 1.1 Hz, 1H), 2.14 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 168.9, 140.2, 138.7, 132.1, 132.0, 131.5, 129.4, 128.4, 128.0, 127.9, 127.8, 127.7, 127.4, 23.1. HRMS(ESI) m/z: [M + H]$^+$ calcd for $C_{14}H_{11}ClNOS$ 276.0244; Found 276.0248.

*1-(2-Nitro-10H-phenothiazin-10-yl)ethan-1-one (**4i**).* Compound **4i** was prepared from **1i** and **2a** following the general procedure. Purification by column chromatography on silica gel (PET/EA = 8:1) yielded **4i** (113 mg, 33%) as a yellow solid. mp: 157.3−159.1 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.44 (s, 1H), 8.15 (dd, J = 8.6, 1.9 Hz, 1H), 7.82 (d, J = 8.7 Hz, 1H), 7.70 (d, J = 7.9 Hz, 1H), 7.61 (d, J = 7.7 Hz, 1H), 7.47 (t, J = 7.6 Hz, 1H), 7.37 (t, J = 7.5 Hz, 1H), 2.19 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 169.0, 146.7, 141.3, 139.0, 138.1, 130.9, 128.9, 128.6, 128.5, 128.1, 127.9, 122.7, 122.1, 23.0. HRMS(ESI) m/z: [M + H]$^+$ calcd for $C_{14}H_{11}N_2O_3S$ 287.0490; Found 287.0485.

*1-(2-(Trifluoromethyl)-10H-phenothiazin-10-yl)ethan-1-one (**4j**).* Compound **4j** was prepared from **1j** and **2a** following the general procedure. Meanwhile, **4j** was also prepared from **1a** and **2d** following the general procedure **4**. Purification by column chromatography on silica gel (PET/EA = 8:1) yielded **4j** (159 mg, 43% or 186 mg, 50%) as a white solid. mp: 224.3−226.1 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.99 (s, 1H), 7.80 (d, J = 8.2 Hz, 1H), 7.70−7.65 (m, 2H), 7.60 (dd, J = 7.8, 1.3 Hz, 1H), 7.45−7.43 (m, 1H), 7.36−7.34 (m, 1H), 2.16 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 168.9, 139.2, 138.5, 137.8, 131.5, 129.2, 128.5, 128.3, 127.9, 124.70, 124.67, 124.3(q, $J_{C\text{-}F}$ = 270.6 Hz), 123.93, 123.90, 23.0. ^{19}F NMR (471 MHz, DMSO-d_6): δ −60.85. HRMS(ESI) m/z: [M + H]$^+$ calcd for $C_{15}H_{11}F_3NOS$ 310.0513; Found 310.0516.

*1-(3-Methyl-10H-phenothiazin-10-yl)ethan-1-one (**4k**).* Compound **4k** was prepared from **1k** and **2a** following the general procedure. Purification by column chromatography on silica gel (PET/EA = 8:1) yielded **4k** (564 mg, 92%) as a white solid. mp: 208.8−210.1 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.60 (d, J = 7.9 Hz, 1H), 7.53 (d, J = 7.7 Hz, 1H), 7.49 (d, J = 8.1 Hz, 1H), 7.40−7.35 (m, 2H), 7.29 (t, J = 7.5 Hz, 1H), 7.19 (d, J = 8.1 Hz, 1H), 2.31 (s, 3H), 2.11 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 169.0, 139.2, 137.1, 136.6, 132.4, 132.2, 128.4, 128.2, 127.9, 127.6, 127.459, 127.451, 127.3, 23.1, 20.8. HRMS(ESI) m/z: [M + H]$^+$ calcd for $C_{15}H_{14}NOS$ 256.0791; Found 256.0798.

*1-(3-Methoxy-10H-phenothiazin-10-yl)ethan-1-one (**4l**).* Compound **4l** was prepared from **1l** and **2a** following the general procedure. Meanwhile, **4l** was prepared from **1a** and **2d** following the general procedure **4**. Purification by column chromatography on silica gel (PET/EA = 8:1) yielded **4l** (289 mg, 89% or 179 mg, 55%) as a white solid. mp: 214.8−217.2 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.60 (d, J = 7.7 Hz, 1H), 7.53 (t, J = 9.2 Hz, 2H), 7.39 (t, J = 7.5 Hz, 1H), 7.30 (t, J = 7.5 Hz, 1H), 7.13 (d, J = 2.2 Hz, 1H), 6.95 (dd, J = 8.8, 2.6 Hz, 1H), 3.78 (s, 3H), 2.10 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 169.1, 158.0, 139.5, 131.9, 128.51, 128.49, 128.2, 127.9, 127.7, 127.3, 113.90, 113.88, 112.7, 56.1, 23.1. HRMS(ESI) m/z: [M + H]$^+$ calcd for $C_{15}H_{14}NO_2S$ 272.0740; Found 272.0745.

*1-(3-Ethoxy-10H-phenothiazin-10-yl)ethan-1-one (**4m**).* Compound **4m** was prepared from **1m** and **2a** following the general procedure. Purification by column chromatography on silica gel (PET/EA = 8:1) yielded **4m** (226 mg, 69%) as a white solid. mp: 204.5−206.8 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.60 (d, J = 7.6 Hz, 1H), 7.54 (dd, J = 7.7, 0.9 Hz, 1H), 7.51 (d, J = 8.6 Hz, 1H), 7.38−7.36 (m, 1H), 7.29 (t, J = 7.4 Hz, 1H), 7.10 (d, J = 2.6 Hz, 1H), 6.93 (dd, J = 8.8, 2.8 Hz, 1H), 4.04 (dd, J = 6.9, 2.6 Hz, 2H), 2.10 (s, 3H), 1.32 (t, J = 7.0 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 169.1, 157.3, 139.5, 131.8, 128.5, 128.2, 127.9, 127.8, 127.61, 127.58, 127.2, 114.3, 113.1, 64.1, 23.1, 15.0. HRMS(ESI) m/z: [M + H]$^+$ calcd for $C_{16}H_{16}NO_2S$ 286.0896; Found 286.0904.

*1-(3-Chloro-10H-phenothiazin-10-yl)ethan-1-one (**4n**).* Compound **4n** was prepared from **1n** and **2a** following the general procedure. Purification by column chromatography on silica gel (PET/EA = 8:1) yielded **4n** (156 mg, 47%) as a white solid. mp: 204.5−206.8 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.70 (d, J = 2.1 Hz, 1H), 7.66−7.61 (m, 2H), 7.57 (d, J = 7.7 Hz, 1H), 7.47−7.40 (m, 2H), 7.33 (t, J = 7.6 Hz, 1H), 2.13 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 168.9, 138.9, 137.9, 134.7, 131.7, 131.5, 130.3,

https://doi.org/10.1021/acs.joc.1c00403
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129.2, 128.4, 128.0, 127.9, 127.7, 127.6, 23.1. HRMS(ESI) m/z: $[M + H]^+$ calcd for $C_{14}H_{11}ClNOS$ 276.0250; Found 276.0244.

*1-(3-Bromo-10H-phenothiazin-10-yl)ethan-1-one (**4o**).* Compound **4o** was prepared from **1o** and **2a** following the general procedure. Purification by column chromatography on silica gel (PET/EA = 8:1) yielded **4o** (310 mg, 81%) as a white solid. mp: 196.9−198.8 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.81 (s, 1H), 7.64 (d, J = 7.9 Hz, 1H), 7.59−7.56 (m, 3H), 7.42 (t, J = 7.5 Hz, 1H), 7.32 (t, J = 7.6 Hz, 1H), 2.13 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 168.8, 138.9, 138.4, 135.0, 131.8, 130.5, 130.4, 129.5, 128.4, 128.0, 127.9, 127.6, 119.7, 23.1. HRMS(ESI) m/z: $[M + H]^+$ calcd for $C_{14}H_{11}BrNOS$ 319.9745; Found 319.9750.

*1-(3-Iodo-10H-phenothiazin-10-yl)ethan-1-one (**4p**).* Compound **4p** was prepared from **1p** and **2a** following the general procedure. Purification by column chromatography on silica gel (PET/EA = 8:1) yielded **4p** (286 mg, 65%) as a white solid. mp: 177.0−178.9 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.93 (d, J = 1.9 Hz, 1H), 7.72 (dd, J = 8.4, 1.9 Hz, 1H), 7.63 (d, J = 7.9 Hz, 1H), 7.55 (dd, J = 7.8, 1.2 Hz, 1H), 7.43−7.39 (m, 2H), 7.32−7.30 (m, 1H), 2.13 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 168.8, 138.9, 136.3, 136.1, 135.0, 131.8, 129.6, 128.4, 128.3, 127.93, 127.88, 127.6, 92.4, 23.1. HRMS(ESI) m/z: $[M + H]^+$ calcd for $C_{14}H_{11}INOS$ 367.9601; Found 367.9604.

*1-(3-(Trifluoromethyl)-10H-phenothiazin-10-yl)ethan-1-one (**4q**).* Compound **4q** was prepared from **1q** and **2a** following the general procedure. Purification by column chromatography on silica gel (PET/EA = 8:1) yielded **4q** (208 mg, 56%) as a white solid. mp: 185.2−187.3 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.97 (s, 1H), 7.83 (d, J = 8.4 Hz, 1H), 7.75 (dd, J = 8.4, 1.4 Hz, 1H), 7.68 (d, J = 7.4 Hz, 1H), 7.58 (dd, J = 7.8, 1.0 Hz, 1H), 7.43 (dd, J = 11.2, 4.1 Hz, 1H), 7.34 (dd, J = 11.2, 3.9 Hz, 1H), 2.17 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 168.8, 142.5, 138.5, 134.0, 131.7, 128.7, 128.5, 128.2, 127.9, 127.8, 125.4(q, J_{C-F} = 289.4 Hz), 125.2, 124.59, 124.56, 23.1. ^{19}F NMR (471 MHz, DMSO-d_6): δ −60.89. HRMS(ESI) m/z: $[M + H]^+$ calcd for $C_{15}H_{11}F_3NOS$ 310.0513; Found 310.0521.

*1-(3-Nitro-10H-phenothiazin-10-yl)ethan-1-one (**4r**).* Compound **4r** was prepared from **1r** and **2a** following the general procedure. Purification by column chromatography on silica gel (PET/EA = 8:1) yielded **4r** (175 mg, 51%) as a white solid. mp: 200.4−202.8 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.40 (d, J = 1.9 Hz, 1H), 8.22 (dd, J = 8.7, 2.0 Hz, 1H), 7.86 (d, J = 8.8 Hz, 1H), 7.69 (d, J = 7.9 Hz, 1H), 7.60 (d, J = 7.7 Hz, 1H), 7.45 (t, J = 7.5 Hz, 1H), 7.36 (t, J = 7.5 Hz, 1H), 2.19 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 168.8, 145.8, 144.5, 138.1, 134.4, 131.3, 128.7, 128.6, 128.4, 128.0, 127.8, 123.4, 122.8, 23.2. HRMS(ESI) m/z: $[M + H]^+$ calcd for $C_{14}H_{11}N_2O_3S$ 287.0490; Found 287.0485.

*1-(3-Chloro-1-fluoro-10H-phenothiazin-10-yl)ethan-1-one (**4s**).* Compound **4s** was prepared from **1s** and **2a** following the general procedure. Purification by column chromatography on silica gel (PET/EA = 8:1) yielded **4s** (134 mg, 38%) as a white solid. mp: 197.1−199.4 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.76 (s, 1H), 7.63−7.50 (m, 3H), 7.46 (s, 1H), 7.37 (s, 1H), 2.13 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 168.4, 157.8(d, J_{C-F} = 249.1 Hz), 138.7, 136.9, 132.3, 128.8, 128.3, 127.8, 126.0, 125.9, 123.5, 115.9, 115.7, 22.4. ^{19}F NMR (471 MHz, DMSO-d_6): δ −112.47. HRMS(ESI) m/z: $[M + H]^+$ calcd for $C_{14}H_{10}ClFNOS$ 294.0150; Found 294.0156.

*1-(2,3-Dimethyl-10H-phenothiazin-10-yl)ethan-1-one (**4t**).* Compound **4t** was prepared from **1t** and **2a** following the general procedure. Purification by column chromatography on silica gel (PET/EA = 8:1) yielded **4t** (178 mg, 55%) as a white solid. mp: 161.9−163.4 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.59 (d, J = 7.9 Hz, 1H), 7.53 (dd, J = 7.7, 0.9 Hz, 1H), 7.40−7.35 (m, 2H), 7.30−7.25 (m, 2H), 2.22 (s, 3H), 2.20 (s, 3H), 2.12 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 169.0, 139.4, 136.9, 136.2, 135.9, 132.7, 129.0, 128.6, 128.4, 128.2, 127.9, 127.4, 127.2, 23.2, 19.5, 19.3. HRMS(ESI) m/z: $[M + H]^+$ calcd for $C_{16}H_{16}NOS$ 270.0947; Found 270.0954.

*1-(1,3-Dimethyl-10H-phenothiazin-10-yl)ethan-1-one (**4u**).* Compound **4u** was prepared from **1u** and **2a** following the general procedure. Purification by column chromatography on silica gel (PET/EA = 8:1) yielded **4u** (145 mg, 45%) as a white solid. mp: 177.5−180.1 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.74 (d, J = 7.6 Hz, 1H), 7.59 (d, J = 7.5 Hz, 1H), 7.42 (t, J = 7.3 Hz, 1H), 7.34 (t, J = 7.3 Hz, 1H), 7.18 (s, 1H), 7.05 (s, 1H), 2.27 (s, 6H), 2.02 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 168.5, 140.4, 136.7, 136.5, 135.7, 134.5, 132.8, 130.2, 128.5, 128.2, 127.9, 127.8, 126.0, 22.9, 20.8, 18.5. HRMS(ESI) m/z: $[M + H]^+$ calcd for $C_{16}H_{16}NOS$ 270.0953; Found 270.0956.

*1-(3-Methoxy-7-(trifluoromethyl)-10H-phenothiazin-10-yl)-ethan-1-one (**4v**).* Compound **4v** was prepared from **1v** and **2c** following the general procedure. Purification by column chromatography on silica gel (PET/EA = 8:1) yielded **4v** (248 mg, 61%) as a white solid. mp: 194.9−196.3 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.97 (d, J = 1.3 Hz, 1H), 7.80 (d, J = 8.4 Hz, 1H), 7.75 (dd, J = 8.4, 1.8 Hz, 1H), 7.57 (d, J = 8.8 Hz, 1H), 7.17 (d, J = 2.8 Hz, 1H), 6.99 (dd, J = 8.8, 2.8 Hz, 1H), 3.79 (s, 3H), 2.14(s, 3H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 169.1, 158.3, 142.9, 133.9, 133.1, 131.2, 128.7, 128.5, 127.8, 124.29, 125.28 (q, J_{C-F} = 279.7 Hz), 124.5, 114.3, 112.9, 56.2, 23.1. ^{19}F NMR (471 MHz, DMSO-d_6): δ −60.83. HRMS(ESI) m/z: $[M + H]^+$ calcd for $C_{16}H_{13}F_3NO_2S$ 340.0619; Found 340.0614.

*10H-Phenothiazine (**5a**).* 1-(10*H*-Phenothiazin-10-yl)ethan-1-one **4a** (0.62 mmol) was dissolved in freshly distilled EtOAc (7 mL), and potassium *tert*-butoxide (0.75 mmol) was added to a flame-dried 25 mL two-neck flask under a nitrogen atmosphere. The reaction mixture was stirred at 20 °C for 2 h and quenched with water. The reaction mixture was partitioned between water and EtOAc. The organic layer was collected, dried over anhydrous sodium sulfate, filtered, concentrated, and purified by silica gel column chromatography using PET/EA = 4:1 as an eluent in increasing polarity to afford the desired compounds **5a** (117.4 mg, 95%). ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.58 (s, 1H), 7.00−6.98 (m, 2H), 6.91 (dd, J = 7.6, 1.2 Hz, 2H), 6.75−6.72 (m, 2H), 6.70 (dd, J = 7.9, 1.1 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 142.5, 128.0, 126.7, 122.2, 116.8, 114.9. HRMS(ESI) m/z: $[M + H]^+$ calcd for $C_{12}H_{10}NS$ 200.0534; Found 200.0538.

*2-Chloro-10H-phenothiazine (**5b**).* The compound **4h** was prepared from **1h** and **2a** following the general procedure **4**. Purification was done by column chromatography on silica gel; 1-(2-chloro-10*H*-phenothiazin-10-yl)ethan-1-one **4h** (0.62 mmol) was dissolved in freshly distilled EtOAc (7 mL), and potassium *tert*-butoxide (0.75 mmol) was added to a flame-dried 25 mL two-neck flask under a nitrogen atmosphere. The reaction mixture was stirred at 20 °C for 2 h and quenched with water. The reaction mixture was partitioned between water and EtOAc. The organic layer was collected, dried over anhydrous sodium sulfate, filtered, concentrated, and purified by silica gel column chromatography using PET/EA = 4:1 as an eluent in increasing polarity to afford the desired compounds **5b** (137.7 mg, 95%). ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.76 (s, 1H), 7.01−6.98 (m, 1H), 6.93 (d, J = 2.1 Hz, 1H), 6.91 (d, J = 2.8 Hz, 1H), 6.81−6.77 (m, 2H), 6.70 (d, J = 2.2 Hz, 1H), 6.67 (dd, J = 7.9, 1.0 Hz, 1H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): 144.0, 141.5, 132.3, 128.2, 127.9, 126.8, 122.8, 121.7, 116.5, 116.0, 115.1, 114.2. HRMS(ESI) m/z: $[M + H]^+$ calcd for $C_{12}H_9NClS$ 234.0144; Found 234.0140.

*3-(2-Chloro-10H-phenothiazin-10-yl)-N,N-dimethylpropan-1-amine (**6a**).* 2-Chlorophenothiazine **5b** (0.59 mmol), KOH (1.42 mmol), 3-chlorodimethylaminopropyl hydrochloride (0.59 mmol), and Aliquat 336 (0.02 mmol) were heated for 2 h at 80 °C. After the mixture had cooled to room temperature, 0.5 g of silica gel was added to retain the catalyst. The mixture was extracted three times with 25 mL of diethyl ether. The crude chlorpromazine was purified by column chromatography (PET/EA/Et_3N = 1:2:0.2) to afford **6a** (159.9 mg, 85%). ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.25−7.20 (m, 1H), 7.17−7.13 (m, 2H), 7.07 (d, J = 1.8 Hz, 1H), 7.06−7.01 (m, 2H), 6.99−6.96 (m, 1H), 3.90 (t, J = 6.8 Hz, 2H), 2.30 (t, J = 6.7 Hz,

https://doi.org/10.1021/acs.joc.1c00403
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2H), 2.10 (s, 6H), 1.77 (t, J = 6.8 Hz, 2H). HRMS(ESI) m/z: $[M + H]^+$ calcd for $C_{17}H_{20}N_2ClS$ 319.1036; Found 319.1026.[22]

*1-(10H-Phenoselenazin-10-yl)ethan-1-one (**7a**).* Compound **7a** was prepared from **1a** and **2f** following the general procedure **4**. Purification by column chromatography on silica gel (PET/EA = 8:1) yielded **7a** (224 mg, 65%) as a yellow oil. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.71 (d, J = 7.6 Hz, 2H), 7.68−7.56 (m, 2H), 7.41 (dd, J = 11.1, 4.1 Hz, 2H), 7.28 (t, J = 7.4 Hz, 2H), 2.05 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 168.9, 139.6, 130.9, 128.6, 128.01, 127.99, 127.6, 23.2. HRMS(ESI) m/z: $[M + H]^+$ calcd for $C_{14}H_{12}NOSe$ 290.0084; Found 290.0088.

*N-(2-((2-Bromophenyl)thio)phenyl)acetamide (**3a**).* *N*-Phenylacetamide **1a** (1.20 mmol, 1.0 equiv), *o*-bromobenzenethiol **2a** (1.20 mmol, 1.0 equiv), $[Cp^*RhCl_2]_2$ (0.060 mmol), AgOAc (3.6 mmol, 3.0 equiv), $Cu(OTf)_2$ (0.24 mmol, 0.2 equiv), and toluene (8 mL) were added in a 10 mL vial, and the reaction mixture was stirred at 100 °C under air for 18 h. Then, the mixture was cooled to room temperature and was filtered using celite and the filtrate was extracted with ethyl acetate. The ethyl acetate layer was washed with brine, dried by anhydrous Na_2SO_4, and concentrated under vacuum to give the crude product. The crude product was then further purified by flash column chromatography on silica gel (PET/EA = 8:1) to afford **3a** as a white solid. Yield: 243 mg (48%). ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.53 (s, 1H), 7.69 (dd, J = 7.8, 7.7 Hz, 2H), 7.45 (t, J = 7.7 Hz, 1H), 7.39 (d, J = 7.6 Hz, 1H), 7.24 (q, J = 8.1 Hz, 2H), 7.14 (t, J = 7.1 Hz, 1H), 6.73 (d, J = 7.6 Hz, 1H), 1.98 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 169.6, 140.6, 138.3, 135.8, 133.9, 130.7, 130.0, 129.4, 128.8, 127.2, 126.7, 126.2, 122.9, 24.2. HRMS(ESI) m/z $[M + H]^+$ calcd for $C_{14}H_{13}BrNOS$ 321.9901; Found 321.9898.

Gram-Scale Experiments. A mixture of substrate **1k** (7.2 mmol), **2a** (7.2 mmol), $[Cp^*RhCl_2]_2$ (0.360 mmol), AgOAc (21.6 mmol), and $Cu(OTf)_2$ (1.4 mmol) was placed in a 100 mL glass vial and dissolved in 48 mL of toluene. The vial was placed in a preheated hot block. After that, the mixture was heated at 100 °C with a heating mantle and stirred for 18 h. Then, N^1,N^2-dimethylethane-1,2-diamine (14.4 mmol) and Cs_2CO_3 (8.64 mmol) were added into the reaction mixture and stirred at 100 °C for 2 h. The mixture was cooled to room temperature and was filtered using celite, and the filtrate was extracted with ethyl acetate. The ethyl acetate layer was washed with brine, dried by anhydrous Na_2SO_4, and concentrated under vacuum to give the crude product. The crude product was then further purified by flash column chromatography on silica gel (PET/EA = 8:1) to supply the product. Yield: **4k** 1.356 g, 74%.

Control Experiments. A mixture of substrate 1a-CH_3 (1.20 mmol), **2a** (1.20 mmol), $[Cp^*RhCl_2]_2$ (0.060 mmol), AgOAc (3.60 mmol, 3.0 equiv), $Cu(OTf)_2$ (0.24 mmol, 0.2 equiv), and toluene (8 mL) was added in a 10 mL vial, and the reaction mixture was stirred at 100 °C under air for 18 h. Then, N^1,N^2-dimethylethane-1,2-diamine (2.40 mmol) and Cs_2CO_3 (1.44 mmol) were added into the mixture, and the mixture was stirred at 100 °C for another 2 h. The mixture was cooled to room temperature, and TLC was used to monitor reaction progress.

Intermolecular Competition. A mixture of **1k** (1.20 mmol), **1r** (1.20 mmol), **2a** (1.20 mmol), $[Cp^*RhCl_2]_2$ (0.060 mmol), AgOAc (3.60 mmol), $Cu(OTf)_2$ (0.24 mmol), and toluene (8 mL) was added in a 10 mL vial, and the reaction mixture was stirred at 100 °C under air for 18 h. Then, N^1,N^2-dimethylethane-1,2-diamine (2.40 mmol) and Cs_2CO_3 (1.44 mmol) were added into the mixture, and the mixture was stirred at 100 °C for another 2 h. The mixture was cooled to room temperature and was filtered using celite, and the filtrate was extracted with ethyl acetate. The ethyl acetate layer was washed with brine, dried by anhydrous Na_2SO_4, and concentrated under vacuum to give the crude product. The crude product was then further purified by flash column chromatography on silica gel (PET/EA = 8:1) to supply the product. Yield: **4k** 122 mg, 40%; **4r** 21 mg, 6%.

KIE Studies. **1a** (1.20 mmol)/**1a-*d*** (1.20 mmol), $[Cp^*RhCl_2]_2$ (0.060 mmol), AgOAc (3.6 mmol), and $Cu(OTf)_2$ (0.24 mmol) contained in two separate tubes were added to a solution of **2a** (1.2 mmol) in toluene (8 mL). Then, the reaction mixture was heated at 100 °C with a heating mantle under air. The corresponding yield of each time was determined by HPLC. A kinetic isotope effect value K_H/K_D = 2.16 was calculated.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c00403.

Optimization data and NMR spectral data of all compounds included (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge the National Science Foundation of China (nos. 81573304 and 81703342), Natural Science Foundation of Jiangsu (no. BK20161050), Natural Science Foundation of Nanjing University of Chinese Medicine (no. NZY81703342), and Postgraduate Research & Practice Innovation Program of Jiangsu Province (no. KYCX19_1261).

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