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# Lewis Basic Sulfide Catalyzed Electrophilic Bromocyclization of Cyclopropylmethyl Amide

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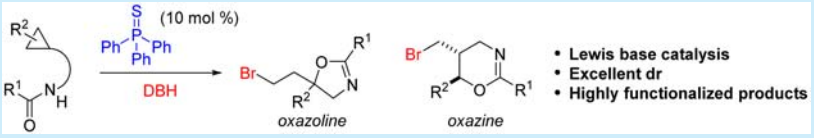
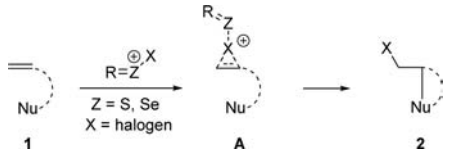
Supporting Information




**ABSTRACT:** A Lewis basic sulfide catalyzed electrophilic bromocyclization of cyclopropylmethyl amide has been developed. The catalytic protocol is applicable to both 1,1- and 1,2-substituted cyclopropylmethyl amides, giving oxazolines and oxazines in good yields and excellent diastereoselectivity.

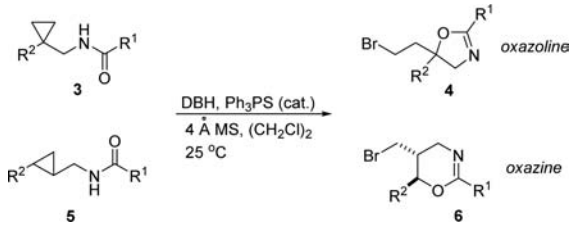
Lewis basic chalcogens including selenides and sulfides are useful catalysts to activate halogens in electrophilic halogenation of olefins. This type of catalytic protocol has been applied in a number of electrophilic halogenation reactions such as bromolactonization.[1] It is believed that the $\pi$-electrons of the olefin **1** can interact with the electrophilic halogen of the Lewis basic chalcogen−halogen reactive species to give the haliranium intermediate **A**, which is then attacked by a nucleophile to give the corresponding 1,2-co-halogenated products **2** (Scheme 1).[2]

**Scheme 1. Electrophilic Cohalogenation of Olefin Catalyzed by Lewis Basic Chalcogen**




It is well-known that cyclopropane has high ring strain, which leads to an ineffective orbital overlapping. As a result, the hybridized orbitals in the bended bonds (also known as "banana-bond") exhibit significant p-character,[3] and the reactivity of cyclopropanes resemble olefins in many cases such as 2 + 2 type cycloaddition and enolate-type reactions, implying that cyclopropane can be a suitable candidate for halogenation reaction in analogue to that of olefin.[4] Indeed, pioneer work by Tikhanushkina and co-workers described an interesting $KICl_2$ mediated cyclopropane ring-opening reaction to yield 1,3-dihalide compounds.[5,6] We envisioned that cyclopropane can be used in place of olefin in the bromocyclization process. Herein, we are pleased to report an efficient and highly chemo- and diastereoselective bromocyclization of cyclopropylmethyl amides **3** and **5** to give substituted oxazilidines **4** and oxazines **6** catalyzed by triphenylphosphine sulfide (Scheme 2).

**Scheme 2. Lewis Basic Sulfide Catalyzed Electrophilic Bromocyclization of Cyclopropylmethyl Amide**




It is noteworthy that oxazoline and oxazine are fundamental units of many bioactive and pharmaceutically important compounds.[7] In addition, ring opening of oxazines can furnish 1,3-amino alcohols, which are valuable building blocks in many research areas such as catalysis, materials, and natural products.[8] Significant endeavors have been devoted to the synthesis of substituted oxazolines and oxazines.[9]

At the outset of our investigation, amide **3a** and *N*-bromosuccinimide (NBS) were used as the substrate and brominating agent, respectively (Table 1). The cyclization was found to be sluggish when no catalyst was applied (Table 1, entry 1). When 10 mol % of triphenylphosphine sulfide was used as the Lewis basic sulfide catalyst, the reaction efficiency was enhanced dramatically and the cyclized product **4a** was obtained in 18% yield after 1 day (Table 1, entry 2). Other Lewis bases including *N*,*N*,*N*′,*N*′-tetramethylthiourea, DABCO, and DMAP were ineffective in catalyzing the reaction (Table 1, entries 3−5). On the other hand, a survey on various

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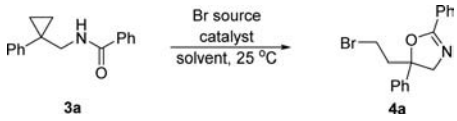
**Table 1. Conditions Optimization**[a]




3a 4a

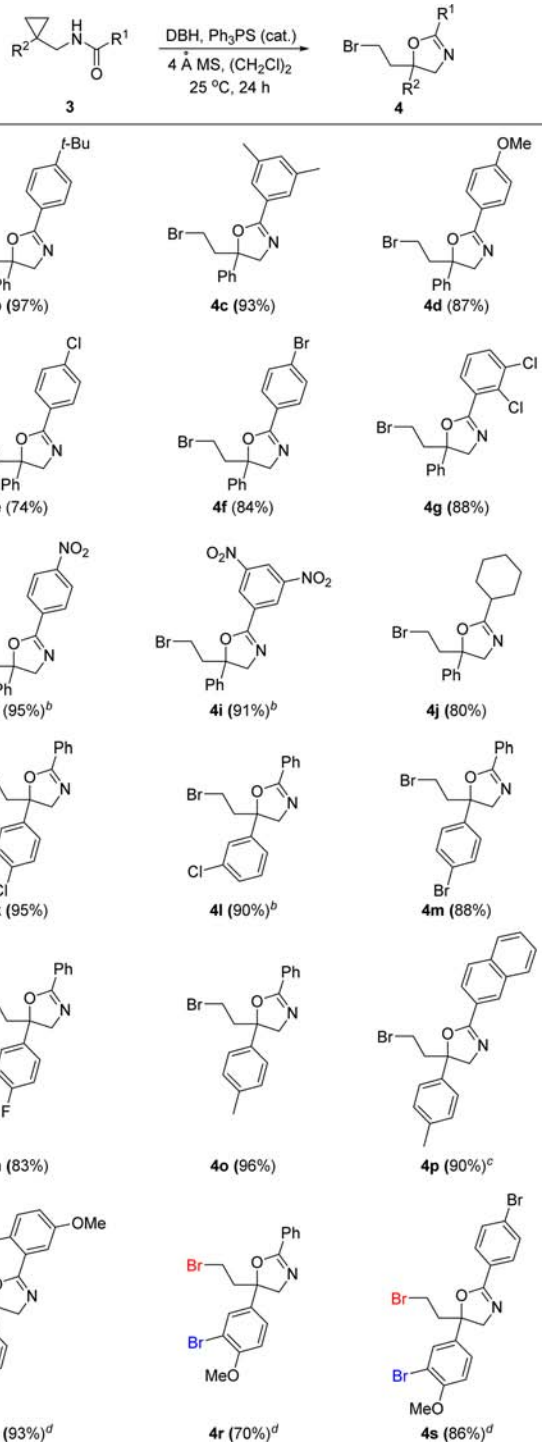
| entry | Br source | catalyst | solvent | time (h) | yield[b] (%) |
|---|---|---|---|---|---|
| 1 | NBS | | $CH_2Cl_2$ | 168 | 16 |
| 2 | NBS | $Ph_3PS$ | $CH_2Cl_2$ | 24 | 18 |
| 3 | NBS | $(Me_2N)_2CS$ | $CH_2Cl_2$ | 24 | NR |
| 4 | NBS | DABCO | $CH_2Cl_2$ | 24 | NR |
| 5 | NBS | DMAP | $CH_2Cl_2$ | 24 | NR |
| 6 | NBP | $Ph_3PS$ | $CH_2Cl_2$ | 24 | 15 |
| 7 | TABCO | $Ph_3PS$ | $CH_2Cl_2$ | 24 | NR |
| 8 | DBH | | $CH_2Cl_2$ | 168 | NR |
| 9 | DBH | $Ph_3PS$ | $CH_2Cl_2$ | 24 | 55 |
| 10 | DBH | $Ph_3PS$ | $CHCl_3$ | 24 | 58 |
| 11 | DBH | $Ph_3PS$ | $(CH_2Cl)_2$ | 24 | 75 |
| 12 | DBH | $Ph_3PS$ | $CH_3CN$ | 24 | 21 |
| 13 | DBH | $Ph_3PS$ | THF | 24 | trace |
| 14 | DBH | $Ph_3PS$ | EtOAc | 24 | 65 |
| 15 | DBH | $Ph_3PS$ | DMF | 24 | 62 |
| **16**[c] | **DBH** | **$Ph_3PS$** | **$(CH_2Cl)_2$** | **24** | **85** |
| **17**[c,d] | **DBH** | **$Ph_3PS$** | **$(CH_2Cl)_2$** | **24** | **82** |
| 18[e] | DBH | $Ph_3PS$ | $(CH_2Cl)_2$ | 48 | 79 |

[a]Reactions were carried out with **3a** (0.2 mmol), Br source (0.4 mmol), and catalyst (0.02 mmol) in solvent (4 mL) at 25 °C in the absence of light. [b]The yields were isolated yields. [c]4 Å molecular sieves were used. [d]4.0 mmol of **3a** was used. [e]1.0 equiv of DBH was used.

brominating agents was conducted and 1,3-dibromo-5,5-dimethylhydantoin (DBH) could offer the product with 55% yield (Table 1, entries 6–9). Again, triphenylphosphine sulfide remains playing a crucial role in activating the Br source (Table 1, entry 8 vs 9).

Next, a series of solvents were screened. Chlorinated solvents, in particular, 1,2-dichloroethane, were found to be more suitable, while other polar solvents such as acetonitrile, THF, DMF, and ethyl acetate were less effective in driving the cyclization (Table 1, entries 9–15). Finally, it was realized that the addition of 4 Å molecular sieves could further improve the yield to 85% (Table 1, entry 16). The reaction could be conducted using 1 g of **3a** with similar conversion, indicating that the reaction is readily scalable (Table 1, entry 17). Although 1 equiv of DBH was found to be sufficient for the high conversion, a relatively longer reaction time was required as compared to that of 2 equiv of DBH (Table 1, entry 16 vs 18). With the optimized conditions in hand, a number of substrates **3** were examined. The scope was found to be quite broad in which various $R^1$ and $R^2$ substitutions could be tolerated under this catalytic protocol (Scheme 3). For the $R^1$ substitution, both electron-donating and electron-withdrawing aryl groups worked well to give the desired oxazolidines **4**. In particular, the 4-*tert*-butylphenyl substrate **3b** gave oxazolidine **4b** in 97% yield. When a cyclohexyl substitution was employed, the alkyl-substituted product **4j** was obtained in 80% yield. The $R^2$ substitution at the cyclopropane could also be varied. As indicated by examples with substrates **3k–o**, a range of substituents including chloro, bromo, fluoro, and methyl groups returned the corresponding oxazilines in good yields. Structurally complicated systems such as **4p** ($R^1$ = 2- naphthyl; $R^2$ = 4-methylphenyl) and **4q** ($R^1$ = 3-methoxyphenyl; $R^2$ = 4-methylphenyl) could be prepared using the same catalytic

**Scheme 3. Scope of the Bromocyclization of 1,1-Substituted Cyclopropylmethyl Amides 3**[a]




[a]Reactions were carried out with **3** (0.2 mmol), DBH (0.4 mmol), 4 Å MS (250 mg), and $Ph_3PS$ (0.02 mmol) in $(CH_2Cl)_2$ (4 mL) at 25 °C in the absence of light. [b]Reaction time was 48 h. [c]Reaction time was 12 h. [d]Only dibrominated product was isolated.

protocol. When 4-methoxyphenyl group was used as the $R^2$ substitution, aromatic bromination took place simultaneously to give dibrominated products (i.e., **4r,s**).

Moreover, 1,2-cyclopropylmethyl amides **5** were found to work equally as well as 1,1-cyclopropylmethyl amides **3**. Some examples are shown in Scheme 4. It is noteworthy that



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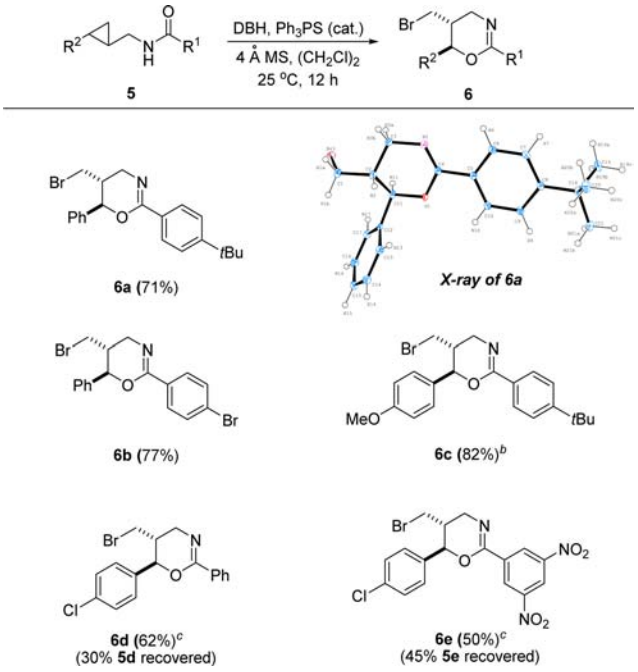
**Scheme 4. Scope of the Bromocyclization of 1,2-Substituted Cyclopropylmethyl Amides 5**[a]

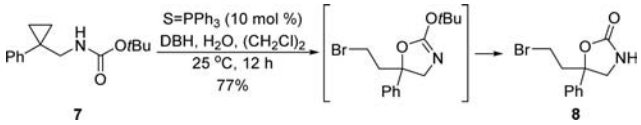



[a]Reactions were carried out with **5** (0.2 mmol), DBH (0.4 mmol), 4 Å MS (250 mg), and $Ph_3PS$ (0.02 mmol) in $(CH_2Cl)_2$ (4 mL) at 25 °C in the absence of light. [b]1.0 equiv of DBH was used. [c]The reaction time was 24 h.

excellent dr was obtained in all cases. The Br handle in **6** allows for further modification flexibly. The relative stereochemistry of **6** was established on the basis of an X-ray crystallographic study of a single-crystal sample of **6a**.

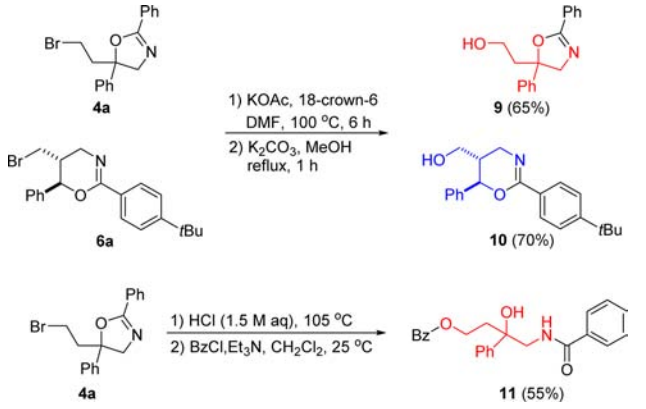
Other than amide, carbamate was also found to be applicable in this type of cyclization. When cyclopropylmethyl carbamate **7** subjected to the optimized conditions, cyclic carbamate **8** was furnished in good yield (Scheme 5). One equivalent of water was required for high reaction conversion, presumably for the hydrolysis of the imine intermediate.

**Scheme 5. Bromocyclization of Cyclopropylmethyl Carbamate 7**



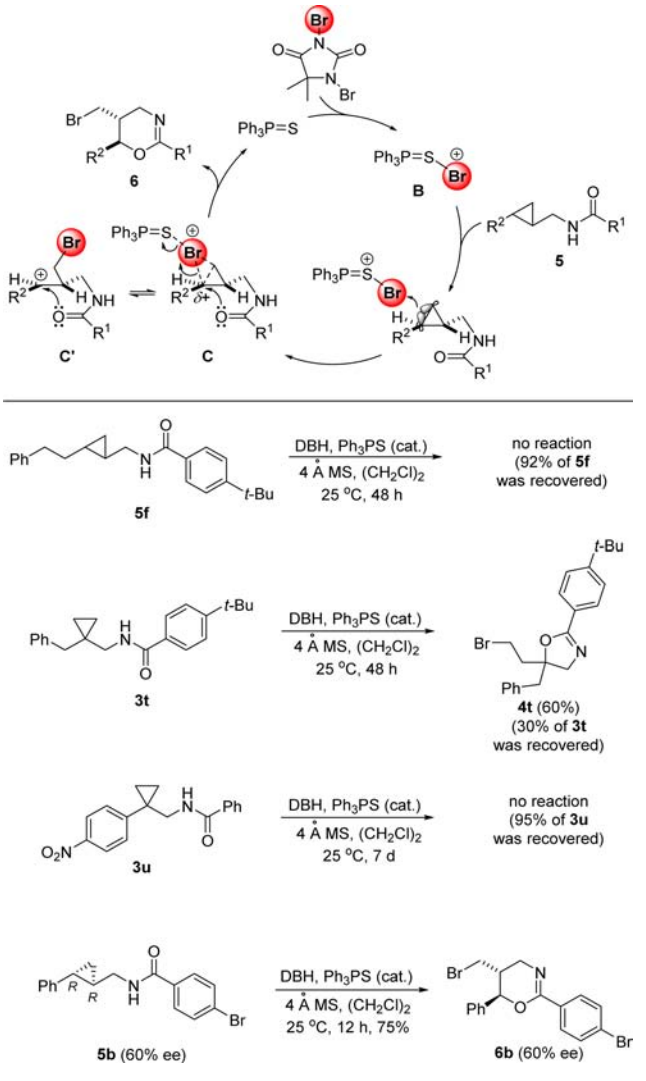

The bromide in **4a** and **6a** could easily be substituted by acetate followed by hydrolysis to give **9** and **10**, respectively. On the other hand, it is well-known that oxazolines and oxazines could readily be opened to furnish the corresponding 1,2- and 1,3-amino alcohol systems.[9] For instance, treatment of oxazoline **4a** with 1.5 M aqueous HCl under reflux gave the corresponding 1,2-amino alcohol. It was found that the Br in **4a** was substituted by a water molecule simultaneously in the reaction. Subsequent selective protection of the primary alcohol yielded **11**. These chemical operations provide a convenient access to various pharmaceutically valuable substituted amino alcohols (Scheme 6).

**Scheme 6. Transformations of Oxazoline 4a and Oxazine 6a**




Although intensive investigation on the mechanism is still underway, we speculate that the reaction might initially involve the attack of the Lewis basic sulfide activated Br (species **B**) by the p-character $\sigma$-bond to give species **C** (Scheme 7). Since excellent dr was obtained in the cyclization of the 1,2-*trans*-substituted cyclopropane **5**, we believe that species **C**, an analogue of bromiranium ion **A** (Scheme 1, X = Br), might be

**Scheme 7. Plausible Reaction Mechanism**



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configurationally stable as evidenced by the excellent dr of the reaction (Scheme 4). The reaction was also found to be enantiospecific when enantioenriched **5b** (60% ee) was used. In addition, the reaction efficiency diminished significantly when the phenyl substituents of cyclopropanes were replaced by aliphatic alkyl groups (**5f** or **3t**) or the highly electron-deficient 4-nitrophenyl group (**3u**), which is similar to the general reaction tendency in electrophilic bromination of olefins observed by our group recently.[10] Nucleophilic substitution of **C** by the amide in an $S_N2$ manner could yield the Markovnikov-selective product **6**. Alternatively, the reaction might proceed through the carbocation intermediate **C′**, a ring-opening species of **C**, followed by a rapid trapping of the carbocation by the amide nucleophile intramolecularly to give **6**.

In summary, we have developed an efficient and diastereoselective electrophilic bromocyclization of cyclopropylmethyl amides catalyzed by triphenylphosphine sulfide. The oxazoline and oxazine products could be transformed into biologically valuable amino alcohol systems.

## ■ ASSOCIATED CONTENT

### Supporting Information

Experimental procedures and characterization data for all new compounds, and CIF file of the X-ray structure. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02557.

X-ray data for compound **6a** (CIF)
Experimental procedures and characterization data for all new compounds (PDF)

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### Author Contributions

§Y.-C.W. and Z.K. contributed equally to this project.


### Notes

The authors declare no competing financial interest.

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