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Intermolecular Oxidative Radical Addition to Aromatic Aldehydes: Direct Access to 1,4- and 1,5-Diketones via Silver-Catalyzed Ring-Opening Acylation of Cyclopropanols and Cyclobutanols

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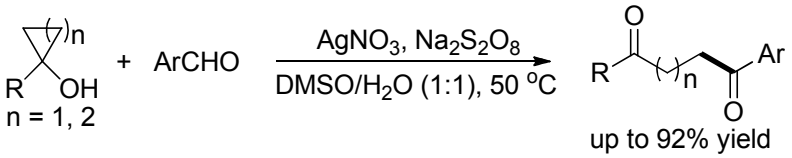


A novel silver-catalyzed ring-opening acylation of cyclopropanols and cyclobutanols is described. The reaction proceeds under mild and neutral conditions and provides a facile access to nonsymmetric 1,4- and 1,5-diketones in promising yields with broad substrate scope. Mechanistic studies including DFT calculations suggest the involvement of an uncommon water-assisted 1,2-HAT process, which is strongly exothermic and thus promotes addition of carbon radicals to aldehydes. In contrast to traditional reductive radical addition protocols, this work represents the first example on the intermolecular oxidative radical addition to aldehydes, thus offering a novel strategy for the direct synthesis of acyclic ketones from readily accessible aldehydes.

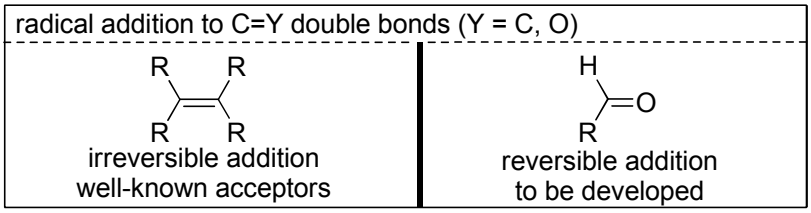
INTRODUCTION

Among the ketone family, 1,4- and 1,5-diketones are common substructures of natural products, medicinal compounds, and functional materials. Moreover, they are versatile building blocks for the assembly of five- or six-membered cycles, including cyclopentenone, thiophene, furan, pyrrole, cyclohexenone, and pyridine derivatives.[1] Therefore, the exploration of efficient methods for the creation of these entities, especially from readily accessible starting materials, has received considerable attention in organic chemistry.[2-7] So far, traditional methods include the conjugate addition of acyl anions or enolates to Michael acceptors,[2] nucleophilic substitution[3] or metal-catalyzed

cross-coupling of α-haloketones,[4] oxidative coupling of enolates,[5] radical addition to alkenes,[6] and Rh-catalyzed hydroacylation.[7] Despite the great progress achieved in this field, the previous reports have focused on the synthesis of either 1,4- or 1,5-diketones, and the development of general methods allowing the construction of both 1,4- and 1,5-diketones remains unexplored.

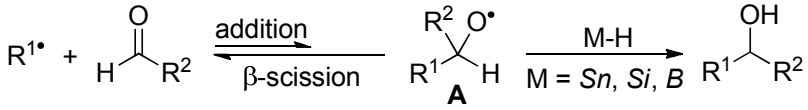
Over the past decades, catalytic radical reactions have become very powerful tools for chemical synthesis. With the rapid development of this area, expanding the scope of radical acceptors is highly demanded. So far, C-C double bonds are the most widely used acceptors for radical addition. In contrast, C-O double bonds have been rarely employed as radical acceptors, since addition of radicals to aldehydes is reversible and the equilibrium lies in favor of β-scission, hence converting the alkoxy radical **A** back into aldehydes (Scheme 1a, top).[8] To facilitate the addition, fast reduction of the alkoxy radical **A** is a common strategy.[9,10] For example, Ryu and co-workers achieved an unprecedented hydroxymethylation of alkyl halides using paraformaldehyde as the radical acceptor and tetrabutylammonium cyanoborohydride as the hydrogen source.[10c] However, the intermolecular addition of carbon radicals to advanced aldehydes still constitutes an unmet goal. Very recently, Glorius disclosed a well-designed strategy for the intermolecular radical addition to carbonyls through visible-light photoredox initiated hole catalysis and in situ Brønsted acid activation of C-O double bonds (Scheme 1a, bottom).[11] It should be noted that these methods fall into the type **I** reaction, reductive radical addition, thus delivering alcohols as final products. On the other hand, oxidative radical addition to aldehydes affording ketones (type **II**), instead of alcohols, still poses a significant challenge. By taking advantage of the intramolecular strategy, we have developed a new methodology[12] for the direct synthesis of cyclic ketones via oxidative radical addition to aldehydes (Scheme 1b, top).[12a] However, the intermolecular oxidative radical addition to aldehydes, permitting the formation of acyclic ketones, is more challenging and has not been achieved yet.

Scheme 1. Intermolecular Addition of Carbon Radicals to Aldehydes

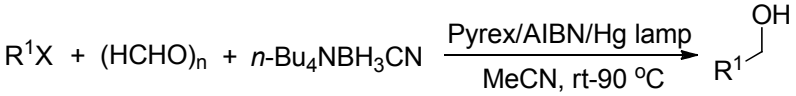


(a) type **I**: reductive radical addition, forming alcohols

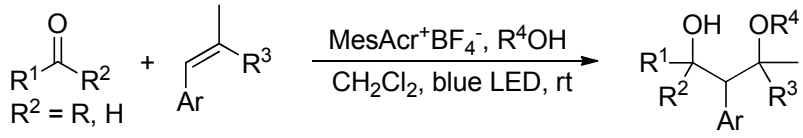
a common strategy: fast reduction



Ryu's work: first intermolecular reductive radical addition to $(HCHO)_n$

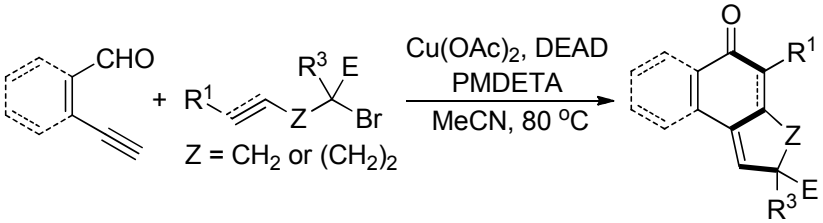


Glorius's strategy: Bronsted acid activation

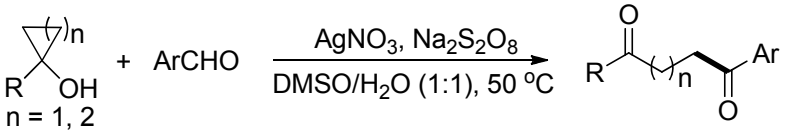


(b) type **II**: oxidative radical addition, forming ketones

previous work: intramolecular oxidative radical addition to aldehydes



this work: first intermolecular oxidative radical addition to aldehydes

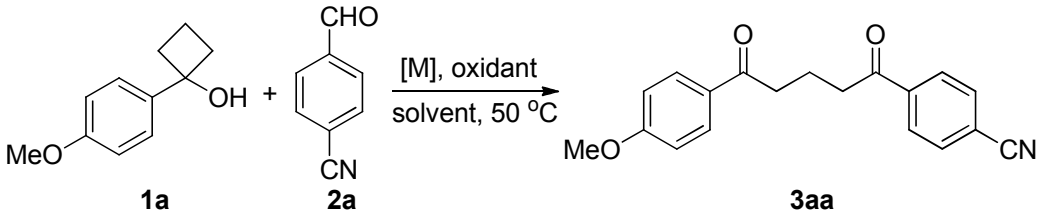


The radical ring-opening of cyclopropanols and cyclobutanols, has emerged as a highly appealing method for the synthesis of functionalized ketones.[13,14] For example, Zhu et. al discovered a series of protocols for the efficient preparation of β- or γ-fluoro, azido, cyano, alkynyl, or thiolated ketones, through Mn- or Ag-catalyzed C-C bond cleavage of cyclopropanols or cyclobutanols.[13] Chen and co-workers achieved a novel visible-light-induced alkynylation or alkenylation of cyclopropanols and cyclobutanols using cyclic iodine(III) reagent catalysis.[14h] Inspired by these elegant works, we envisioned that the strain release might offer an opportunity for the realization of intermolecular

addition of carbon radicals to aldehydes. Herein, we report the first intermolecular oxidative radical addition to aromatic aldehydes, initiated by Ag-catalyzed ring-opening of cyclopropanols and cyclobutanols, which produces both 1,4- and 1,5-diketones under mild and neutral reaction conditions (Scheme 1b, bottom). DFT calculations indicate that an unusual water-assisted 1,2-HAT is involved in the catalytic cycle. Moreover, the water-assisted 1,2-HAT is strongly exothermic, thus offering a driving force for achieving the thermodynamically unfavorable addition of carbon radicals to aldehydes. Clearly, it will be valuable for the development of novel reactions using aldehydes as radical acceptors.

RESULTS AND DISCCUSION

Table 1. Optimization of Reaction Conditions[a]



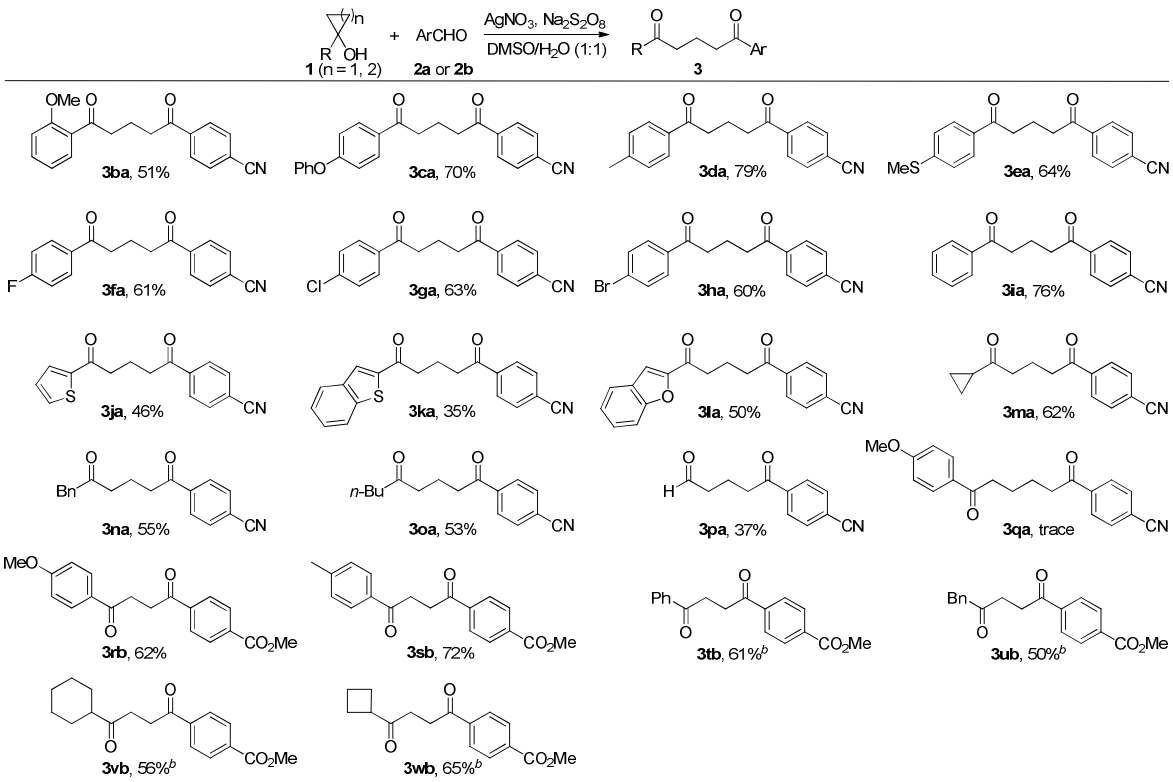
1a **2a** **3aa**

entry	[M]	oxidant	solvent	yield (%)[b]
1[c]	$Mn(OAc)_3$	none	MeCN	nr
2[d]	$Mn(OAc)_3$	BIOH	MeCN	nr
3	$Mn(OAc)_3$	$PhI(OAc)_2$	MeCN	nr
4	$AgNO_3$	$Na_2S_2O_8$	MeCN	nr
5	$AgNO_3$	$Na_2S_2O_8$	MeCN/H_2O (1:1)	5
6	$AgNO_3$	$Na_2S_2O_8$	acetone/H_2O (1:1)	16
7	$AgNO_3$	$Na_2S_2O_8$	DMF/H_2O (1:1)	10
8	$AgNO_3$	$Na_2S_2O_8$	DMSO/H_2O (1:1)	85
9	$AgNO_3$	$Na_2S_2O_8$	DMSO	12
10	$AgBF_4$	$Na_2S_2O_8$	DMSO/H_2O (1:1)	68
11	AgOTf	$Na_2S_2O_8$	DMSO/H_2O (1:1)	31
12	AgOAc	$Na_2S_2O_8$	DMSO/H_2O (1:1)	45
13	$AgNO_3$	$(NH_4)_2S_2O_8$	DMSO/H_2O (1:1)	45
14	$AgNO_3$	$K_2S_2O_8$	DMSO/H_2O (1:1)	23
15	none	$Na_2S_2O_8$	DMSO/H_2O (1:1)	trace
16	$AgNO_3$	none	DMSO/H_2O (1:1)	nr

[a]Reaction conditions: **1a** (0.75 mmol), **2a** (0.25 mmol), [M] (10 mol %), oxidant (0.75 mmol), solvent, under N_2, 50 °C, 16 h. [b]Isolated yield. [c]0.75 mmol of $Mn(OAc)_2$ was used. [d]Run at 70 °C. nr = No reaction.

Initially, we chose the cyclobutanol **1a** and aldehyde **2a** as model substrates to evaluate the reaction parameters. In the presence of 3 equiv of $Mn(OAc)_3$, no detectable product **3aa** was observed (Table 1, entry 1). Zhu's conditions, including the $Mn(OAc)_3$/BIOH[13b] and $Mn(OAc)_3$/$PhI(OAc)_2$ combination,[13c] were totally ineffective for the reaction (entries 2 and 3). To our delight, upon treatment with 10 mol % of $AgNO_3$ and 3 equiv of $Na_2S_2O_8$ in a 1:1 mixture of DMSO and H_2O at 50 ^oC for 16 h, 85% yield of the 1,5-diketone **3aa** was obtained (entry 8). In contrast, a dramatic decrease in the yield (12%) was observed when the reaction was conducted in dry DMSO (entry 9), thus highlighting the crucial role of water in this reaction. Other silver salts, such as $AgBF_4$, AgOTf, and AgOAc, were less efficient for the transformation (entries 10-12). Switching the oxidant from $Na_2S_2O_8$ to $K_2S_2O_8$ or $(NH_4)_2S_2O_8$ resulted in a decline of the yield (entries 13 and 14). Both the silver catalyst and oxidant are essential for the transformation, since no reaction occurred in the absence of $AgNO_3$ or $Na_2S_2O_8$ (entries 15 and 16). Therefore, the optimized reaction conditions for Ag-catalyzed cycloalkanol ring-opening acylation comprised 10 mol % of $AgNO_3$ and 3 equiv of $Na_2S_2O_8$ in a 1:1 mixture of DMSO and H_2O at 50 ^oC for 16 h.

Scheme 2. Scope of Cyclopropanols and Cyclobutanols[a]



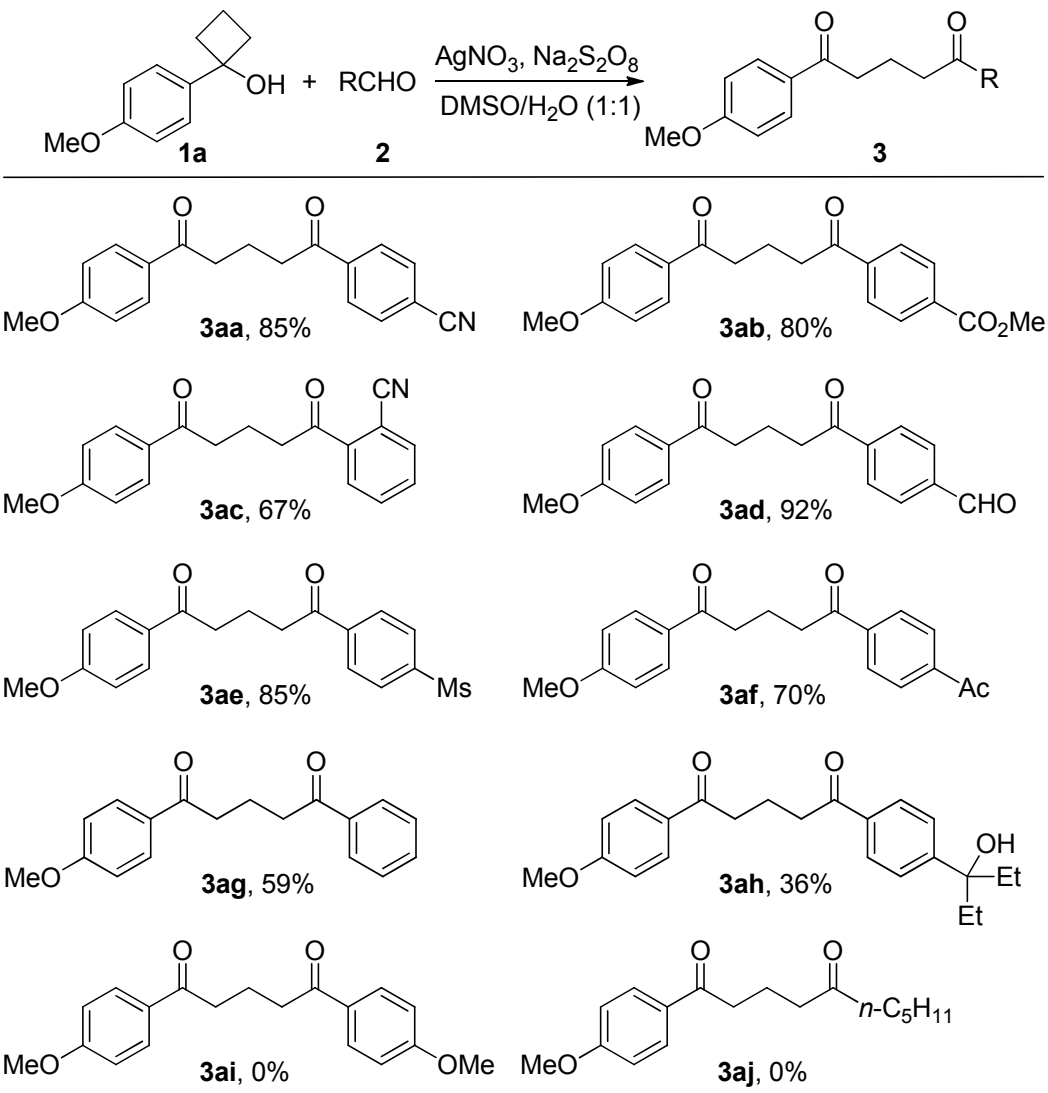
[a]Reaction conditions: **1** (0.75 mmol), **2** (0.25 mmol), $AgNO_3$ (10 mol %), $Na_2S_2O_8$ (0.75 mmol), DMSO/H_2O (v/v = 1:1), under N_2, 50 ^oC, 16 h. Isolated yields were reported. [b]12 h.

With the optimized reaction conditions in hand, the scope of this reaction with respect to cyclopropanols and cyclobutanols were explored, and the results are summarized in Scheme 2. A variety of cyclobutanols were first tested. Compared with the reaction of **1a**, the *ortho*-methoxy substrate **1b** led to the production of **3ba** in a relatively lower yield (51%). The increased steric hindrance of **1b** may account for the decline of yield. Halogen atoms including fluoro, chloro, and bromo were well tolerated under the reaction conditions, which may be attractive for further manipulations via transition-metal-catalyzed cross-coupling reactions (**3fa**-**3ha**). In addition, heterocycles, such as thiophene, benzo[*b*]thiophene, and benzofuran, were also compatible for the process (**3ka**-**3la**). The reaction of alkyl-substituted cyclobutanols took place smoothly as well, producing **3ma**-**3oa** in good yields. Besides tertial cyclobutanols, secondary cyclobutanols also worked well for this reaction. For example, the coupling of **1p** with **2a** formed **3pa** in 37% yield. In contrast, the cyclopentanol **1q** was incompatible with the reaction. For cyclopropanols, the reaction

with the aldehyde **2b** occurred efficiently to afford a set of 1,4-diketones in promising yields (**3rb-3wb**). Therefore, we have developed a broadly applicable method for the construction of both 1,4- and 1,5-diketones.

In the meantime, we examined the reactivity of various aldehydes (Scheme 3). As compared to **2a**, the reaction of **2c** led to the generation of 1,5-diketone **3ac** in a slightly lower yield (67%), again highlighting the influence of steric hindrance. Benzaldehydes possessing strong electron-withdrawing groups, such as CO_2Me, CHO, Ms, and Ac, were excellent coupling partners, giving **3ab**, and **3ad-3af** in 70-92% yields. In contrast, PhCHO (**2g**) was transformed into the desired 1,5-diketone **3ag** in 59% yield. These results indicated that the electronic effect of the aryl ring of **2** has an important impact on the reaction efficiency. Furthermore, **2h**, a compound with a free hydroxy group, was also suitable substrate, albeit in a moderate yield (**3ah**). Unfortunately, 4-methoxybenzaldehyde (**2i**) and alkyl aldehyde **2j** were ineffective substrates (**3ai** and **3aj**).

Scheme 3. Scope of Aldehydes[a]

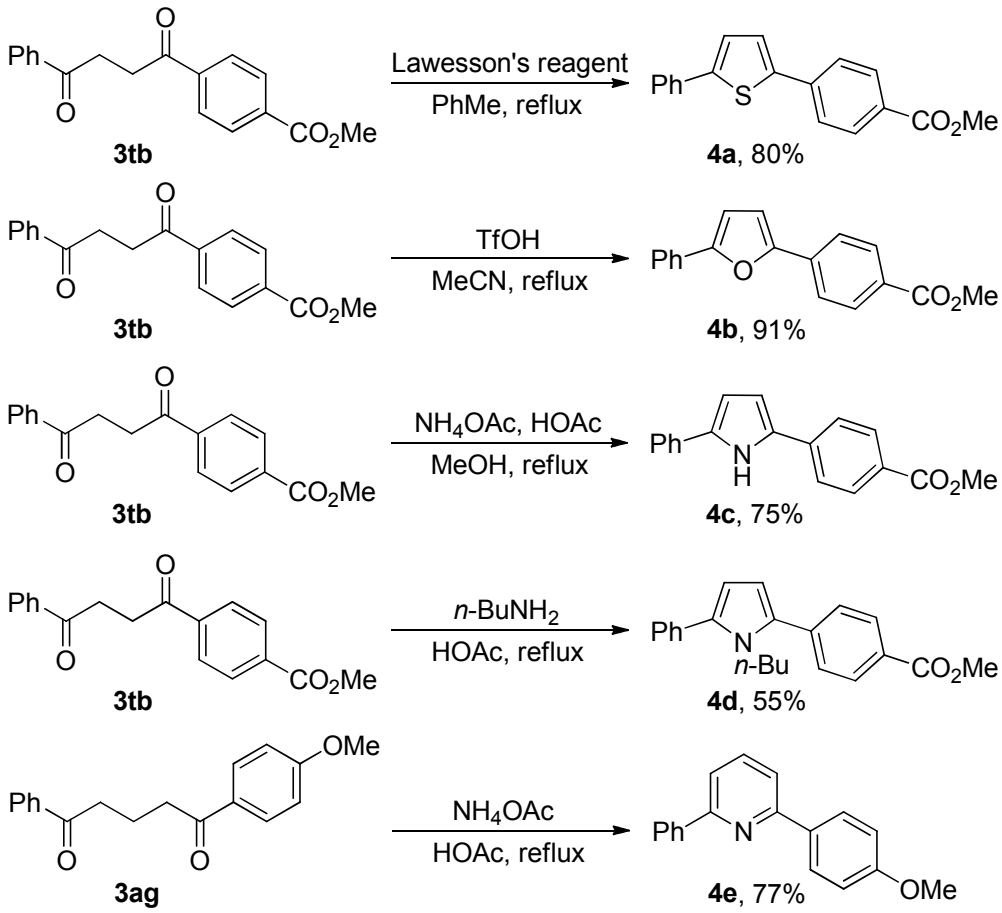


[a]Reaction conditions: **1a** (0.75 mmol), **2** (0.25 mmol), $AgNO_3$ (10 mol %), $Na_2S_2O_8$ (0.75 mmol), DMSO/H_2O (v/v = 1:1), under N_2, 50 ^oC, 16 h. Isolated yields were reported.

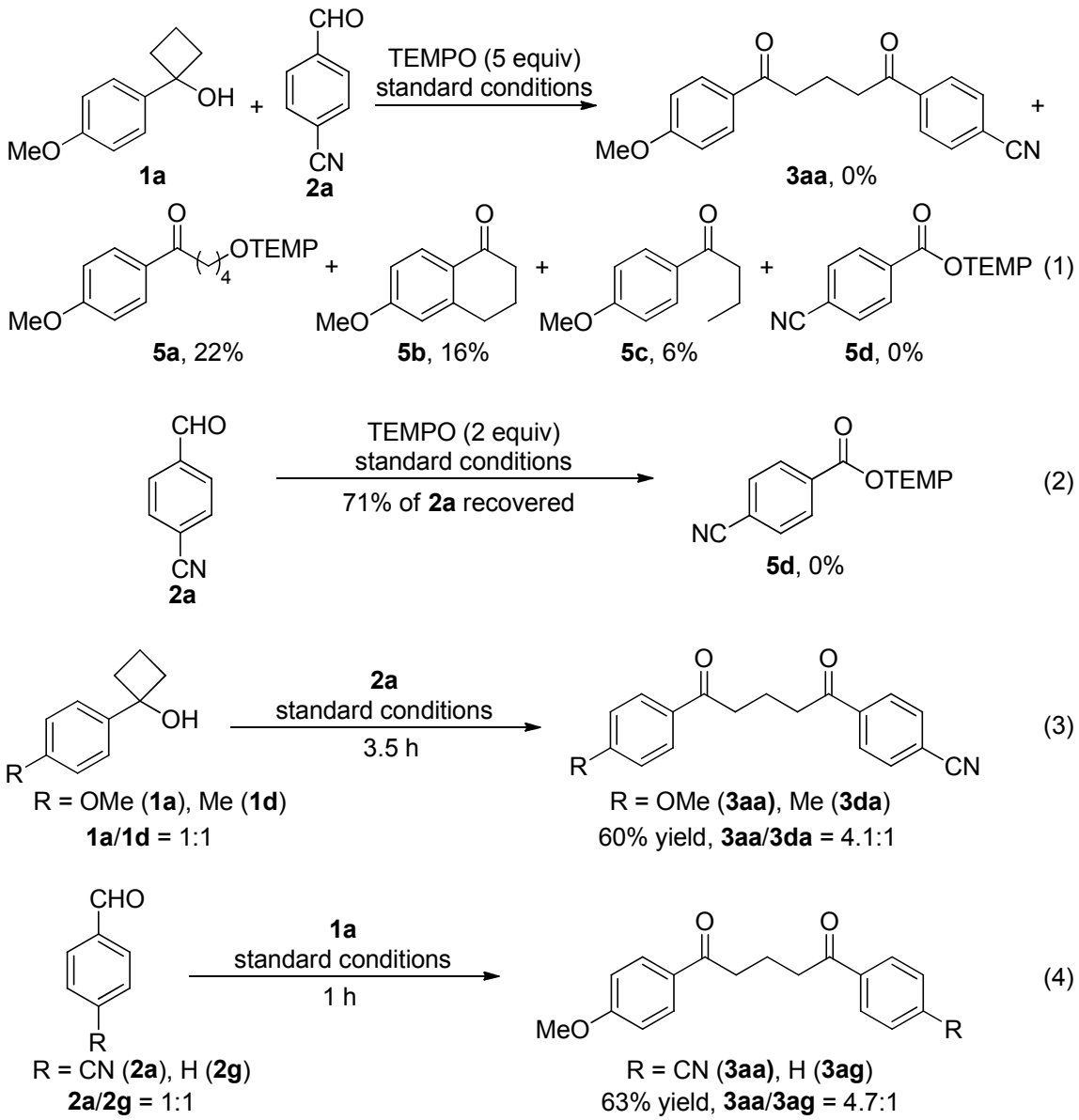
As mentioned before, 1,4- and 1,5-diketones are versatile building blocks for the synthesis of carbo- and heterocycles. As such, the transformation of resultant 1,4- or 1,5-diketones was then conducted (Scheme 4). Upon treatment of **3tb** with Lawesson's reagent in refluxing toluene for 6 h, the 2,5-disubstituted thiophene **4a** was obtained in 80% yield. In the presence of TfOH, **3tb** was converted into the furan product **4b** in 91% yield. Cyclization of **3tb** with either NH_4OAc or *n*-$BuNH_2$ successfully produced the pyrrole derivatives **4c** and **4d** in 75% and 55% yield, respectively. Additionally, treating **3ag** with NH_4OAc in HOAc at reflux provided the pyridine derivative **4e** in a

high yield.

Scheme 4. Synthetic Utility



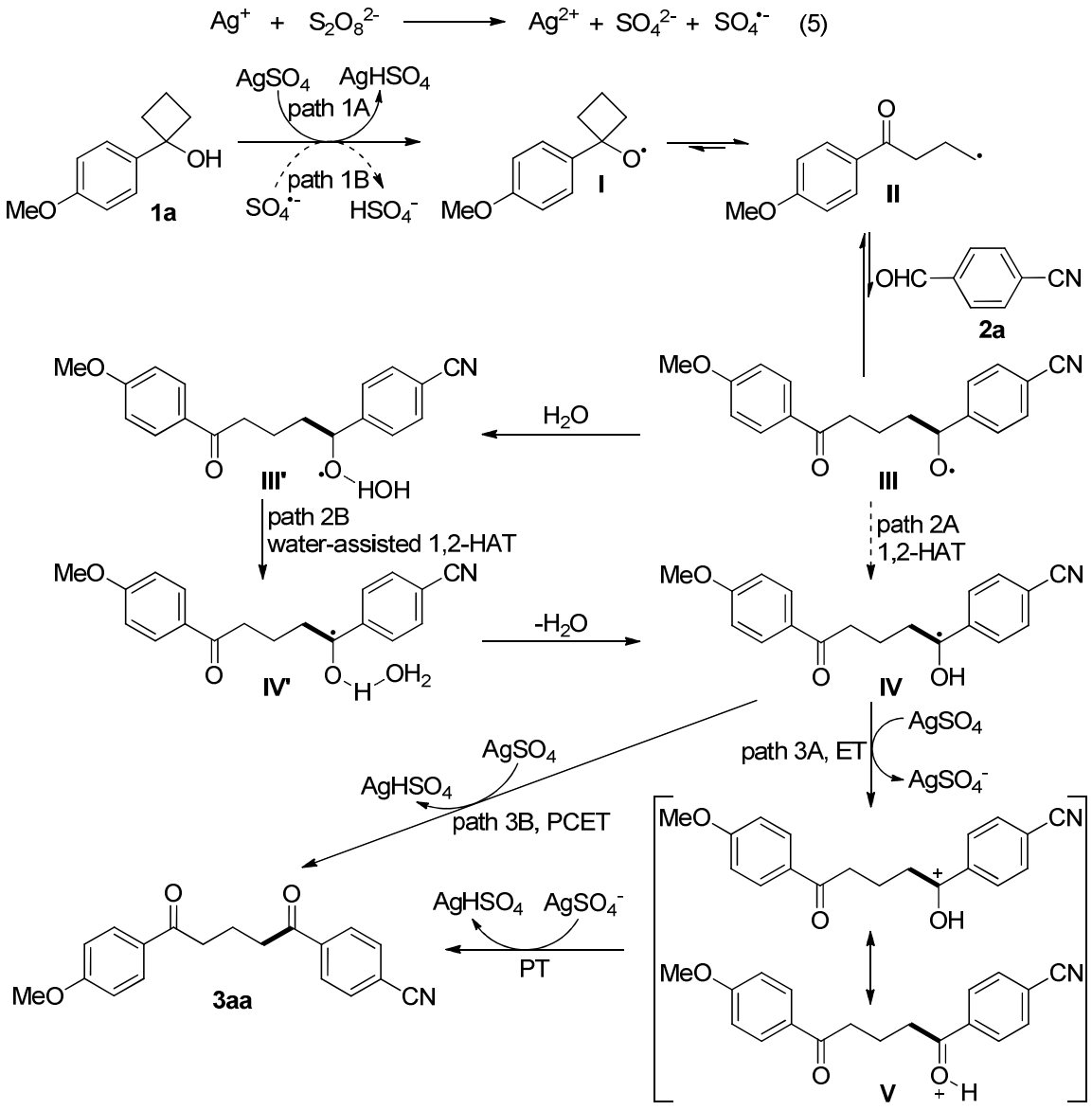
To gain insights into the reaction mechanism, the standard reaction between **1a** and **2a** was conducted with addition of TEMPO (5 equiv). As a result, the TEMPO-adduct **5a** was obtained in 22% yield, accompanied by the formation of **5b** and **5c** in 16% and 5% yield, respectively, while the acyl adduct **5d** could not be detected, even in the absence of **1a** (eqs 1 and 2). These results implied that the formation of acyl radical intermediate shoud be less likely. When a 1:1 mixture of **1a** and **1d** was subjected to the reaction conditions, a 4.1:1 mixture of **3aa** and **3da** was obtained after 3.5 h, indicating that introducing electron-donating groups onto the aryl ring of **1** is beneficial for the reaction (eq 3). Additionally, the competitive reaction of **2a** and **2g** with **1a** afforded a mixture of **3aa** and **3ag** in a 4.7:1 ratio, pointing out that the electronic effect of aldehyde plays a key role in this reaction (eq 4).



Based on the above results and our previous reports,[12] a possible mechanism for this Ag-catalyzed ring-opening acylation of cyclopropanols and cyclobutanols is portrayed in Scheme 5 using **1a** and **2a** as the representative starting materials. Initially, a cycloalkanoxyl radical **I** is produced via oxidation of the cyclobutanol **1a**, either by Ag(II) species[13e] or sulfate radical ($SO_4^{\bullet-}$)[14d] (paths 1A and 1B), both of which can be generated by the reaction between $AgNO_3$ and $Na_2S_2O_8$ (eq 5).[15] The ring-opening of **I** followed by an intermolecular addition to the aldehyde **2a** affords a new alkoxy radical **III**. Increasing the electrophilic property of the carbonyl group of **2** may be beneficial for the intermolecular addition. Subsequently, the alkoxy radical **III** can be converted into the α-hydroxy

carbon radical **IV** via a direct or water-assisted 1,2-hydrogen atom transfer (1,2-HAT) (paths 2A and 2B).[16] The lack of conjugation effect between the carbon radical and aryl ring may be responsible for the failure of the reaction of aliphatic aldehydes. Finally, a single electron transfer (SET) oxidation of **IV** by Ag(II) species like $AgSO_4$, either via a stepwise electron transfer/proton transfer (ET/PT, path 3A) or concerted proton-coupled electron transfer (PCET, path 3B) pathway,[17] results in the formation of **3aa** and Ag(I) catalyst, which can be re-oxidized to Ag(II) species by $Na_2S_2O_8$.

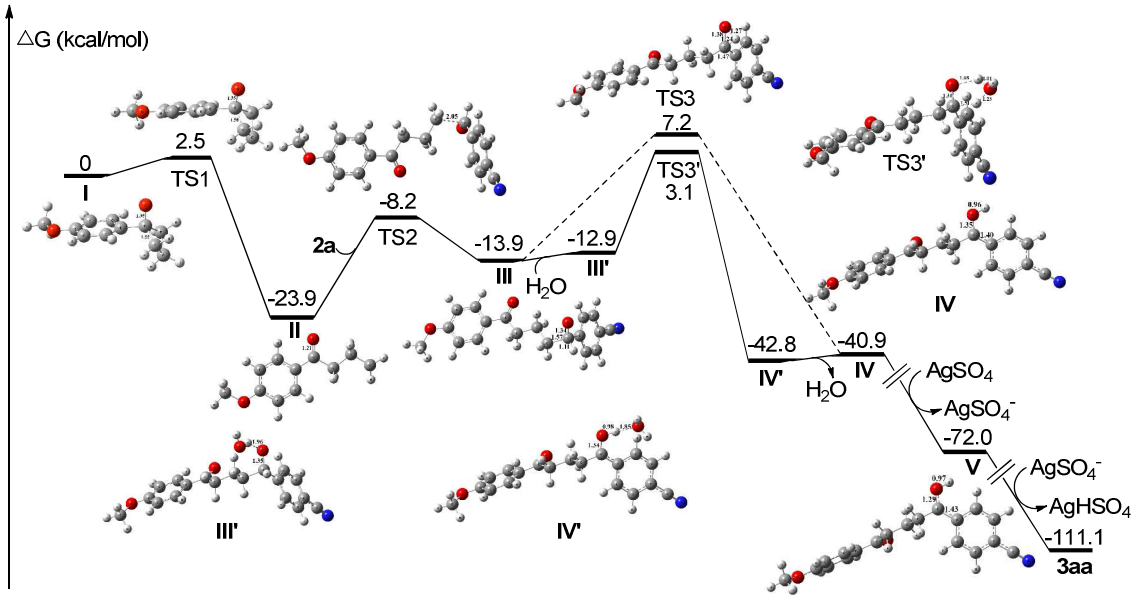
Scheme 5. Proposed Mechanism



A computational study with density functional theory (DFT) at the M06/6-311+G(d,p) level was

performed to shed light on the mechanism (Scheme 6). The oxidation of **1a** by $AgSO_4$ (path 1A) is exothermic by 13.0 kcal/mol, while the energy release enabled by sulfate radical ($SO_4^{\bullet-}$) (path 1B) is only 6.4 kcal/mol. Although both Ag(II) species[13e] and sulfate radical[14d] have been suggested as the oxidant for the generation of cycloalkanoxyl radicals, our data support Ag(II) species like $AgSO_4$ to be the preferred choice. After a small energy barrier (2.5 kcal/mol), the radical **I** is transformed to a carbon-centered radical **II** with a release of 23.9 kcal/mol energy. Consistent with the previous reports,[8] addition of **II** to the aldehyde **2a** yielding the alkoxy radical **III** is thermodynamically unfavorable, as it is endothermic by 10.0 kcal/mol. As for the 1,2-HAT, the energy barrier for an intramolecular 1,2-HAT, directly transforming the radical **III** to **IV** (path 2A), is 21.1 kcal/mol, while that for the water-assisted 1,2-HAT[16c] proceeding via a five-membered ring like transition state TS3' (path 2B) is 16.0 kcal/mol. Therefore, the water-assisted 1,2-HAT, instead of the direct intramolecular 1,2-HAT, is suggested for the pathway, which may be responsible for the crucial role of water in this reaction. It is noteworthy that the water-assisted 1,2-HAT is exothermic by 29.9 kcal/mol, thus offering a driving force for moving the equilibrium from **II** to **III**. Hence, in addition to the traditional fast reduction strategy, 1,2-HAT may serve as an alternative strategy for facilitating the radical addition to aldehydes. After the release of H_2O, the intermediate **IV** can be formed, followed by an electron transfer to $AgSO_4$ ($\Delta G^{\ddagger}$ = -31.1 kcal/mol) and a subsequent proton transfer with $AgSO_4^-$ ($\Delta G^{\ddagger}$ = -39.1 kcal/mol) to give **3aa** as the final product (path 3A). Of course, the concerted PCET between **IV** and $AgSO_4$ ($\Delta G^{\ddagger}$ = -70.2 kcal/mol) is also feasible for the transformation (path 3B).

Scheme 6. Free Energy Profile for the Transformation from I to 3aa. Bond Lengths Are Shown in Å.



CONCLUSION

In conclusion, we have developed an unprecedented intermolecular oxidative radical addition to aldehydes via a silver-catalyzed ring-opening acylation of cyclopropanols and cyclobutanols. Both 1,4- and 1,5-diketones can be efficiently synthesized via this protocol. The reaction proceeds under mild and neutral conditions and tolerates a wide range of functional groups. A mechanism involving the radical-mediated C-C bond cleavage, intermolecular addition to aldehyde, water-assisted 1,2-HAT, and SET oxidation has been proposed. As compared to the traditional reductive radical addition protocols that deliver alcohols, this reaction provides a novel strategy for the step- and atom-economic approach to acyclic ketones from readily available aldehydes. DFT calculations indicate that the water-assisted 1,2-HAT is strongly exothermic, thus offering a driving force for the promotion of the thermodynamically unfavorable addition of carbon radicals to aldehydes, a formidable challenge for the potential use of aldehydes as radical acceptors. With this advance, new reactions using aldehydes as radical acceptors will be feasible in the near feature.

EXPERIMENTAL SECTION

General. The column chromatography was performed with silica gel (300−400 mesh) using petroleum ethers/EtOAc as the eluent. ^{1}H, ^{13}C, and ^{19}F NMR spectra were measured on a 600 or 400

MHz NMR spectrometer using $CDCl_3$ as the solvent. The chemical shifts are given in δ relative to TMS, and the coupling constants are given in Hertz. The high-resolution mass spectra (HRMS) analyses were conducted using a TOF MS instrument with an ESI source. Melting points were measured by a melting point instrument and were uncorrected.

General Procedure for the Silver-Catalyzed Ring-Opening Acylation of Cyclopropanols and Cyclobutanols. To a mixture of $AgNO_3$ (4.2 mg, 0.025 mmol) and $Na_2S_2O_8$ (178.6 mg, 0.75 mmol) was added a solution of **1a** (133.6 mg, 0.75 mmol) and **2a** (32.8 mg, 0.25 mmol) in 3 mL of DMSO/H_2O (v/v = 1:1) under a nitrogen atmosphere. After stirring at 50 ^oC for 16 h, the reaction mixture was quenched with water, extracted with EtOAc, washed with brine, dried over anhydrous Na_2SO_4, and concentrated. Column chromatography on silica gel (EtOAc/petroleum ether = 1:5) gave 65 mg of **3aa** (yield: 85%) as a white solid, mp 118–120 ^oC. 622 mg (yield: 81%) of **3aa** was obtained from **2a** (328 mg, 2.5 mmol) using the general procedure. ^1H NMR (600 MHz, $CDCl_3$) δ 2.16−2.22 (m, 2H), 3.08 (t, J = 6.8 Hz, 2H), 3.13 (t, J = 7.0 Hz, 2H), 3.87 (s, 3H), 6.94 (d, J = 8.9 Hz, 2H), 7.77 (d, J = 8.5 Hz, 2H), 7.92−7.98 (m, 2H), 8.04−8.10 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 18.5, 36.8, 38.0, 55.4, 113.7, 116.2, 117.9, 128.4, 129.8, 130.2, 132.4, 139.6, 163.5, 198.1, 198.5; HRMS (ESI) calcd for $C_{19}H_{17}NO_3Na$ $(M + Na)^+$ 330.1101, found 330.1096.

*Compound **3ba***. 51% yield (39 mg); white solid, mp 109–111 ^oC; ^1H NMR (600 MHz, $CDCl_3$) δ 2.11−2.18 (m, 2H), 3.06−3.16 (m, 4H), 3.89 (s, 3H), 6.95−7.14 (m, 2H), 7.44−7.50 (m, 1H), 7.71 (dd, J = 1.8, 7.7 Hz, 1H), 7.74−7.79 (m, 2H), 8.05−8.10 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 18.7, 38.2, 42.5, 55.5, 111.6, 116.2, 118.0, 120.7, 128.0, 128.5, 130.2, 132.5, 133.6, 139.8, 158.6, 198.7, 201.9; HRMS (ESI) calcd for $C_{19}H_{17}NO_3Na$ $(M + Na)^+$ 330.1101, found 330.1108.

*Compound **3ca***. 70% yield (65 mg); white solid, mp 99–101 ^oC; ^1H NMR (600 MHz, $CDCl_3$) δ 2.15−2.23 (m, 2H), 3.04−3.16 (m, 4H), 6.97−7.09 (m, 2H), 7.04−7.09 (m, 2H), 7.18−7.22 (m, 1H), 7.37−7.42 (m, 2H), 7.76−7.78 (m, 2H), 7.91−7.98 (m, 2H), 8.04−8.09 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 18.4, 37.0, 37.9, 116.2, 117.2, 117.9, 120.1, 124.6, 128.4, 130.0, 130.2, 131.3, 132.4, 139.6, 155.3, 162.0, 198.1, 198.4; HRMS (ESI) calcd for $C_{24}H_{19}NO_3Na$ $(M + Na)^+$ 392.1257, found 392.1268.

*Compound **3da***. 79% yield (58 mg); white solid, mp 124–126 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.15−2.18 (m, 2H), 2.41 (s, 3H), 3.07−3.15 (m, 4H), 7.26 (d, J = 8.4 Hz, 2H), 7.77 (d, J = 8.3 Hz, 2H), 7.87 (d, J = 8.1 Hz, 2H), 8.07 (d, J = 8.3 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 18.4, 21.6, 37.1, 38.0, 116.3, 117.9, 128.1, 128.5, 129.3, 132.5, 134.2, 139.7, 144.0, 198.5, 199.2; HRMS (ESI) calcd for $C_{19}H_{17}NO_2Na$ $(M + Na)^+$ 314.1151, found 314.1148.

*Compound **3ea***. 64% yield (52 mg); white solid, mp 120–122 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.14−2.24 (m, 2H), 2.52 (s, 3H), 3.06−3.15 (m, 4H), 7.24−7.28 (m, 2H), 7.75−7.78 (m, 2H), 7.86−7.90 (m, 2H), 8.05−8.08 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 14.7, 18.4, 37.0, 37.9, 116.2, 117.9, 124.9, 128.4, 128.4, 132.5, 132.9, 139.6, 146.0, 198.4, 198.5; HRMS (ESI) calcd for $C_{19}H_{17}NO_2SNa$ $(M + Na)^+$ 346.0872, found 346.0859.

*Compound **3fa***. 61% yield (45 mg); white solid, mp 107–109 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.16−2.23 (m, 2H), 3.08−3.17 (m, 4H), 7.11−7.16 (m, 2H), 7.78 (d, J = 8.3 Hz, 2H), 7.98−8.03 (m, 2H), 8.08 (d, J = 8.3 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 18.3, 37.1, 37.8, 115.7 (d, J = 21.8 Hz), 116.3, 117.9, 128.4, 130.6 (d, J = 9.3 Hz), 132.5, 133.10 (d, J = 3.1 Hz), 139.6, 165.7 (d, J = 255.1 Hz), 197.9, 198.3; ^{19}F NMR (565 MHz, $CDCl_3$) δ –105.0; HRMS (ESI) calcd for $C_{18}H_{14}FNO_2Na$ $(M + Na)^+$ 318.0901, found 318.0892.

*Compound **3ga***. 63% yield (49 mg); white solid, mp 111–113 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.15−2.24 (m, 2H), 3.07−3.16 (m, 4H), 7.42-7.47 (m, 2H), 7.76-7.80 (m, 2H), 7.90-7.94 (m, 2H), 8.06-8.09 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 18.2, 37.2, 37.8, 116.3, 117.9, 128.4, 128.9, 129.3, 129.4, 132.5, 134.9, 139.6, 198.3, 198.3; HRMS (ESI) calcd for $C_{18}H_{14}ClNO_2Na$ $(M + Na)^+$ 334.0605, found 334.0591.

*Compound **3ha***. 60% yield (53 mg); white solid, mp 116–118 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.15−2.25 (m, 2H), 3.04−3.17 (m, 4H), 7.58−7.80 (m, 2H), 7.78 (d, J = 8.4 Hz, 2H), 7.80−7.87 (m, 2H), 8.07 (d, J = 8.4 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 18.2, 37.2, 37.8, 116.4, 117.9, 128.5, 129.4, 129.5, 132.0, 132.5, 138.0, 139.6, 198.3, 198.5; HRMS (ESI) calcd for $C_{18}H_{14}BrNO_2Na$ $(M + Na)^+$ 378.0100, found 378.0109.

*Compound **3ia***. 76% yield (53 mg); white solid, mp 130–132 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ

2.16−2.25 (m, 2H), 3.09−3.17 (m, 4H), 7.43−7.51 (m, 2H), 7.54−7.60 (m, 1H), 7.77 (d, J = 8.3 Hz, 2H), 7.98 (d, J = 7.4 Hz, 2H), 8.08 (d, J = 8.3 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 18.3, 37.2, 37.9, 116.3, 117.9, 128.0, 128.5, 128.6, 132.5, 133.2, 136.7, 139.7, 198.4, 199.5; HRMS (ESI) calcd for $C_{18}H_{16}NO_2$ $(M + H)^+$ 278.1176, found 278.1181.

Compound ***3ja***. 46% yield (33 mg); white solid, mp 90–92 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.16−2.24 (m, 2H), 3.08 (t, J = 6.8 Hz, 2H), 3.14 (t, J = 7.0 Hz, 2H), 7.14 (dd, J = 3.8, 4.9 Hz, 1H), 7.65 (dd, J = 1.1, 4.9 Hz, 1H), 7.75 (dd, J = 1.1, 3.8 Hz, 1H), 7.72−7.80 (m, 2H), 8.02−8.10 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 18.6, 37.8, 37.9, 116.3, 117.9, 128.2, 128.5, 132.0, 132.5, 133.7, 139.6, 144.0, 192.6, 198.3; HRMS (ESI) calcd for $C_{16}H_{13}NO_2SNa$ $(M + Na)^+$ 306.0559, found 306.0558.

Crystal data for **3ja** ($C_{16}H_{13}NO_2S$, 283.33): triclinic, space group $P2(1)/n$, a = 14.755(2) Å, b = 6.0419(7) Å, c = 16.653(2) Å, U = 1428.3(3) Å^3, Z = 4, T = 296(2) K, absorption coefficient 0.226 mm^{-1}, reflections collected 21063, independent reflections 3399 [R(int) = 0.088], refinement by full-matrix least-squares on F^2, data/restraints/parameters 3399/0/181, goodness-of-fit on F^2 = 1.152, final R indices [$I>2\sigma(I)$] R_1 = 0.0874, wR_2 = 0.1472, R indices (all data) R_1 = 0.1683, wR_2 = 0.1776, largest diff. peak and hole 0.249 and –0.224e· Å^{-3}. Crystallographic data for the structure **3ja** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 1580484.

Compound ***3ka***. 35% yield (29 mg); white solid, mp 115–117 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.21−2.28 (m, 2H), 3.14−3.20 (m, 4H), 7.39−7.50 (m, 2H), 7.75−7.78 (m, 2H), 7.86−7.90 (m, 2H), 8.00 (s, 1H), 8.05−8.09 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 18.6, 37.7, 37.8, 116.4, 117.9, 123.0, 125.1, 125.9, 127.5, 128.5, 129.2, 132.5, 139.1, 139.6, 142.4, 143.4, 194.1, 198.3; HRMS (ESI) calcd for $C_{20}H_{15}NO_2SNa$ $(M + Na)^+$ 356.0716, found 356.0708.

Compound ***3la***. 50% yield (40 mg); white solid, mp 113–115 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.20−2.27 (m, 2H), 3.11−3.17 (m, 4H), 7.29−7.34 (m, 1H), 7.45−7.50 (m, 1H), 7.53−7.58 (m, 2H), 7.69−7.78 (m, 3H), 8.05−8.08 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 18.2, 37.5, 37.7, 112.3, 112.9, 116.3, 117.9, 123.3, 123.9, 126.9, 128.3, 128.4, 132.4, 139.6, 152.3, 155.5, 190.7, 198.2; HRMS (ESI) calcd for $C_{20}H_{15}NO_3Na$ $(M + Na)^+$ 340.0944, found 340.0940.

*Compound **3ma***. 62% yield (37 mg); white solid, mp 103–105 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85−0.92 (m, 2H), 1.00−1.05 (m, 2H), 1.90−2.09 (m, 3H), 2.72 (t, J = 6.8 Hz, 2H), 3.04 (t, J = 7.1 Hz, 2H), 7.77 (d, J = 8.3 Hz, 2H), 8.06 (d, J = 8.3 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 10.7, 18.1, 20.5, 37.9, 41.9, 116.2, 117.9, 128.4, 132.5, 139.7, 198.4, 210.2; HRMS (ESI) calcd for $C_{15}H_{16}NO_2$ $(M + H)^+$ 242.1176, found 242.1175.

*Compound **3na***. 55% yield (40 mg); white solid, mp 97–99 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.95−2.02 (m, 2H), 2.61 (t, J = 6.7 Hz, 2H), 2.94 (t, J = 7.1 Hz, 2H), 3.70 (s, 2H), 7.18−7.35 (m, 5H), 7.73−7.76 (m, 2H), 7.97−8.01 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 17.9, 37.6, 40.4, 50.2, 116.3, 117.9, 127.1, 128.4, 128.7, 129.3, 132.4, 133.9, 139.6, 198.3, 207.8; HRMS (ESI) calcd for $C_{19}H_{17}NO_2Na$ $(M + Na)^+$ 314.1151, found 314.1146.

*Compound **3oa***. 53% yield (34 mg); white solid, mp 94–96 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.90 (t, J = 7.4 Hz, 3H), 1.30−1.34 (m, 2H), 1.52−1.59 (m, 2H), 1.98−2.04 (m, 2H), 2.41 (t, J = 7.5 Hz, 2H), 2.56 (t, J = 6.8 Hz, 2H), 3.03 (t, J = 7.1 Hz, 2H), 7.75−7.79 (m, 2H), 8.04−8.07 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 13.8, 18.0, 22.3, 25.9, 37.9, 41.2, 42.6, 116.3, 117.9, 128.5, 132.5, 139.6, 198.4, 210.7; HRMS (ESI) calcd for $C_{16}H_{19}NO_2Na$ $(M + Na)^+$ 280.1308, found 280.1303.

*Compound **3pa***. 37% yield (19 mg); white solid, mp 104–106 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.04−2.13 (m, 2H), 2.63 (td, J = 1.0, 6.9 Hz, 2H), 3.08 (t, J = 7.0 Hz, 2H), 7.75−7.81 (m, 2H), 8.02−8.08 (m, 2H), 9.82 (t, J = 0.9 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 16.2, 37.6, 42.8, 116.4, 117.9, 128.4, 132.5, 139.5, 198.0, 201.7; HRMS (ESI) calcd for $C_{12}H_{11}NO_2Na$ $(M + Na)^+$ 224.0682, found 224.0679.

*Compound **3rb***. 62% yield (51 mg); white solid, mp 121–123 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.41−3.48 (m, 4H), 3.88 (s, 3H), 3.96 (s, 3H), 6.92−6.98 (m, 2H), 7.99−8.04 (m, 2H), 8.09 (d, J = 8.4 Hz, 2H), 8.14 (d, J = 8.4 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 32.2, 33.0, 52.4, 55.5, 113.7, 128.0, 129.7, 129.8, 130.4, 133.8, 140.0, 163.6, 166.3, 196.9, 198.5; HRMS (ESI) calcd for $C_{19}H_{19}O_5$ $(M + H)^+$ 327.1227, found 327.1232.

*Compound **3sb***. 72% yield (56 mg); white solid, mp 124–126 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.42 (s, 3H), 3.41−3.50 (m, 4H), 3.96 (s, 3H), 7.24−7.29 (m, 2H), 7.94 (d, J = 8.0 Hz, 2H), 8.09 (d, J = 8.1

Hz, 2H), 8.14 (d, J = 8.1 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 21.6, 32.4, 32.9, 52.4, 128.0, 128.2, 129.3, 129.8, 133.8, 134.1, 140.0, 144.0, 166.2, 198.0, 198.3; HRMS (ESI) calcd for $C_{19}H_{18}O_4Na$ (M + Na)$^+$ 333.1097, found 333.1096.

Compound ***3tb***. 61% yield (45 mg); white solid, mp 110–112 ^{o}C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.43−3.52 (m, 4H), 3.95 (s, 3H), 7.46−7.50 (m, 2H), 7.56−7.60 (m, 1H), 8.02−8.16 (m, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 32.5, 32.8, 52.4, 128.0, 128.0, 128.6, 129.8, 133.2, 133.8, 136.6, 139.9, 166.2, 198.2, 198.4; HRMS (ESI) calcd for $C_{18}H_{16}O_4Na$ (M + Na)$^+$ 319.0941, found 319.0924.

Compound ***3ub***. 50% yield (39 mg); white solid, mp 100–102 ^{o}C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.89−2.94 (m, 2H), 3.25−3.29 (m, 2H), 3.83 (s, 2H), 3.95 (s, 3H), 7.23−7.37 (m, 5H), 7.99−8.02 (m, 2H), 8.09−8.12 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 32.8, 35.6, 50.2, 52.5, 127.1, 127.9, 128.7, 129.5, 129.8, 133.9, 134.1, 139.8, 166.2, 198.1, 206.9; HRMS (ESI) calcd for $C_{19}H_{18}O_4Na$ (M + Na)$^+$ 333.1097, found 333.1094.

Compound ***3vb***. 56% yield (42 mg); white solid, mp 98–100 ^{o}C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.18−1.43 (m, 5H), 1.65−1.71 (m, 1H), 1.77−1.83 (m, 2H), 1.91−1.95 (m, 2H), 2.43−2.50 (m, 1H), 2.89−2.94 (m, 2H), 3.26−3.31 (m, 2H), 3.95 (s, 3H), 8.01−8.05(m, 2H), 8.10−8.13 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 25.6, 25.8, 28.5, 32.6, 34.1, 50.8, 52.4, 127.9, 129.7, 133.8, 139.9, 166.2, 198.3, 212.4; HRMS (ESI) calcd for $C_{18}H_{22}O_4Na$ (M + Na)$^+$ 325.1410, found 325.1407.

Compound ***3wb***. 65% yield (45 mg); white solid, mp 107–109 ^{o}C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.81−1.87 (m, 1H), 1.95−2.03 (m, 1H), 2.17−2.34 (m, 4H), 2.81−2.84 (m, 2H), 3.28−3.31 (m, 2H), 3.35−3.41 (m, 1H), 3.95 (s, 3H), 8.03−8.05 (m, 2H), 8.11−8.14 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 17.8, 24.4, 32.5, 33.4, 45.4, 52.4, 127.9, 129.8, 133.8, 139.9, 166.2, 198.3, 210.2; HRMS (ESI) calcd for $C_{16}H_{18}O_4Na$ (M + Na)$^+$ 297.1097, found 297.1093.

Compound ***3ab***. 80% yield (68 mg); white solid, mp 98–100 ^{o}C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.16−2.22 (m, 2H), 3.07 (t, J = 6.9 Hz, 2H), 3.14 (t, J = 7.0 Hz, 2H), 3.87 (s, 3H), 3.95 (s, 3H), 6.93 (d, J = 8.9 Hz, 2H), 7.96 (d, J = 8.9 Hz, 2H), 8.00−8.05 (m, 2H), 8.09−8.13 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 18.7, 37.0, 38.0, 52.4, 55.4, 113.7, 127.9, 129.8, 129.8, 130.3, 133.7, 140.0, 163.4, 166.2, 198.3, 199.4; HRMS (ESI) calcd for $C_{20}H_{20}O_5Na$ (M + Na)$^+$ 363.1203, found 363.1198.

Compound ***3ac***. 67% yield (51 mg); white solid, mp 112–114 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.17−2.23 (m, 2H), 3.10 (t, J = 6.8 Hz, 2H), 3.16 (t, J = 6.9 Hz, 2H), 3.87 (s, 3H), 6.90−6.96 (m, 2H), 7.65 (td, J = 1.2, 7.6 Hz, 1H), 7.71 (td, J = 1.4, 7.7 Hz, 1H), 7.82 (dd, J = 1.2, 7.6 Hz, 1H), 7.92−7.97 (m, 2H), 7.99 (dd, J = 0.9, 7.9 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 18.6, 36.8, 38.7, 55.4, 110.9, 113.7, 118.1, 129.4, 129.8, 130.3, 132.3, 132.5, 135.3, 139.6, 163.5, 198.2, 198.2; HRMS (ESI) calcd for $C_{19}H_{17}NO_3Na$ $(M + Na)^+$ 330.1101, found 330.1095.

Compound ***3ad***. 92% yield (71 mg); white solid, mp 122–124 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.16−2.24 (m, 2H), 3.09 (t, J = 6.8 Hz, 2H), 3.16 (t, J = 7.0 Hz, 2H), 3.87 (s, 3H), 6.91−6.96 (m, 2H), 7.93−8.00 (m, 4H), 8.11−8.14 (m, 2H), 10.10 (s, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 18.6, 36.9, 38.1, 55.4, 113.7, 128.5, 129.8, 130.2, 138.9, 140.9, 163.4, 191.6, 198.2, 199.3; HRMS (ESI) calcd for $C_{19}H_{18}NaO_4$ $(M + Na)^+$ 333.1097, found 333.1090.

Compound ***3ae***. 85% yield (77 mg); white solid, mp 99–101 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.15−2.22 (m, 2H), 3.04−3.12 (m, 5H), 3.15 (t, J = 7.0 Hz, 2H), 3.87 (s, 3H), 6.94 (d, J = 8.8 Hz, 2H), 7.96 (d, J = 8.8 Hz, 2H), 8.04 (d, J = 8.4 Hz, 2H), 8.15 (d, J = 8.4 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 18.5, 36.8, 38.1, 44.2, 55.4, 113.7, 127.7, 128.9, 129.7, 130.2, 140.6, 144.0, 163.5, 198.1, 198.6; HRMS (ESI) calcd for $C_{19}H_{20}SO_5Na$ $(M + Na)^+$ 383.0924, found 383.0912.

Compound ***3af***. 70% yield (57 mg); white solid, mp 102–104 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.16−2.22 (m, 2H), 2.65 (s, 3H), 3.08 (t, J = 6.9 Hz, 2H), 3.15 (t, J = 7.0 Hz, 2H), 3.87 (s, 3H), 6.91−6.96 (m, 2H), 7.94−7.99 (m, 2H), 8.00−8.08 (m, 4H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 18.7, 26.8, 37.0, 38.0, 55.4, 113.7, 128.2, 128.4, 129.8, 130.3, 140.0, 140.0, 163.5, 197.5, 198.2, 199.4; HRMS (ESI) calcd for $C_{20}H_{20}O_4Na$ $(M + Na)^+$ 347.1254, found 347.1247.

Compound ***3ag***.[18] 59% yield (42 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.15−2.22 (m, 2H), 3.03−3.14 (m, 4H), 3.86 (s, 3H), 6.93 (d, J = 8.8 Hz, 2H), 7.42−7.58 (m, 3H), 7.90−8.00 (m, 4H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 18.9, 37.2, 37.6, 55.4, 113.7, 128.0, 128.5, 130.0, 130.3, 133.0, 136.9, 163.4, 198.5, 199.9.

Compound ***3ah***. 36% yield (33 mg); white solid, mp 95–97 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.73−0.79 (m, 6H), 1.81−1.94 (m, 4H), 2.17−2.24 (m, 2H), 3.00−3.16 (m, 4H), 3.88 (s, 4H),

6.92−6.97 (m, 2H), 7.45−7.52 (m, 2H), 7.91−8.01 (m, 4H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 7.7, 19.0, 35.1, 37.3, 37.6, 55.4, 77.5, 113.7, 125.8, 127.9, 130.3, 135.0, 151.3, 163.4, 198.5, 199.7; HRMS (ESI) calcd for $C_{23}H_{28}O_4Na$ $(M + Na)^+$ 391.1880, found 391.1879.

Experimental Procedure for the Synthesis of Compound 4a. To a solution of **3ta** (74.0 mg, 0.25 mmol) in 1.5 mL of toluene was added Lawesson's reagent (121.3 mg, 0.30 mmol). After stirring at reflux for 6 h, the reaction mixture was cooled to room temperature then quenched with water, extracted with EtOAc, washed with brine, dried over anhydrous Na_2SO_4, and concentrated. Column chromatography on silica gel (EtOAc/petroleum ether = 1:10) gave 59 mg of **4a** (yield: 80%) as a white solid, mp 150–152 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.93 (s, 3H), 7.23−7.34 (m, 3H), 7.36−7.44 (m, 3H), 7.61−7.71 (m, 3H), 8.01−8.09 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 52.1, 124.2, 125.1, 125.5, 125.7, 127.9, 128.7, 129.0, 130.3, 134.0, 138.5, 142.1, 145.2, 166.7; HRMS (ESI) calcd for $C_{18}H_{14}SO_2Na$ $(M + Na)^+$ 317.0607, found 317.0613.

Experimental Procedure for the Synthesis of Compound 4b. To a solution of **3ta** (74.0 mg, 0.25 mmol) in 2.5 mL of MeCN was added TfOH (43.1 mg, 0.25 mmol) dropwise under a nitrogen atmosphere. After stirring at 85 ^{o}C for 1 h, the reaction mixture was cooled to room temperature then quenched with water, extracted with EtOAc, washed with brine, dried over anhydrous Na_2SO_4, and concentrated. Column chromatography on silica gel (EtOAc/petroleum ether = 1:10) gave 63 mg of **4b** (yield: 91%) as a white solid, mp 154–156 ^{o}C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.92 (s, 3H), 6.75 (d, J = 3.5 Hz, 1H), 6.85 (d, J = 3.5 Hz, 1H), 7.26−7.32 (m, 1H), 7.37−7.44 (m, 2H), 7.72−7.79 (m, 4H), 8.04−8.07 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 52.1, 107.5, 109.5, 123.2, 123.9, 127.8, 128.4, 128.7, 130.1, 130.3, 134.6, 152.2, 154.4, 166.8; HRMS (ESI) calcd for $C_{18}H_{14}O_3Na$ $(M + Na)^+$ 301.0835, found 301.0834.

Experimental Procedure for the Synthesis of Compound 4c. To a mixture of NH_4OAc (192.8 mg, 2.5 mmol) and AcOH (150.3 mg, 2.5 mmol) was added a solution of **3ta** (74.0 mg, 0.25 mmol) in 2.5 mL of MeOH. After stirring at reflux for 3 h, the reaction mixture was cooled to room temperature then quenched with water, extracted with EtOAc, washed with brine, dried over anhydrous Na_2SO_4, and concentrated. Column chromatography on silica gel (EtOAc/petroleum ether = 1:3) gave 52 mg of

4c (yield: 75%) as a white solid, mp 161–163 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.92 (s, 3H), 6.58−6.63 (m, 1H), 6.70−6.74 (m, 1H), 7.22−7.28 (m, 1H), 7.36−7.44 (m, 2H), 7.53−7.60 (m, 4H), 8.01−8.07 (m, 2H), 8.74 (br s, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 52.1, 108.4, 109.9, 123.0, 124.0, 126.8, 127.4, 129.0, 130.4, 131.9, 132.1, 134.5, 136.5, 166.9; HRMS (ESI) calcd for $C_{18}H_{15}NO_2Na$ $(M + Na)^+$ 300.0995, found 300.1004.

Experimental Procedure for the Synthesis of Compound 4d. To a solution of **3ta** (74.0 mg, 0.25 mmol) in 1.5 mL of HOAc was added *n*-$BuNH_2$ (21.9 mg, 0.3 mmol). After stirring at 120 °C for 2 h, the reaction mixture was cooled to room temperature then quenched with water, extracted with EtOAc, washed with brine, dried over anhydrous Na_2SO_4, and concentrated. Column chromatography on silica gel (EtOAc/petroleum ether = 1:8) gave 46 mg of **4d** (yield: 55%) as a white solid, mp 143–145 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.53 (t, J = 7.4 Hz, 3H), 0.76−0.88 (m, 2H), 1.10−1.19 (m, 2H), 3.93 (s, 3H), 4.10 (t, J = 7.2 Hz, 2H), 6.27 (d, J = 3.5 Hz, 1H), 6.35 (d, J = 3.5 Hz, 1H), 7.30−7.35 (m, 1H), 7.38−7.48 (m, 4H), 7.53 (d, J = 8.2 Hz, 2H), 8.09 (d, J = 8.2 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 13.3, 19.2, 32.6, 45.2, 52.0, 110.8, 120.9, 127.1, 128.0, 128.1, 128.4, 129.0, 129.8, 133.7, 135.4, 138.1, 138.6, 166.9; HRMS (ESI) calcd for $C_{22}H_{23}NO_2Na$ $(M + Na)^+$ 356.1621, found 356.1618.

Experimental Procedure for the Synthesis of Compound 4e.[6e] To a solution of **3ag** (70.5 mg, 0.25 mmol) in 1.5 mL of HOAc was added NH_4OAc (192.8 mg, 2.5 mmol). After stirring at 120 °C for 3 h, the reaction mixture was cooled to room temperature then quenched with water, extracted with EtOAc, washed with brine, dried over anhydrous Na_2SO_4, and concentrated. Column chromatography on silica gel (EtOAc/petroleum ether = 1:3) gave 50 mg of **4e** (yield: 77%) as a white solid, mp 168–170 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.82 (s, 3H), 6.96−7.02 (m, 2H), 7.37−7.50 (m, 3H), 7.54−7.60 (m, 2H), 7.67−7.73 (m, 1H), 8.06−8.16 (m, 4H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 55.3, 114.0, 117.7, 117.8, 126.9, 128.2, 128.6, 128.8, 132.0, 137.3, 139.5, 156.3, 156.5, 160.4; HRMS (ESI) calcd for $C_{18}H_{16}NO$ $(M + H)^+$ 262.1226, found 262.1229.

*Compound **5a***. It was obtained from **1a** and **2b** under the standard reaction conditions in the presence of 5 equivalents of TEMPO in 22% yield (54 mg), based on **1a**, as a colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.09 (s, 6H), 1.15 (s, 6H), 1.28−1.61 (m, 6H), 1.92−2.00 (m, 2H), 3.01−3.07 (m, 2H), 3.82 (t,

J = 6.2 Hz, 2H), 3.86 (s, 3H), 6.90−6.96 (m, 2H), 7.93−7.99 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 17.0, 20.0, 23.7, 33.0, 35.0, 39.5, 55.3, 59.6, 75.5, 113.6, 130.0, 130.2, 163.2, 198.6; HRMS (ESI) calcd for $C_{20}H_{32}NO_3$ $(M + H)^+$ 334.2377, found 334.2372.

Compound ***5b***.[19] It was obtained from **1a** and **2b** under the reaction conditions in the presence of 5 equivalents of TEMPO in 16% yield (21 mg), based on **1a**, as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.07−2.15 (m, 2H), 2.58−2.62 (m, 2H), 2.92 (t, J = 6.1 Hz, 2H), 3.85 (s, 3H), 6.70 (d, J = 2.4 Hz, 1H), 6.82 (dd, J = 2.5, 8.7 Hz, 1H), 8.01 (d, J = 8.7 Hz, 1H).

Compound ***5c.***[20] It was obtained from **1a** and **2b** under the reaction conditions in the presence of 5 equivalents of TEMPO in 5% yield (7 mg), based on **1a**, as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.00 (t, J = 7.4 Hz, 3H), 1.70−1.80 (m, 2H), 2.89 (t, J = 7.3 Hz, 2H), 3.86 (s, 3H), 6.90−6.96 (m, 2H), 7.91−7.97 (m, 2H).

Supporting Information. Spectroscopic data of products **3-5**, crystallographic data for **3ja**, and computational data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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