Zn- and Cu-Catalyzed Coupling of Tertiary Alkyl Bromides and Oxalates to Forge Challenging C−O, C−S, and C−N Bonds

Yuxin Gong, Zhaodong Zhu, Qun Qian,* Weiqi Tong, and Hegui Gong*

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- readily accessible C-O and C-Br electrophiles
- easy-to-operate and mild reaction conditions
- good coupling efficiency
- broad substrate scope
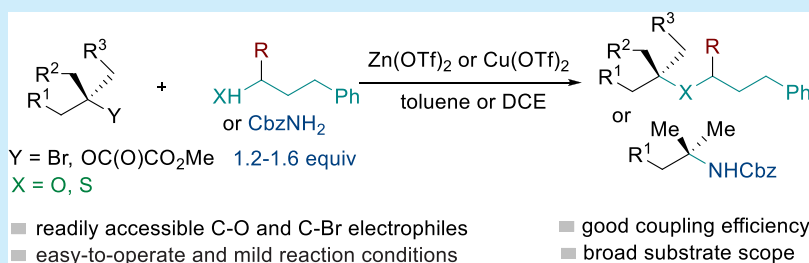
ABSTRACT: We describe here the facile construction of sterically hindered tertiary alkyl ethers and thioethers via the Zn(OTf)$_2$-catalyzed coupling of alcohols/phenols with unactivated tertiary alkyl bromides and the Cu(OTf)$_2$-catalyzed thiolation of unactivated tertiary alkyl oxalates with thiols. The present protocol represents one of the most effective unactivated tertiary C(sp^3)−heteroatom bond-forming conditions via readily accessible Lewis acid catalysis that is surprisingly less developed.

Sterically demanding tertiary alkyl ethers and thiothers are ubiquitous structural units in nature and drug compounds (e.g., telithromycin and clofibrate used to treat certain types of pneumonia and to lower high levels of cholesterol, respectively).[1,2] The synthesis of challenging tertiary alkyl ethers building on the coupling of unactivated tertiary alkyl electrophiles with ROH has continuously attracted growing attention.[3−9] The conventional methods largely require harsh or strong acidic conditions to provoke the S$_N$1 reaction of tertiary alkyl electrophiles with alcohols and phenols.[3,4] For instance, the etherification of tertiary alkyl bromides with alcohols has been carried out using toxic Hg catalysts.[4] The mild Lewis-acid-catalyzed tertiary C(sp^3)−O bond-forming reactions have been sparsely reported and are generally constrained to activated alkyl electrophiles.[5] Surprisingly, one of the most effective methods reported to date relies on the expensive($160/1 g, Aldrich) perfluorotriphenylboron-catalyzed nucleophilic substitution of tertiary alkyl fluorides.[6a] The preparation of tertiary alkyl fluorides usually requires expensive fluorination reagents (e.g., (diethylamine)sulfur trifluoride (DST), $34/1 g) under harsh conditions, rendering alkyl fluoride substrates practically less attractive.[6a] In addition, the mild Lewis-acid-catalyzed thiolation of tertiary alcohols to create tertiary C−S bonds has been densely centered on activated allyl and benzyl alcohols and their derivatives.[10] Only a few examples have been discretely reported for the thiolation of unactivated tertiary alkyl electrophiles under Lewis-acid-catalyzed reaction conditions, for example, the ZrCl$_4$-catalyzed thiolation of tertiary butanol with benzenethiol (Scheme 1).[11]

Thus the preparation of tertiary alkyl ethers and thioethers from readily accessible electrophile precursors under more available and mild catalytic conditions is in high demand. Recently, the photoredox and electrochemical decarboxylation of *N*-hydroxyphthalimide (NHP) esters and acids enabled the S$_N$1-type nucleophilic capture of the putative carbocation intermediates with alcohols, amines, and thiols.[12−15] These methods feature the oxidation of tertiary alkyl radicals to carbocations and thus significantly broaden the scope of alkyl electrophiles for C−X (X = O, S, N) bond formation.[16] We envisioned that exploiting easily accessible and inexpensive Lewis acid catalysts to forge C(sp^3)−heteroatom bonds from readily accessible tertiary alkyl electrophiles is worth revisiting, which may provide a facile and synthetically practical protocol for the construction of sterically hindered carbon−heteroatom bonds. In this work, we report the use of Zn(OTf)$_2$ and Cu(OTf)$_2$ as the Lewis acids to catalyze the etherification of unactivated tertiary alkyl halides with alcohols and phenols and the thiolation of unactivated tertiary alkyl oxalates with thiols via the S$_N$1 process. The reaction conditions are mild and tolerate a wide range of functional groups and can be extended to C−N bond formation via amination with carbamates and sulfonyl amides. We believe that this work offers a general C−O, C−S, and C−N bond-forming method based on unactivated tertiary alkyl substrates, in particular, alcohol-
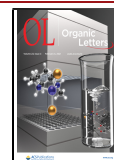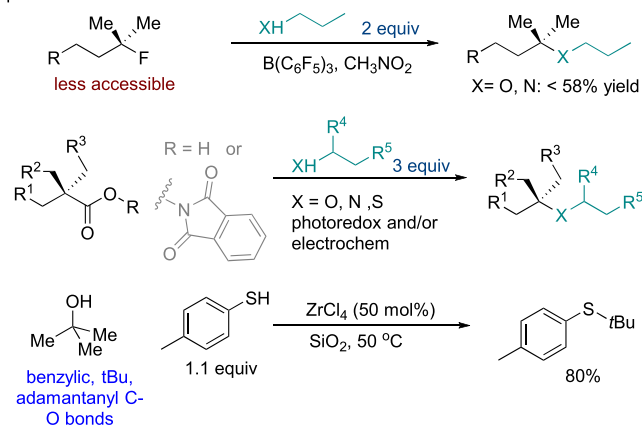
Scheme 1. Prominent Examples of C−X (X = O, S, N) Bond-Forming Methods Building on Tertiary Alkyl Substrates

- ■ readily accessible C-O and C-Br electrophiles
- ■ easy-to-operate and mild reaction conditions
- ■ good coupling efficiency
- ■ broad substrate scope

Table 1. Optimization of the Reaction of Tertiary Alkyl Bromide 1 with Primary Alcohol 2[a]

entry	X:1	variation of standard conditions	yield%[b]
1	1.6:1	none	84[c]
2	1.6:1	Zn(OTf)$_2$ (39 mol %), w/o Zn	73
3	1.6:1	20% of Zn used	72
4	1.6:1	10% of Zn used	71
5	1.6:1	50% of Zn used	81
6	1.6:1	w/o Zn	61
7	1.6:1	w/o molecular sieve	31
8	1.4:1	none	78
9	1.2:1	10% of Zn used	73
10	1.2:1	30% of Zn used	77
11	1.6:1	Cu(OTf)$_2$ instead of Zn(OTf)$_2$	76
12	1.6:1	Ni(OTf)$_2$ instead of Zn(OTf)$_2$	nd
13	1.6:1	Sc(OTf)$_2$ instead of Zn(OTf)$_2$, 25 °C	77
14	1.6:1	BF$_3$OEt instead of Zn(OTf)$_2$, 25 °C	nd

[a]Standard reaction conditions: 1 (1.6 equiv), 2 (0.3 mmol, 1 equiv), Zn(OTf)$_2$ (9 mol %), Zn (30 mol %), 4 Å molecular sieves (150 mg), toluene (1 mL), 12 h. [b]Yield was referred to an NMR yield using 2,5-dimethyl furan as a standard. [c]Isolated yield.
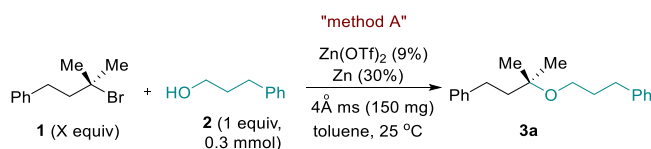
derived oxalates, that has not been used for amination and thiolation.

We set out to investigate the reaction of (3-bromo-3-methylbutyl)benzene **1** with 3-phenyl-1-propanol **2**. After an extensive survey of the reaction conditions, we identified that a combination of 9 mol % of Zn(OTf)$_2$ and 30 mol % Zn powder along with 4 Å molecular sieves in toluene at ambient temperature furnished the ether product **3a** in a highest 84% isolated yield (Table 1, entry 1). By comparison, the use of 39 mol % Zn(OTf)$_2$ generated **3a** in 73% yield (entry 2), indicating that the use of Zn powder as an additive is more effective than an increase in the loading of Zn(OTf)$_2$, likely due to the neutralization of in situ generated HBr. The amount of Zn was briefly screened but did not provide better results (entries 3−5), wherein without Zn, the reaction afforded **3** in 61% yield (entry 6). The use of 1.2 equiv of **1** and 10 mol % of Zn led to **3a** in a synthetically useful 73% yield (entry 9), which was boosted to 77% in the presence of 30 mol % of Zn (entry 10). The examination of other Lewis acids did not result in improved yields (entries 11−14 and Tables S5 and S7).[17]

The optimized etherification method A, as in Table 1, entry 1, was compatible with a wide array of alcohols (Figure 1). The primary and secondary alcohols, as exemplified in **3b−j** and **4a−h**, were effective to couple to tertiary butyl bromide and (3-bromo-3-methylbutyl)benzene **1**. The functionalized phenols also delivered the aryl alky ethers **4i−m** in moderate to good yields. The compatible functional groups on the primary alcohols included 1-bromo, terminal alkyne, ester, thiophenyl, and benzophenone. The secondary alcohols derived from Bn-protected 1-glucose (**4d**) and amino acids (**4a**, **4e**, and **4g**) afforded the products in good yields, manifesting that the scope of the alcohols was broad. The substituents on the phenols include 4-iodo, MeO, Bpin, and CHO. Remarkable chemoselectivity for 4-methoxyphenol was observed, where a

potential competing Friedel−Crafts alkylation of the benzene moiety did not occur.

The scope of tertiary alkyl bromides was surveyed next. A benzoyl-attached gem-dimethyl substrate afforded the ether products **5a** and **5b** in 60% and 50% yields. The decreased efficiency with respect to that of **1** was likely due to the inductive effect invoked by the benzoyl moiety, which destabilizes the putative carbocation intermediate. An increase in the sizes of tertiary alkyl moieties proved to be influential on the reaction yields. Replacement of one gem-methyl with an ethyl group led to a decrease in yields, as evident in products **6** and **7a−c**. The coupling of the sterically more demanding 3-bromo-3-ethylpentane to primary and secondary alcohols and 4-methoxyphenol was moderately effective, generating **8a−c** respectively. The tertiary alkyl bromides within cyclic scaffolds also afforded the products, as evident in the examples of **9−11**. In **11** and the secondary benzyl ether **12**, the β-bromides were intact and could be used for further functionalization. No reaction took place for the unactivated secondary alkyl bromide.

The etherification protocol is suitable for the amination and thiolation of tertiary alkyl bromides containing a gem-dimethyl with primary amides and thiols, in which a molecular sieve or a base additive was not needed.[18] Whereas Cbz-protected amine, tosyl, and thiophenylsulfonyl amides delivered the tertiary alkyl amine and amides **13−15** in good yields,[19] the thiolation process was competent with a set of primary and secondary alkyl thiols and aryl thiols that delivered the thioethers **16a−d** in good to excellent yields.

The Zn(OTf)$_2$-mediated carbon−heteroatom bond-forming conditions via tertiary C(sp^3)−Br bond breakage (method A) proved to be effective for the thiolation and amination of more accessible tertiary alkyl oxalates (Scheme 2). By slightly altering the reaction conditions using 1,2-dichloroethane as the solvent without external additives, the coupling of di-t-
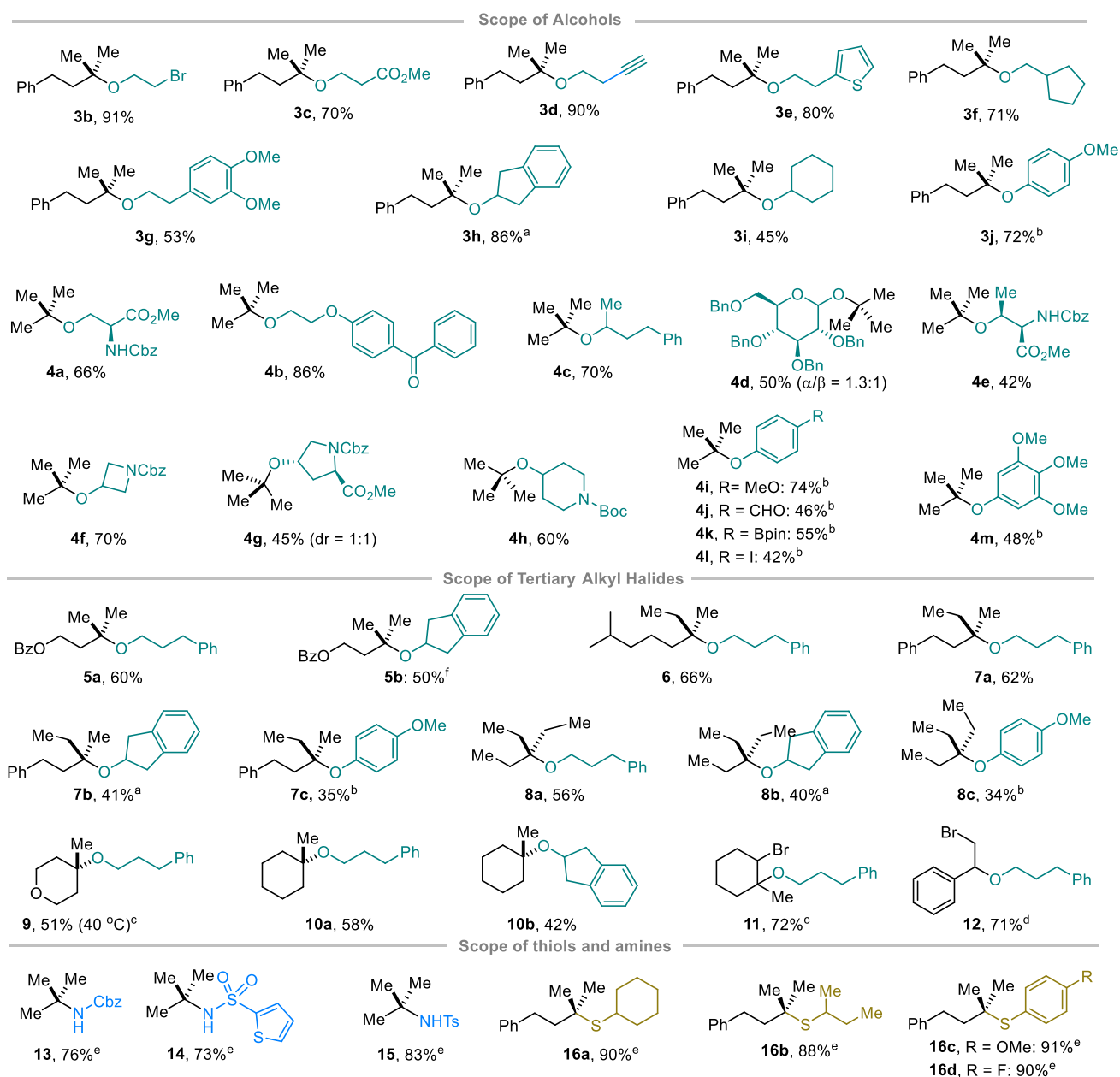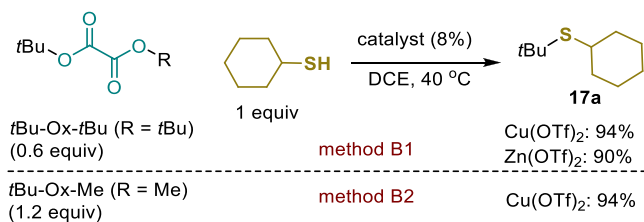
Figure 1. Unless otherwise noted, method A (Table 1, entry 1) was used. [a]MgCO$_3$ (1 equiv) was added. [b]The reaction was performed at 40 °C. [c]The reaction was run at 40 °C for 72 h. [d]The reaction was run at 80 °C for 2 h. [e]Zn (1 equiv) was added in DCE (1 mL). [f]The reaction was run at 40 °C for 48 h.

Scheme 2. Optimized Reaction Conditions for the Thiolation of *t*Bu−Ox−*t*Bu/*t*Bu−Ox−Me with Cyclohexanethiol

butyloxalate *t*Bu−Ox−*t*Bu with cyclohexanethiol delivered **17a** in 90% yield (with respect to the thiol), wherein the use of Cu(OTf)$_2$ (8%) is equally effective (method B1, Scheme 2). Control experiments indicated that the use of triflate as a

counteranion is critical, likely due to the need for enhanced Lewis acidity of the triflate salts (Table S9).[17] Other metal salts (e.g., Cu^{I}OTf) and solvents were inferior (Tables S8−S10).[17] The reaction was also carried out on a gram scale without deteriorating the yield. Finally, the thiolation protocol was extendable for to the coupling of cyclohexanethiol with the unsymmetrical tertiary butyl methyl oxalate (*t*Bu−Ox−Me), which furnished **17a** in 94% yield (method B2, Scheme 2). A wide range of tertiary alkyl oxalates were found to be suitable for the thiolation conditions. For tertiary alkyl-bearing geminal methyl groups, thiolation with aryl, primary, and secondary alkyl thiols delivered the thioethers in high yields, as exemplified by **17−21** (Figure 2). No reaction took place when tertiary butyl thiol was subjected to the reaction, which is indicative of the dependence of coupling efficiency on the steric encumbrance. Replacing the geminal methyl groups with
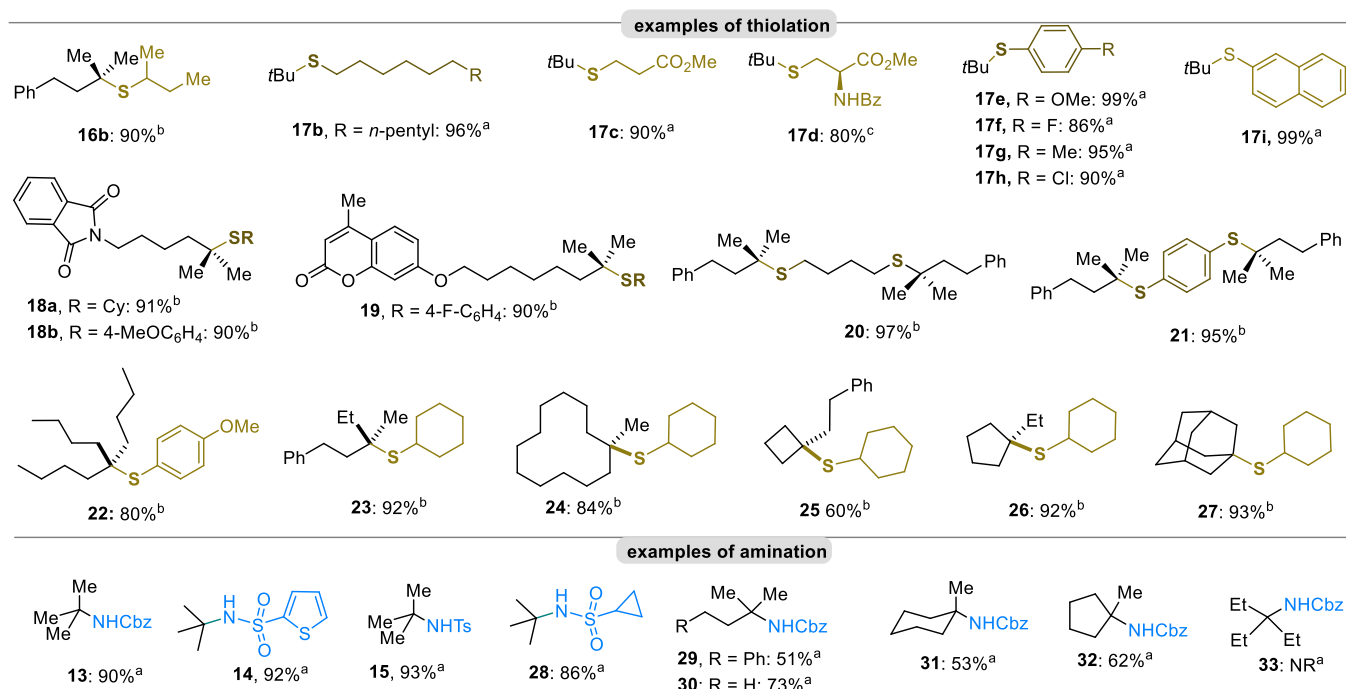
Figure 2. Substrate scope for thiolation and amination. [a]Method B1: 0.6 equiv of *t*R−Ox−*t*R was used. [b]Method B2: 1.2 equiv of *t*R−Ox−Me was used. [c]Tertiary alkyl bromine was used instead of oxalate in the presence of Zn (100 mol %).

ethyl and more hindered butyl groups did not result in an appreciable decrease in the yields, as manifested by the examples of **22** and **23**. The cyclic tertiary alkyl oxalates were also effective for the preparation of thiol ethers. These include 4-, 5-, and 12-membered rings (e.g., **24−27**).

The conditions for the thiolation of dialkyloxalates were also applicable for the amidation of *tert*-R−Ox−Me with sulfonamides and Cbz−NH$_2$, delivering the tertiary alkyl amines and amides **13−15** and **28−32** in moderate to excellent yields. The sterically more hindered tertiary alkyl oxalates appeared to inhibit the amination efficiency. For instance, the amination process was not compatible with the oxalates arising from 3-ethylpentan-3-ol; no reaction occurred in an attempt to access **33**.

We speculate that the reaction should proceed through a Lewis-acid-mediated S$_N$1-type nucleophilic attack of in situ formed carbocations. The thiolation of methyl (*R*)-1-phenyl-1-ethyl oxalate with 4-fluorobenzenethiol gave the thioether **34** in 90% yield constituting a 1:1 mixture of enantiomers (eq 1). The racemization of the oxalate in the thiolation event supports a mechanistic scenario that proceeds through a carbocation intermediate. In light of this mechanism, the tertiary benzylic alcohol, for example, 2-phenylpropan-2-ol, was effectively thiolated to give **35** in excellent yield (eq 2).

(1)

(2)
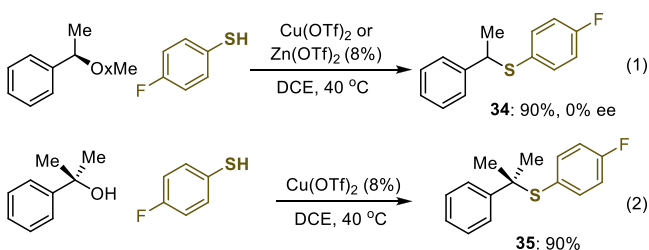
In conclusion, we have developed a Zn(OTf)$_2$- and Cu(OTf)$_2$-catalyzed etherification, thiolation, and amination of unactivated tertiary alkyl bromides and oxalates with easily accessible alcohols, thiols, and amines/amides. The mild and easy-to-operate reaction conditions offer promise for the preparation of challenging sterically congested C−O, C−S, and C−N bonds, which are suitable for a wide range of unactivated tertiary alkyl electrophiles including acyclic and cyclic stereogenic centers bearing longer chains. A variety of functional groups are tolerated. The utility of the present work was showcased in the facile alkylation of the hydroxyl and thiol groups within sugar and amino acids.

■ ASSOCIATED CONTENT

ⓢ Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c04206.

> Detailed experimental procedures and characterization of new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

Hegui Gong − *Center for Supramolecular Chemistry and Catalysis, Department of Chemistry, Shanghai University, Shanghai 200444, China;* ⓘ orcid.org/0000-0001-6534-5569; Email: hegui_gong@shu.edu.cn

Qun Qian − *Center for Supramolecular Chemistry and Catalysis, Department of Chemistry, Shanghai University, Shanghai 200444, China;* ⓘ orcid.org/0000-0003-2741-0491; Email: qianqun@shu.edu.cn

Authors

Yuxin Gong − *Center for Supramolecular Chemistry and Catalysis, Department of Chemistry, Shanghai University, Shanghai 200444, China;* ⓘ orcid.org/0000-0002-1915-7978

Zhaodong Zhu − *Center for Supramolecular Chemistry and Catalysis, Department of Chemistry, Shanghai University,*

Shanghai 200444, China; ⊙ orcid.org/0000-0002-9618-956X

Weiqi Tong − *Center for Supramolecular Chemistry and Catalysis, Department of Chemistry, Shanghai University, Shanghai 200444, China;* ⊙ orcid.org/0000-0002-8416-1631

Complete contact information is available at:
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Notes

The authors declare no competing financial interest.

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