OL | Organic Letters

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

Silver-Catalyzed Site-Selective Ring-Opening and C−C Bond Functionalization of Cyclic Amines: Access to Distal Aminoalkyl-Substituted Quinones

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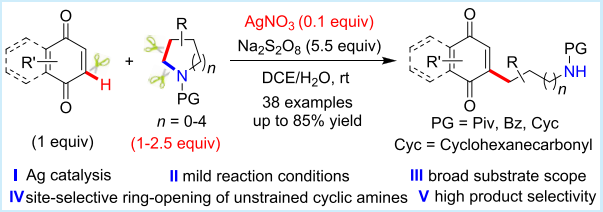
Supporting Information

ABSTRACT: Distal aminoalkyl-substituted quinones have been efficiently prepared through silver-catalyzed site-selective deconstruction and C−C bond transformation of unstrained *N*-acylated cyclic amines. This method enjoys mild reaction conditions, high selectivity, a broad scope of substrates, and a low catalytic loading of silver. This strategy can also be applied to the modification of peptides bearing cyclic amine residues.



Quinone, a vital scaffold, is present in medicines, functional materials, and natural products.[1] Quinone derivatives possess a broad spectrum of biological and pharmacological activities in living organisms for their unique properties of electron and proton metastasis.[2,3] Among them, many aminoalkyl-substituted quinones exhibit pharmacological activities (Figure 1).[3] Considering the significance of function-

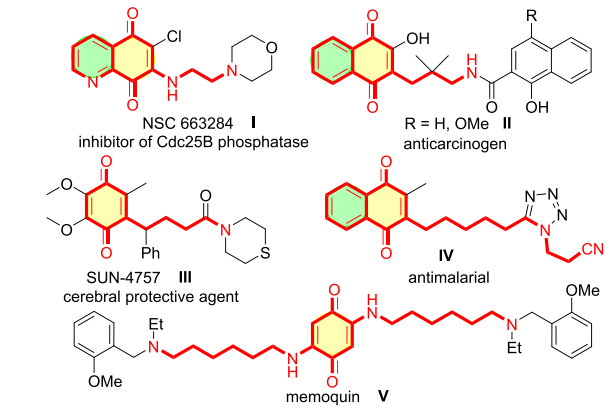


Figure 1. Drugs and bioactive molecules containing aminoalkyl-substituted quinones.

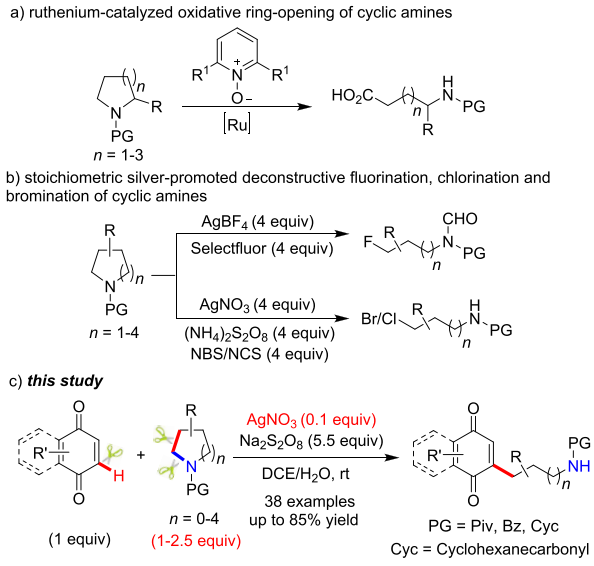
alized quinones, a great deal of tactics for the incorporation of simple aryl and alkyl groups into quinones have been developed.[4] However, the construction of aminoalkyl-substituted quinones has been rarely achieved.[5] In those sparse strategies, the multistep transformation[3b] or the use of diversity-limited short chain amino acids as starting materials has to be relied on.[5] The research on the directly preparation of aminoalkyl-substituted quinones from the multitudinous and readily available sources still remains challenging.

Catalytic ring-opening and C−C bond functionalization of strained cyclic compounds has been well explored in the past few years for their privileged advantages to modifying and reorganizing the scaffolds of commonplace compounds to more valuable molecules.[6] However, the unstrained cyclic compounds are seldom used in these strategies because of their inherent low ring-strain energy.[7] Saturated unstrained *N*-heterocycles such as piperidines and pyrrolidines are plentiful and useful chemicals. Their frameworks are widely distributed in many natural products and pharmaceutical molecules including proline, paroxetine, and pholcodine. Thus, the transformation of simple cyclic amines to more complex compounds and the modification of pharmaceutical molecules bearing cyclic amines groups are both attractive to chemists and pharmacologists.[7a−e,8] Among them, most strategies focus on the direct functionalization of C−H bonds on cyclic amines,[9] whereas the deconstruction of cyclic amines involving the heterocyclic ring-opening and C−C transformation to reorganize their core skeletons have less been achieved.[7a−e] Higuchi's group presented the first transformation of *N*-acylated cyclic amines to amino acids by ruthenium-catalyzed oxidative ring-opening of cyclic amines (Scheme 1, a).[7a] Very recently, Sarpong's group reported an unprecedented stoichiometric silver-promoted deconstructive fluorination of cyclic amines through an alkoxy radical-involved process (Scheme 1, b).[7b] The same group also developed a protocol for the deconstructive chlorination and bromination of cyclic amines through a different process of sequential C−N cleavage and C−C bond conversion by using stoichiometric amount of silver salt (Scheme 1, b).[7c] Given the importance of deconstructive functionalization of cyclic amines, we herein report the first silver-catalyzed oxidative ring-opening/degra-

Received: April 29, 2019

DOI: 10.1021/acs.orglett.9b01496
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 1. Methods for the Ring-Opening and Functionalization of *N*-Acylated Cyclic Amines

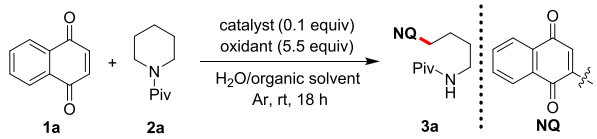


dation/C−C functionalization of cyclic amines by the reaction of them with simple quinones (Scheme 1, c). From economic and environmental perspective, the low catalytic loading of silver salt will be useful to reduce the cost of practical deconstructive conversion of cyclic amines. This method was also successfully applied to the transformation of various peptides bearing cyclic amine residues. Consequently, a variety of aminoalkyl-substituted quinones were effectively prepared by this strategy.

We initiated this research by subjecting a mixture of 1,4-naphthoquinone **1a** and *N*-pivaloyl piperidine **2a** to the dark conditions of $Na_2S_2O_8$ and $AgPF_6$ in 1,2-dichloroethane aqueous solution under argon atmosphere for 18 h. The desired reaction occurred spontaneously at room temperature, giving aminoalkyl-substituted quinones **3a** in 45% yield (Table 1, entry 1). Encouraged by the result, we subsequently screened a series of silver catalysts such as AgOAc, $AgNO_3$, and AgTFA (Table 1, entries 2−4). All of those silver salts promoted this reaction readily, $AgNO_3$ was selected as the best catalyst, and the yield of **3a** was increased to 81% (Table 1, entry 3). In contrast, other transition-metal catalysts such as $Cu(NO_3)_2{\cdot}3H_2O$ and $Fe(NO_3)_3{\cdot}9H_2O$ were inoperative in this reaction (Table 1, entries 5 and 6). Next, a variety of organic and inorganic oxidants were also investigated. Besides $Na_2S_2O_8$, $(NH_4)_2S_2O_8$ and $K_2S_2O_8$ were applicable oxidants for this tactic as well, delivering **3a** in comparable yields (Table 1, entries 7 and 8). Peroxides such as TBHP and DTBP were ineffective for this reaction (Table 1, entries 9 and 10). No better result was obtained when other organic solvents such as acetone, DCM, toluene, and acetonitrile were involved (Table 1, entries 11−14). Moreover, no reaction took place without either silver salts or peroxysulfates (Table 1, entries 15 and 16). The yield of **3a** could not be further improved by screening the dosage of $AgNO_3$ (Table 1, entries 17 and 18).

Having established the optimum conditions (Table 1, entry 3), the scope of *N*-acylated cyclic amines **2** was first examined (Scheme 2). Piperidines **2a−c** with various *N*-protecting groups such as Piv (pivaloyl), Bz (benzoyl), and Cyc (cyclohexanecarbonyl) participated readily in this strategy, affording the desired products **3a−c** in nice yields. The

Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	organic solvent[f]	oxidant	yield[b] (%)
1	$AgPF_6$	DCE	$Na_2S_2O_8$	45
2	AgOAc	DCE	$Na_2S_2O_8$	80
3	$AgNO_3$	DCE	$Na_2S_2O_8$	81
4	AgTFA	DCE	$Na_2S_2O_8$	70
5	$Cu(NO_3)_2{\cdot}3H_2O$	DCE	$Na_2S_2O_8$	0
6	$Fe(NO_3)_3{\cdot}9H_2O$	DCE	$Na_2S_2O_8$	0
7	$AgNO_3$	DCE	$(NH_4)_2S_2O_8$	79
8	$AgNO_3$	DCE	$K_2S_2O_8$	76
9	$AgNO_3$	DCE	TBHP	0
10	$AgNO_3$	DCE	DTBP	0
11	$AgNO_3$	acetone	$Na_2S_2O_8$	15
12	$AgNO_3$	DCM	$Na_2S_2O_8$	76
13	$AgNO_3$	$PhCH_3$	$Na_2S_2O_8$	17
14	$AgNO_3$	CH_3CN	$Na_2S_2O_8$	7
15		DCE	$Na_2S_2O_8$	0
16[c]	$AgNO_3$	DCE		0
17[d]	$AgNO_3$	DCE	$Na_2S_2O_8$	61
18[e]	$AgNO_3$	DCE	$Na_2S_2O_8$	79

[a]Reaction conditions: quinone **1a** (0.2 mmol, 1 equiv), amine **2a** (0.2 mmol, 1 equiv), catalyst (0.02 mmol, 0.1 equiv), solvent (2 mL of H_2O and 0.4 mL of organic solvent), rt, Ar, dark, 18 h. [b]Isolated yield. [c]$AgNO_3$ (0.8 mmol, 4 equiv) was used as the oxidant. [d]$AgNO_3$ (0.01 mmol, 0.05 equiv) was used. [e]$AgNO_3$ (0.03 mmol, 0.15 equiv) was used. [f]DCE = 1,2-dichloroethane, DCM = dichloromethane, TBHP = *tert*-butyl hydroperoxide, DTBP = di-*tert*-butyl peroxide.

generation of product **3c** was accompanied by the formation of a small amount of *N*-formyl byproduct **3c′**. In addition, piperidines **2d−h** bearing a 4-substituent, such as Me, MeO, Ph, CO_2Me, or F, were all compatible for the reaction, providing the corresponding products **3d−h** in moderate to good yields. Notably, 2-methylpiperidine **2i** was a good candidate to react with **1a** via the eminently site-selective ring-opening, giving rise to product **3i** in satisfying yield. Product **3j** was obtained in excellent yield when 3,5-dimethylpiperidine **2j** was used for the reaction, promising the successful conversion of the tertiary carbon in the tactic. Both spiropiperidine **2k** and fused piperidine **2l** could be used as the reaction partners with **1a**, furnishing the corresponding products **3k** and **3l** in moderate yields. Among them, the slightly lower yields of **3g** and **3k** could be attributed to the easy oxidation of both the benzylic C−H bond of **2g** and the activated C−H bonds of glycol ether moiety of **2k** to form complex mixtures in the reaction. Significantly, morpholine **2m** was a befitting partner for this reaction, providing the product **3m** in 65% yield. Besides piperidine, the cyclic amines **2n−q** with different ring sizes transformed smoothly in this reaction, gaining the quinones bearing aminoalkyl chains of varying lengths in good yields (**3n−q**). A small amount of *N*-formyl byproduct **3q′** was obtained when **2q** was involved. When cyclic amines bearing a chiral ester group such as methyl (*S*)-piperidine-2-carboxylate **2r** and L-proline methyl ester **2s** were subjected to this reaction, the chirality retained products **3r** and **3s** were formed in moderate to good yields.

DOI: 10.1021/acs.orglett.9b01496
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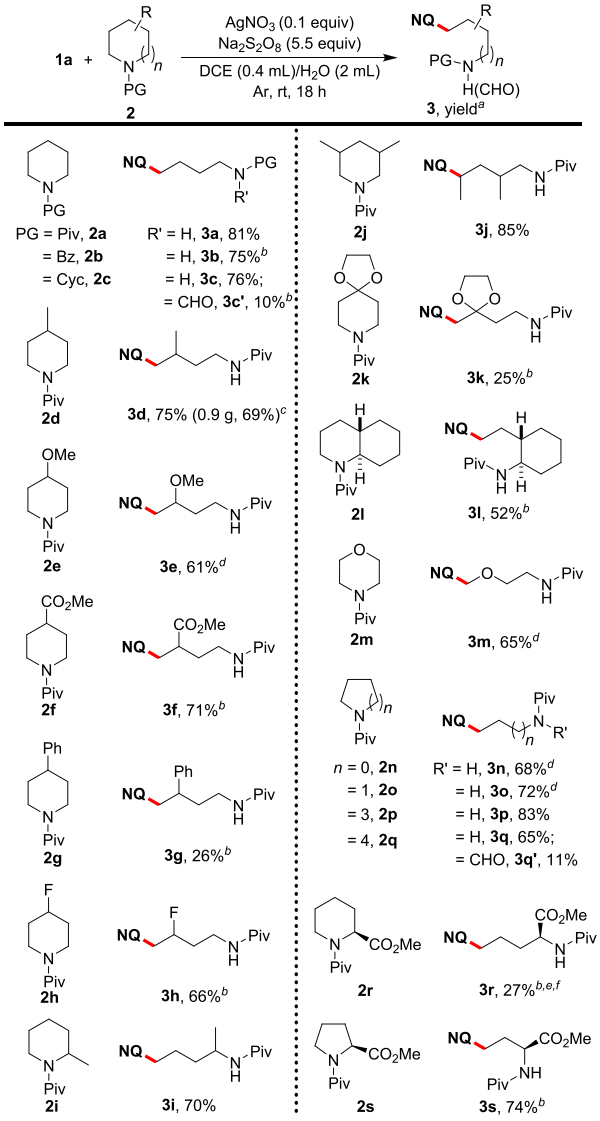
Scheme 2. Scope of Cyclic Amines

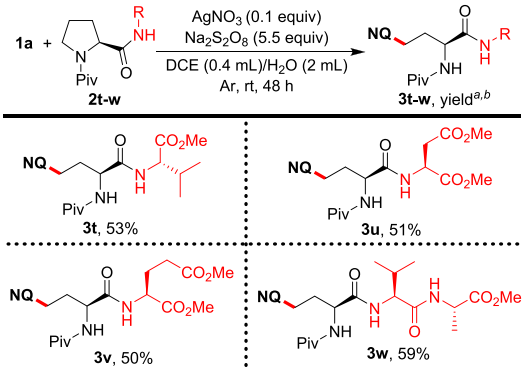


[a]Isolated yields. [b]Amine **2** (0.5 mmol, 2.5 equiv) was used, and the reaction time was prolonged to 30 h. [c]Quinone **1a** (4.0 mmol) and amine **2** (4.0 mmol, 1.0 equiv) were used, and the reaction time was prolonged to 30 h. [d]Amine **2** (0.24 mmol, 1.2 equiv) was used. [e]The reaction time was prolonged to 48 h. [f]67% of **1a** and 86% of **2r** were recovered.

To further verify the utility of this approach, peptides containing cyclic amine residues were also investigated (Scheme 3). Dipeptides **2t**–**v** derived from the condensation of L-proline with various amino acid derivatives such as L-valine, L-aspartic acid, and L-glutamic acid reacted with **1a** very well, affording the chirality retained products **3t**–**v** in moderate yields. L-Proline-involved tripeptide **2w** was also a suitable reactant for this protocol and generated the corresponding **3w** in 59% yield.

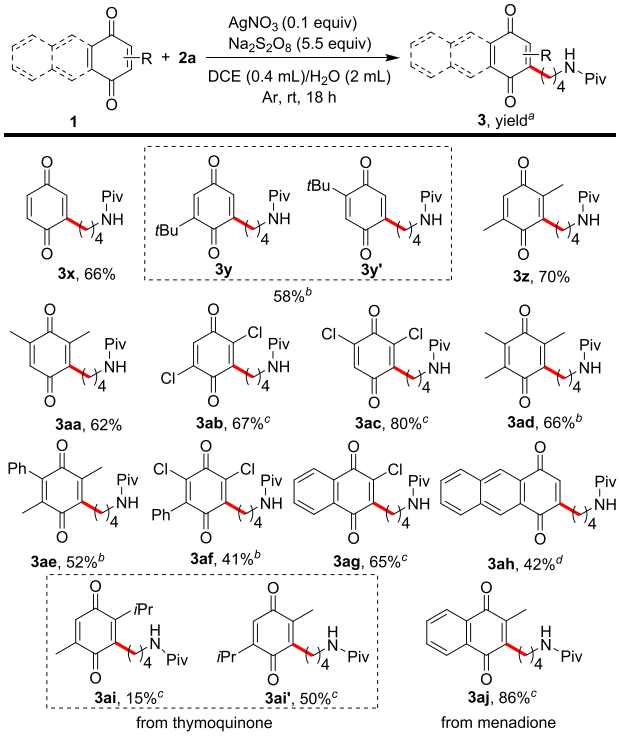
Next, the scope of quinones was examined by their reaction with **2a**, and the results are described in Scheme 4. Unsubstituted benzoquinone proceeded smoothly and gave the anticipated product **3x** in 66% yield. When asymmetric monosubstituted benzoquinone participated in the reaction, as in the case of 2-*tert*-butylbenzoquinone, a mixture of the positional isomers **3y** and **3y′** was procured in 58% yield. A

Scheme 3. Transformations of Di- and Tripeptides Containing L-Proline Residue



[a]Isolated yields. [b]Amine **2** (0.5 mmol, 2.5 equiv) was used, and the reaction time was prolonged to 48 h.

Scheme 4. Scope of Quinones



[a]Isolated yields. [b]Amine **2a** (0.5 mmol, 2.5 equiv) was used, and the reaction time was prolonged to 48 h. [c]Amine **2a** (0.3 mmol, 1.5 equiv) was used, and the reaction time was prolonged to 30 h. [d]DCM (1 mL) was used.

variety of disubstituted and trisubstituted benzoquinones were all applicable for this conversion, providing the desired products **3z**–**af** in moderated to good yields. In addition, when 2-Cl-1,4-naphthoquinone and 1,4-anthraquinone were subjected to the reaction, the desired products **3ag** and **3ah** were formed in 65% and 42% yields, respectively. It is worth noting that thymoquinone,[10a] which possesses anticancer activity, was also applicable to this strategy and provided the desired products **3ai** and **3ai′** in a combined yield of 65%. Moreover, menadione,[10b] a drug for the treatment of hypoprothrombinemia, participated very well in the reaction, producing the desired product **3aj** in 86% yield.

DOI: 10.1021/acs.orglett.9b01496
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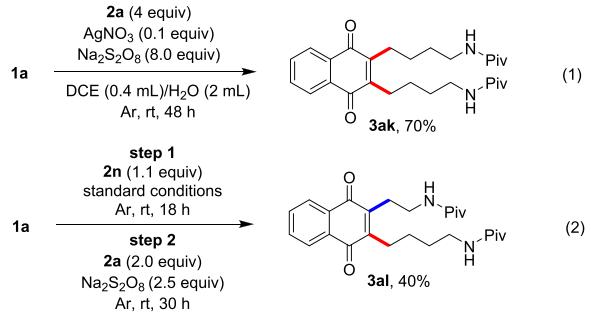
The protocol was also suitable for the synthesis of disubstituted quinones by incorporating symmetrical and nonsymmetrical aminoalkyl chains in one pot. By increasing the usage amount of amine **2a** and oxidants, symmetrical disubstituted product **3ak** was efficiently synthesized (Scheme 5, eq 1). In addition, nonsymmetrical diaminoalkyl-substituted

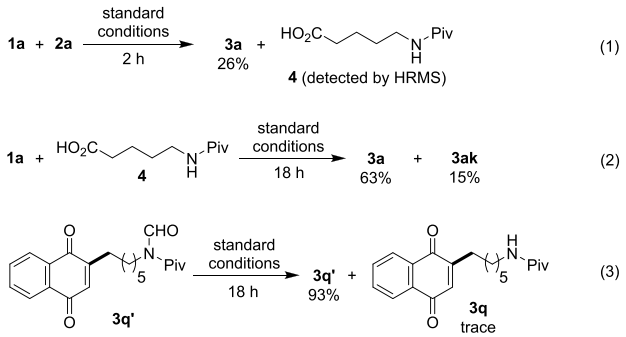
Scheme 5. Synthesis of Symmetrical and Nonsymmetrical Diaminoalkyl-Substituted Naphthoquinones



naphthoquinone **3al** could be easily prepared by the sequential addition of different cyclic amines to the reaction in one pot (Scheme 5, eq 2).

To shed light on the mechanism of this reaction, control experiments were carried out (Scheme 6). When the sample

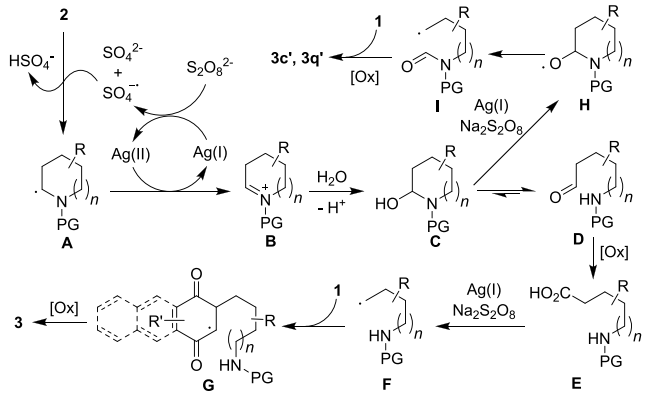
Scheme 6. Control Experiments



reaction was interrupted after 2 h, 26% of **3a** was obtained and the *N*-acylated amino acid **4** was detected by the HRMS from the reaction system (Scheme 6, eq 1). When the *N*-acylated amino acid **4** was subjected to the optimal conditions, the desired product **3a** was formed in 63% yield accompanied by the symmetrical disubstituted byproduct **3ak** in 15% yield. This result clearly indicates that the aminoalkyl-substituted quinone was produced by silver-catalyzed radical decarboxylation of *N*-acylated amino acid to generate the degraded aminoalkyl radical, which then occurred alkylation with quinone (Scheme 6, eq 2). Notably, the *N*-formyl product **3q′** could not be transformed to **3q** under the optimal conditions (Scheme 6, eq 3). This result manifests that the formation of **3q** did not experience the deformylation process of *N*-formyl product **3q′**.[7b]

On the grounds of previous studies on deconstructive conversion of cyclic amines and the results of control experiments, a possible mechanism is proposed in Scheme 7. Initially, Ag(I) reacts with persulfate anion to form the Ag(II), sulfate, and sulfate radical anion.[11a] *N*-Acylated cyclic amine **2** reacts first with a sulfate radical anion via a hydrogen atom

Scheme 7. Proposed Mechanism



transfer (HAT) process to yield the C-radical intermediate **A** which is subsequently oxidized by Ag(II) to give the iminium ion **B**.[7b,c,11b] Compound **B** is immediately trapped by water to generate hemiaminal **C**, which is in equilibrium with the linear aldehyde **D** via C−N cleavage of cyclic amine.[7a−d] The intermediate **D** is subsequently oxidized to *N*-acylated amino acid **E**, which further undergoes the well-known silver-catalyzed radical decarboxylation to yield the corresponding alkyl radical **F**.[12] In the capture of **F** by quinone **1** to form the carbon radical **G**, the latter is finally oxidized to product **3**. On the other hand, hemiaminal **C** can also experience a competitive reaction through silver-catalyzed oxidation to produce the alkoxy radical **H**. The radical ring-opening of **H** gives the corresponding alkyl radical **I** as well. The interception of **I** by quinone **1**, followed by subsequent oxidation, yields the byproduct **3c′** or **3q′**.

In summary, a facile and practical silver-catalyzed oxidative strategy of tandem site-selective ring-opening/carbon degradation/C−C bond functionalization of *N*-acylated cyclic amines has been developed by using quinones and cyclic amines as the commercially available starting materials and persulfate as the oxidant. By using this method, a variety of distal aminoalkyl-substituted quinones were effectively prepared. Moreover, this protocol features mild reaction conditions, high product selectivity, and broad substrate scope. The site-selective chemical modification of the core framework of peptides bearing cyclic amine residues by installing useful quinones might find applications in new bioactive molecules and pharmaceutical discovery.[13]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01496.

Detailed experimental procedures and spectral data for all products (PDF)

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DOI: 10.1021/acs.orglett.9b01496
Org. Lett. XXXX, XXX, XXX−XXX

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the National Natural Science Foundation of China (Nos. 21873041, 21632001, and 21422205), the Fundamental Research Funds for the Central Universities (Nos. lzujbky-2016-ct02 and lzujbky-2016-ct08), Program for the Changjiang Scholars and Innovative Research Team in University (IRT-15R28), and the "111" Project for financial support.

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DOI: 10.1021/acs.orglett.9b01496
Org. Lett. XXXX, XXX, XXX−XXX