Cyclopropanation

Stereoselective Synthesis of (Sulfonimidoyl)cyclopropanes with (R)-PhSO(NTs)CH₂Cl and α,β-Unsaturated Weinreb Amides: Tuning the Selectivity between C–Cl and C–S Bond Cleavage

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Abstract: (Sulfonimidoyl)cyclopropanes have become the subject of special interest since they combine the advantages of two chemical leads (cyclopropane and sulfoximine). However, their synthesis is limited, and the stereoselective synthesis of optically enriched (sulfonimidoyl)cyclopropanes still remains an unsolved task. Here we report the first stereoselective (sulfonimidoyl)cyclopropanation reaction using α,β-unsaturated Weinreb amides and (R)-PhSO(NTs)CH₂Cl [(R)-1]. This reaction possesses a broad substrate scope, and the products can be easily transformed into other useful cyclopropyl-containing and/or sulfonimidoyl-containing compounds. The Weinreb amide group and the counter cation of the base were found to be important for the selective C–Cl bond cleavage.

Introduction

The cyclopropyl group is an important pharmacophore, and many well-established drugs, such as Odanacatib, Singulair and Ciprofloxacin contain this prestigious group.[1] Recently, sulfoximines have gained increasing attention in drug design because of their unique physical, chemical, and biological properties.[2] In this context, (sulfonimidoyl)cyclopropanes have become the subject of special interest since they combine the advantages of two chemical leads. Several methods were reported on the nonstereoselective synthesis of (sulfonimidoyl)cyclopropanes,[3] but the stereoselective synthesis of optically enriched (sulfonimidoyl)cyclopropanes still remains an unsolved task.[4] In 1993, Jackson reported an addition/elimination reaction between α-phenylthio-substituted vinylsulfoximine and [(phenylsulfonyl)-(phenylthio)methyl]lithium, but the (sulfonimidoyl)cyclopropane was obtained (75 % yield) with only 3:1 diastereomeric ratio (dr).[4a] Craig’s transannular, decarboxylative Claisen rearrangement of an unsaturated ε-lactone bearing an α-arylsulfonyliminyl substituent afforded a (sulfonimidoyl)cyclopropane in 69 % yield, with only 3:2 dr.[4b] Herein, we report a conceptually different approach for the synthesis of optically enriched (sulfonimidoyl)cyclopropanes through the use of (R)-PhSO(NTs)CH₂Cl and (R)-PhSO(NTBS)CH₂Cl reagents [see Scheme 1 (b)]. Our Michael addition/elimination strategy distinguishes itself by operational simplicity, broad substrate scope, and excellent stereoselectivity.

Scheme 1. Fluorocyclopropanation and (sulfonimidoyl)cyclopropanation of α,β-unsaturated Weinreb amides.

Sulfoximines have been used in nucleophilic alkylidene transfer reactions, and C–S bond cleavage of the sulfoximines took place in all of these reactions.[5a–5c,5e–5g,6b,6e,6f] Taking advantage of the better leaving-group ability of the PhSO(NTs) functionality (compared to fluorine), we had developed the first enantioselective fluorocyclopropanation reaction of α,β-unsaturated Weinreb amides with (R)-PhSO(NTs)CH₂F with excellent stereoselectivity [Scheme 1, (a)].[6b] Only C–S bond cleavage was found in this fluorocyclopropanation.[6b] However, the cyclopropanation reactions reported herein show that the chemoselectivity between C–Cl and C–S bond cleavage of (R)-PhSO(NTs)CH₂Cl can be tuned by changing either the counter cation of the base or the Michael acceptor.

Results and Discussion

Optically pure chloromethyl sulfoximine (R)-1 was readily prepared from (S)-2 by a trichlorination/dechlorination process in
The substrate scope of the (sulfonimidoyl)cyclopropanation reaction was tested under the conditions described in Table 1, Entry 3. As shown in Scheme 4, the reaction turned out to be general, and chloromethyl sulfoximine (R)-1 could react with a variety of structurally diversified α,β-unsaturated Weinreb amides to afford the corresponding (sulfonimidoyl)cyclopropanes 4 in moderate to excellent yield (62–98%) and with good to excellent diastereoselectivities (93:7 to > 99:1 dr). The reaction tolerates alkanyl, alkynyl, bromo, fluoro, methoxy, and thiophen-2-yl groups. A naphthyl-substituted unsaturated Weinreb amide was also successfully cyclopropanated to give product 4i in 88% yield with a 99:1 dr. This cyclopropanation reaction is also amenable to alkyl-substituted unsaturated Weinreb amides to give the (sulfonimidoyl)cyclopropanes in 62–98% yields, with 98:2–99:1 dr (Table 2, 4j–4m). It is worth noting that the diastereoselectivity of our previous fluoro cyclopropanation of substrate 3j with (R)-PhSO(NTs)CH2F is much lower than that of the present (sulfonimidoyl)cyclopropanation of 3j with (R)-PhSO(NTs)CH2Cl, indicating the different reactivity of the two sulfoximine reagents.6b The absolute configuration of product 4c was confirmed by its single-crystal X-ray structure analysis (Table 2), and the others were assigned by analogy.

Table 2. (Sulfonimidoyl)cyclopropanation of α,β-unsaturated Weinreb amides.6b

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Solvent</th>
<th>Yield of 4a [%], dr[a]</th>
<th>Yield of 5 [%], dr, ee [%][b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>KHMDS</td>
<td>THF</td>
<td>63, 85:15</td>
<td>27, 95:5, 3</td>
</tr>
<tr>
<td>2</td>
<td>NaHMDS</td>
<td>THF</td>
<td>78, 83:17</td>
<td>5, 80:20, 51</td>
</tr>
<tr>
<td>3</td>
<td>LiHMDS</td>
<td>THF</td>
<td>89, &gt;99:1</td>
<td>&lt;1, n.d., n.d.</td>
</tr>
<tr>
<td>4</td>
<td>LiHMDS</td>
<td>THF/HMPA (10:1, v/v)</td>
<td>64, 86:14</td>
<td>22, 93:7, 72</td>
</tr>
</tbody>
</table>

[a] Experimental procedure: to a mixture of (R)-3-(4-fluorophenyl)-N-methoxy-N-methylacrylamide (3a) (0.5 mmol) and (R)-1 (0.65 mmol, 1.3 equiv) in solvent at –78 °C was added base (THF solution, 0.6 mmol, 1.2 equiv); after 20 min, the dry-ice bath was removed and the reaction mixture was stirred at room temp. for 2 h. [b] Yield refers to isolated yield and the dr, which refers to the ratio of major diastereoisomer to all other diastereoisomers, was determined by 1H NMR spectroscopy. [c] The ee of the major diastereoisomer was determined by chiral HPLC. n.d. = not determined.

The Ts protecting group in sulfoximine (R)-1 can be easily removed with H2SO4 (18.4 M), providing the opportunity to synthesize other N-protected optically pure chloromethyl sulfoximines. According to a two-step process shown in Scheme 4, N-TBS-substituted sulfoximine (R)-6 was obtained in 88% yield without loss of optical purity at the sulfur stereogenic center.
Sulfoximine \( (R) \cdot 6 \) can also undergo cyclopropanation reaction with \( \alpha,\beta \)-unsaturated Weinreb amide \( 3a \) to afford the (sulfonimidoyl)cyclopropane \( 4n \) in 90 % yield and with a 92:8 dr, and the major diastereoisomer was isolated in 84 % yield (Scheme 3).

The reaction between optically pure sulfoximine \( (S) \cdot 2 \) and \( \alpha,\beta \)-unsaturated Weinreb amide \( 3a \) afforded cyclopropane \( 7 \) in 86 % yield with a \( > 99:1 \) dr, but only moderate enantioselectivity was observed (53 % ee, Scheme 4).\(^8\) However, when compound \( 4a \) was treated under easy-to-handle reductive desulfonimidoylation conditions by using \( \text{MgBrCH}_2\text{CH}_2\text{Br/MeOH} \), the sulfonimidoyl group could be removed to afford compound \( 7 \) in 76 % yield with a \( > 99:1 \) dr, and a \( > 99 \) % ee (Scheme 4).

Scheme 3. Synthesis of sulfoximine \( (R) \cdot 6 \) and its application in the synthesis of (sulfonimidoyl)cyclopropane \( 4n \).

The Weinreb amide group has been proven to be a powerful functional group for synthetic transformations.\(^9\) To further demonstrate the potential applications of our cyclopropanation method, we studied the reaction of (sulfonimidoyl)cyclopropane \( 4a \) with organolithium reagents. After treating phenylacetylene with \( n\text{BuLi at } -78 \) °C to room temp. for 0.5 h, compound \( 4a \) was added at \(-78 \) °C, and the solution was stirred for 2 h. Eventually, compound \( 8 \) was obtained in 77 % yield (Scheme 5).

Scheme 5. Synthetic application of product \( 4h \).

Encouraged by the successful stereoselective synthesis of (sulfonimidoyl)cyclopropanes with \( \alpha,\beta \)-unsaturated Weinreb amides, we tried the reaction between \( (R) \cdot 1 \) and \( \alpha,\beta \)-unsaturated ketone \( 9 \) under similar reaction conditions (Scheme 6). In contrast to the exclusive formation of (sulfonimidoyl)cyclopropane \( 4b \) in the reaction of \( (R) \cdot 1 \) with \( N \)-methoxy-\( N \)-methylcinnamamide \( (3b) \), both (sulfonimidoyl)cyclopropane \( 10 \) and chlorocyclopropane \( 11 \) formed in the reaction of \( (R) \cdot 1 \) and \( 9 \). Interestingly, when 2-benzylidenedimalononitrile \( (12) \) was applied to the reaction of \( (R) \cdot 1 \) under the same conditions, a different chemoselectivity was observed, that is, the sulfonimidoyl group, instead of the chlorine atom, served as a leaving group. The two diastereoisomers of chlorocyclopropane \( 14 \) were separated by silica gel column chromatography to afford the trans isomer (major product) in 64 % yield, with a 72 % ee, and the cis isomer (minor product) in 32 % yield, with a 50 % ee (Scheme 6). The absolute configurations of the two isomers of \( 14 \) were confirmed by their single-crystal X-ray structure analysis (see Supporting Information).\(^{110}\)

The selectivity between \( \text{C--Cl} \) and \( \text{C--S} \) bond cleavages in the cyclopropanation reactions of \( \alpha,\beta \)-unsaturated Weinreb amides \( 3 \), \( \alpha,\beta \)-unsaturated ketone \( 9 \), and 2-benzylidenedimalononitrile \( 12 \) is intriguing. Although further study is needed to elucidate the detailed mechanism, we propose that a chelated intermediate, such as \( \text{A} \) in Figure 1, is involved in the reaction of sulfoximine \( (R) \cdot 1 \) with \( \alpha,\beta \)-unsaturated Weinreb amides. Sulfoximines are coordinative and have been widely used as ligands in Lewis acid mediated reactions.\(^{111}\) Although a steric repulsion between the sulfonimidoyl group and Ph can be envisioned in \( \text{A} \), the complexation of the lithium ion with the sulfonimidoyl group probably make it more preferable than \( \text{B} \) (see Figure 1).\(^{112}\) The proposal of chelated intermediates is supported by the following experimental results: (1) the ratio of \( 4a/5 \) increased when the cation of the base changed from the less coordinating \( \text{K} \) ion to the more coordinating \( \text{Na} \) and \( \text{Li} \) ions (Table 1, Entries 1–3);\(^{112}\) (2) addition of the coordinating solvent \( \text{HMPA} \) decreased the ratio of \( 4a/5 \) (Table 1, Entry 4). Our proposal is also in accordance with Pyne’s mechanistic proposal for

Figure 1. Proposed intermediates.
the cyclopropanation of α,β-unsaturated ketones with lithiated PhSO(NTs)CH2CH=CH2.[13] The less coordinating ability of the ketone in comparison with the Weinreb amide group might account for the decreased selectivity for the C–Cl bond cleavage in the reaction between (R)-1 and compound 9. The structural property of substrate 12 substituted with two linear CN groups probably makes the expected sulfoximine-chelated conformation less stable than the sulfoximine-nonchelated conformation.

Conclusions

An efficient synthesis of enantiomerically enriched (sulfoximidoyl)cyclopropanes with broad substrate scope, good yields, and excellent diastereoselectivities by the reaction between optically pure chloromethyl sulfoximines and α,β-unsaturated Weinreb amides has been disclosed. To the best of our knowledge, this is the first (sulfoximidoyl)cyclopropanation reaction of Michael acceptors. The counter cation of the base and the Weinreb amide group were found to be important for the selective C–Cl bond cleavage of (R)-PhSO(NTs)CH2Cl. The easy removal of the sulfoximidoyl group and the transformation of the Weinreb amide functionality demonstrate the synthetic utility of this method.

CCDC 1448852 (for 4c), 1448777 (for trans-14), and 1448778 (for cis-14) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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