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RESEARCH ARTICLE

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Enantioselective Synthesis of Cyclopropanone Equivalents and Application to the Formation of Chiral β-Lactams

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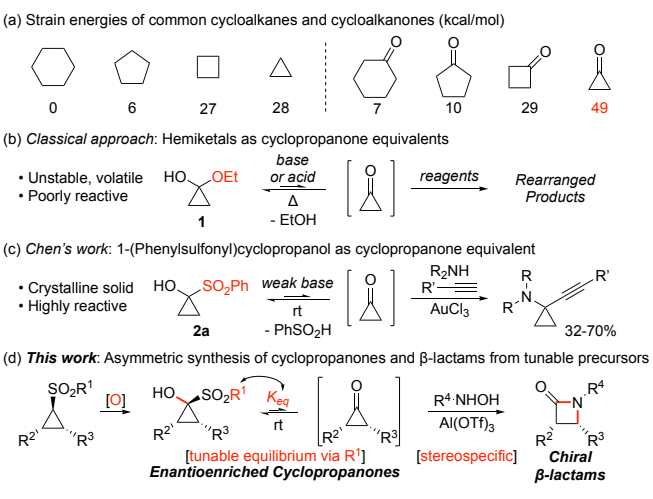
Abstract: Cyclopropanone derivatives have long been considered unsustainable synthetic intermediates due to their extreme strain and kinetic instability. Herein, we report the enantioselective synthesis of 1-sulfonylcyclopropanols as stable yet powerful equivalents of the corresponding cyclopropanone derivatives, via α-hydroxylation of sulfonylcyclopropanes using a bis(silyl) peroxide as electrophilic oxygen source. This work constitutes the first general approach to enantioenriched cyclopropanone derivatives. Both the electronic and steric nature of the sulfonyl moiety, which serves as a base-labile protecting group and confers crystallinity to these cyclopropanone precursors, were found to have a crucial impact on the rate of equilibration to the corresponding cyclopropanone, highlighting their modular nature and the potential for their widespread adoption as synthetic intermediates. The utility of these cyclopropanone surrogates is demonstrated in a mild and stereospecific formal [3+1] cycloaddition with simple hydroxylamines acting here as nitrene equivalents, leading to the efficient formation of chiral β-lactam derivatives.

Introduction

The rearrangement of strained ketone derivatives, typically yielding ring-expanded or ring-opened products, constitutes a key strategy for the elaboration of complex molecules relevant to the pharmaceutical industry.[1] While myriad transformations have been developed with small cyclic ketones such as cyclobutanones,[2] the analogous use of cyclopropanone derivatives as substrates has seriously lagged behind due to the kinetic instability often associated with these compounds, as a result of their extreme strain and multiple decomposition pathways. Indeed, while cyclopropane and cyclobutane derivatives generally possess similar strain energies, the corresponding cycloalkanones differ in this regard by *ca.* 20 kcal/mol (Scheme 1a).[3] Although cyclobutanone derivatives are known to be relatively stable and in some cases are commercially available, cyclopropanones often decompose instantly at room temperature, as they are kinetically unstable to heat, light and moisture.[4] The most common decomposition pathways involve either polymerization (heat- and moisture-induced), decarbonylation to alkenes (light-induced), or nucleophilic ring-opening as in the Favorskii rearrangement.[5] Nevertheless, cyclopropanone itself has been previously prepared by reaction of diazomethane with ketene at –78 °C followed by distillation at the same temperature,[6] affording an ethereal solution that must be used immediately at low temperature. A more common and practical approach popularized by Wasserman in the 1960's involves the use of alcohol adducts of cyclopropanone derivatives, such as cyclopropanone hemiketal **1**, that can be transformed *in situ* to the corresponding strained ketone *via* base- or acid-induced α-elimination (Scheme 1b).[4d,7] Due in part to the poor leaving group ability of alkoxides, these unstable precursors require harsh conditions to equilibrate to the corresponding cyclopropanones, which is problematic considering the kinetic instability of these highly strained species. This paradox is the critical reason why these hemiketal precursors to cyclopropanone are rarely suitable substrates and often lead to low yields of desired rearranged products.[4d] The absence of a general class of well-behaved cyclopropanone precursors has thus largely defined these highly strained species as chemical curiosities rather than useful building blocks in organic synthesis. By analogy to the use of sulfinic acid adducts as base-labile protecting groups for unstable aldehydes and imines in nucleophilic addition chemistry,[8] Chen reported that the phenylsulfinic acid adduct of unsubstituted cyclopropanone **2a**, a white crystalline solid, is more reactive and surprisingly well-behaved as compared with classical hemiketals, with equilibration to cyclopropanone taking place in mildly basic conditions at room temperature or below (Scheme 1c).[9]

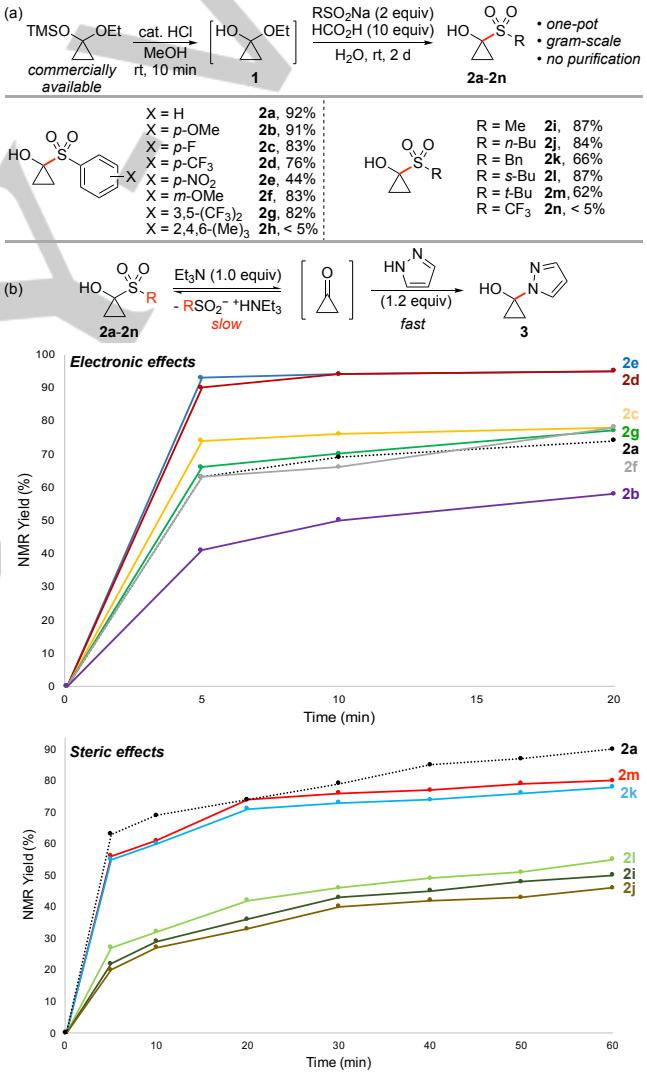


Scheme 1. Reactivity of cyclopropanone and its precursors.

We reasoned that such stability *and* increased reactivity of 1-sulfonylcyclopropanols could be key to unlocking the tremendous potential of cyclopropanone derivatives as synthetic intermediates, allowing reactions to proceed under mild conditions and thus suppressing undesired decomposition pathways. Moreover, the steric and electronic tunability of the sulfinic acid leaving group in these compounds could prove beneficial to establishing a general class of cyclopropanone precursors. Herein, we report the first enantioselective synthesis of 1-sulfonylcyclopropanols *via* an unprecedented α-hydroxylation of readily accessible cyclopropylsulfones using a bis(silyl) peroxide reagent as oxidant, and their application as substrates in a novel stereospecific formal [3+1] cycloaddition with simple hydroxylamines, leading to enantioenriched β-lactams (Scheme 1d). Kinetic studies using a pyrazole trapping reaction reveal the crucial influence of the sulfinic acid leaving group's steric and electronic properties, where hindered and/or electron-poor derivatives led to considerably faster equilibration to cyclopropanone, highlighting the modular reactivity of these substrates. Considering the breadth of reported transformations using strained ketones in organic synthesis,[1] our studies, which constitute the first general enantioselective approach to cyclopropanone derivatives,[10] should prove to be useful in the elaboration of complex molecules using previously inaccessible cyclopropanone-based rearrangements.

Results and Discussion

Synthesis of unsubstituted derivatives and kinetic study of their equilibration to cyclopropanone. We theorized that establishing the equilibrium between 1-sulfonylcyclopropanols and cyclopropanones would be key to subsequent reaction development efforts using these substrates. To do so, we sought to access electronically and sterically differentiated achiral sulfonylcyclopropanols (**2**) to evaluate the effect of the leaving group on such an equilibrium (Scheme 2). Prior to this work, only the phenylsulfonyl- (R = Ph, **2a**) and *p*-tolylsulfonyl- (R = 4-Me-C_6H_4) substituted achiral sulfonylcyclopropanols had been reported by Chen in moderate yields, and the procedure required distillation and isolation of hemiketal intermediate **1**,[7c] as well as recrystallization of the final product.[9a] Building on this approach, we first optimized a practical and general one-pot protocol leading to variously substituted 1-sulfonylcyclopropanols **2a–2n** in moderate to excellent yields (Scheme 2a). Starting from commercially available (1-ethoxycyclopropoxy)trimethylsilane, acid-mediated cleavage of the silyl group rapidly affords a solution of hemiketal **1**, which is directly treated with the corresponding sodium sulfinate salt in presence of formic acid and water at room temperature. Using these conditions, cyclopropanone precursors **2a–2n** were directly obtained in pure form after aqueous workup without the need for isolation of **1**, and the procedure was applied on gram-scale with similar efficiency.[11] With these substrates in hand, we employed a novel pyrazole substitution reaction leading to adduct **3** to evaluate the relative rate of conversion of the sulfonylcyclopropanols to cyclopropanones (Scheme 2b). Such a trapping reaction was found to be particularly clean and occurred at a rate that was easy to follow by NMR at room temperature. Considering the highly strained and energetic character of cyclopropanone,[3,4] it is anticipated that the initial equilibrium leading to its formation is rate-limiting of the overall process. Hence, the relative rates measured for each precursor **2** in this reaction should be indicative of their relative propensity to equilibrate to cyclopropanone. In a general manner, electron-poor sulfinate adducts were found to react faster (e.g. see **2a–2c** vs **2d–2e**), presumably due to the increased electronic stabilization and reduced nucleophilicity[12] of the corresponding sulfinate anion leaving group RSO_2H•NEt_3 (Scheme 2b, top). Moreover, evaluation of alkylsulfinic acid adducts **2i–2m** enabled an assessment of the effect of steric hindrance on the sulfonylcyclopropanol's propensity to equilibrate to cyclopropanone, where encumbered substrates (e.g. **2m**) were generally found to be more reactive (Scheme 2b, bottom). This is likely due to the fact that sterically congested sulfonylcyclopropanols benefit from a greater torsional (Pitzer) strain release during the rate-limiting α-elimination process, even though ring (Baeyer) strain is significantly increased in all cases.



Scheme 2. a) Synthesis of unsubstituted 1-sulfonylcyclopropanols (isolated yields). b) Structure-reactivity relationship in a pyrazole substitution. NMR yields for each timepoint were determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as standard.

These observed trends are further reinforced by the fact that particularly hindered **2h** or electron-poor **2n** 1-sulfonylcyclopropanols could not be obtained using our optimized procedure, as they were found to be too unstable to isolation and only led to decomposition, likely due to spontaneous equilibration to cyclopropanone.[13] The results of the kinetics observed using **2a–2n** highlight the modular nature of 1-sulfonylcyclopropanols as cyclopropanone equivalents, where a wide spectrum of equilibration rates could be obtained through simple modification of the sulfonyl group. Considering the high propensity of cyclopropanones to polymerize,[4] such modularity should prove highly useful to future reaction development efforts using these reagents, allowing one to minimize the concentration of the cyclopropanone intermediate and match its rate of formation to the desired rearrangement.

Enantioselective synthesis of cyclopropanone equivalents. In order to apply the procedure detailed above to the formation of chiral, *substituted* 1-sulfonylcyclopropanol derivatives, one would need to access the corresponding enantioenriched hemiketal intermediates prior to addition of the sulfinate salt. While the Simmons-Smith cyclopropanation of α-substituted silyl ketene acetals, leading to such hemiketals, has previously been reported,[14] it is not general, leads to mixtures of diastereomers, and to date, cannot be efficiently performed in an enantioselective manner (Figure 1a, left). Alternatively, one could envision a reductive cyclization of enantioenriched α-substituted β-chloroesters (Figure 1a, right),[10] although such a process is only known for a 2-methyl-substituted hemiketal (R^1 = H, R^2 = Me). Moreover, the radical character of this transformation strongly limits the nature of the possible substituents around the cyclopropane ring, in addition to the fact that access to such halogenated substrates in their enantioenriched form is not straightforward and generally requires multiple steps. For these reasons, the procedure presented in Scheme 2 is largely limited to achiral, unsubstituted derivatives, and we thus decided to design and optimize a more direct and practical approach involving a base-mediated α-hydroxylation of enantioenriched sulfonylcyclopropanes (Figure 1b), which are readily accessible substrates via known synthetic methods,[15] with a wide variety of possible substitution patterns (*vide infra*).

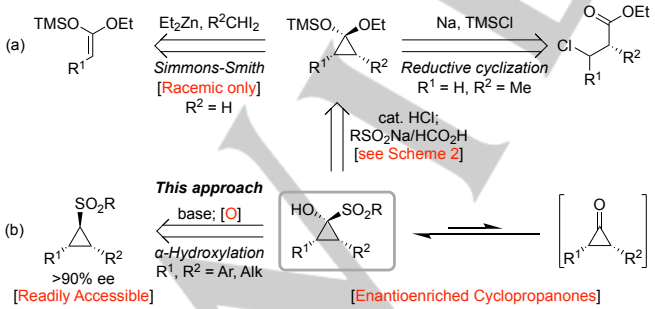
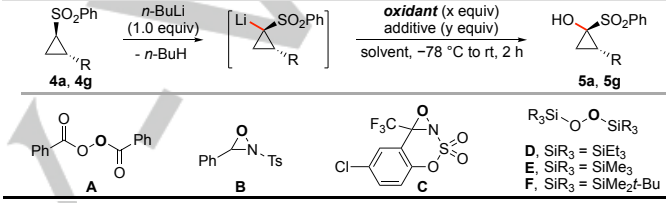


Figure 1. Comparison of various routes considered to access enantioenriched 1-sulfonylcyclopropanols: (a) *via* deprotection/sulfinate substitution of ketals; (b) *via* α-hydroxylation of sulfonylcyclopropanes (*this approach*).

Unlike with carbonyl compounds and carboxylic acid derivatives, a significant challenge inherent to the α-hydroxylation of sulfones is the propensity of the resulting α-sulfonyl alkoxide intermediates to decompose to the corresponding carbonyl compound and sulfinic acid salt through α-elimination.[8,16] In this case, such an event would lead to the cyclopropanone that would likely decompose under the reaction conditions. Because of the endothermic nature of this undesired elimination, it was reasoned that performing the reaction with a highly reactive electrophilic reagent at –78 °C could minimize this undesired pathway and allow us to isolate reasonable amounts of the chiral 1-sulfonylcyclopropanols (Table 1). While the use of common electrophilic hydroxylation reagents such as oxaziridines led to either poor yield or undesired side-products (entries 1-3), it was found that the use of bis(triethylsilyl) peroxide **D** as oxidant,[17] previously reported for the radical alkylation of amides,[18,19] afforded promising results when added in the presence of BF_3•OEt_2 (entries 4-9).[11,20,21]

Table 1. Optimization of the α-hydroxylation of sulfonylcyclopropanes using substituted substrates **4a** and **4g**.

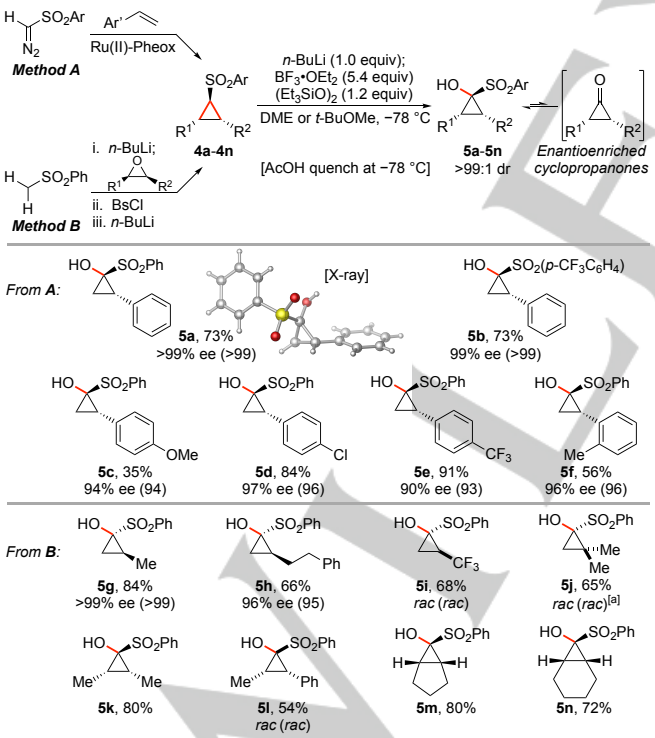


Entry	R	Oxidant (equiv)	Additive (equiv)	Solvent	Yield[a]
1	Ph	**A** (1.2)	-	THF	<5[b]
2	Ph	**B** (1.2)	-	THF	<5
3[c]	Ph	**C** (1.2)	-	THF	23
4	Ph	**D** (1.2)	-	THF	<5[d]
5[c]	Ph	**D** (1.5)	-	THF	10
6[c]	Ph	**D** (1.5)	BF_3•OEt_2 (0.5)	THF	20
7[c]	Ph	**E** (1.5)	BF_3•OEt_2 (0.5)	THF	13
8[c]	Ph	**F** (2.0)	BF_3•OEt_2 (1.2)	THF	<10
9[c]	Ph	**D** (2.0)	BF_3•OEt_2 (1.2)	THF	26
10[c]	Ph	**D** (2.0)	BCl_3 (1.0)	THF	<10
11[c]	Ph	**D** (2.0)	BBr_3 (1.0)	THF	<10
12[c]	Ph	**D** (2.0)	BF_3•OEt_2 (1.2)	Et_2O	20
13[c]	Ph	**D** (2.0)	BF_3•OEt_2 (1.2)	*i*-Pr_2O	13
14[c]	Ph	**D** (2.0)	BF_3•OEt_2 (1.2)	*t*-BuOMe	44[e]
15[c]	Ph	**D** (2.0)	BF_3•OEt_2 (1.2)	DME	45[e]
16[c]	Ph	**D** (1.2)	BF_3•OEt_2 (5.4)	DME	68[e]
17[c,f]	**Ph**	**D (1.2)**	**BF_3•OEt_2 (5.4)**	**DME**	**77 (73)**[e]
18[c,g]	Me	**D** (1.2)	BF_3•OEt_2 (5.4)	DME	47
19[c,f]	Me	**D** (1.2)	BF_3•OEt_2 (5.4)	*t*-BuOMe	76
20[c,g]	**Me**	**D (1.2)**	**BF_3•OEt_2 (5.4)**	***t*-BuOMe**	**84 (84)**[e]

[a] Determined by ^{1}H NMR analysis of the crude mixture using either 1,3,5-trimethoxybenzene or maleic acid as standard. [b] The α-benzoylated product (57%) was obtained. [c] The reaction was quenched at –78 °C with a solution of AcOH in toluene prior to warming to rt. [d] An α-dihydro-cinnamoylated product (23%) was obtained resulting from equilibration to cyclopropanone.[11] [e] Isolated yield. [f] Quenched after 15 min. [g] Quenched after 1 h.

In order to obtain a substantial yield of the hydroxylated product, it was found that quenching the reaction at –78 °C using a solution of AcOH in toluene was necessary to protonate the α-sulfonyl alkoxide intermediate initially formed at low temperature, and thus suppress its decomposition following α-elimination (entries 4-5). Changing the solvent from THF to either *t*-BuOMe or DME significantly increased the yield (entries 14-15), both affording similar results for **5a** but later found to give significantly different yields depending on the substrate, likely due to variations in solubility (entries 18-20).[11]

A number of enantioenriched aryl-substituted substrates (**4a–4f**) were readily prepared using Iwasa's Ru-catalyzed asymmetric cyclopropanation of alkenes with α-diazomethyl aryl sulfones (Scheme 3, Method A).[15a] Using our α-hydroxylation conditions, highly enantioenriched cyclopropanone equivalents **5a–5f** were obtained in moderate to excellent yields as single diastereomers with retention of configuration at the α-position, as evidenced by X-ray crystallographic analysis (**5a**).[22,23,24] The general reactivity trend observed revealed that electron-poor substrates afford higher isolated yields in this transformation (e.g. **5d** and **5e**), with most reactions proceeding with complete retention of stereochemical information.

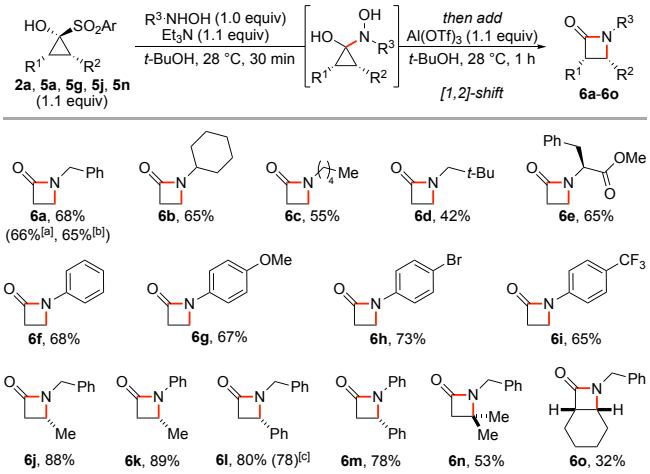


Scheme 3. Scope of accessible substituted 1-sulfonylcyclopropanols via α-hydroxylation of cyclopropylsulfones. All yields correspond to yields of isolated product. Enantiomeric excesses were determined by HPLC analysis using a chiral stationary phase (ee of starting material **4** in parentheses). [a] The corresponding cyclopropanone is achiral.

Aliphatic substrates **4g–4n** were synthesized in a single step from phenyl methyl sulfone and the corresponding epoxides, building on a one-pot ring-opening / activation / substitution sequence first reported by Tanaka and co-workers on racemic epoxides (Method B).[15c] To our delight, this procedure was found to be fully stereospecific to form the alkyl-substituted sulfonylcyclopropanes **4g** and **4h** when starting from an enantioenriched epoxide, subsequently allowing us to efficiently access cyclopropanone precursors **5g** and **5h** in high enantioselectivities using our hydroxylation procedure. Importantly, trifluoromethyl-substituted cyclopropanone equivalent **5i** could also be accessed by this protocol, in addition to sterically congested 2,2-dimethyl-substituted derivative **5j**. 2,3-Disubstituted analogs **5k** and **5l** were also found to be accessible by our method, as well as achiral ring-fused derivatives **5m** and **5n**. Interestingly, these bicyclic derivatives constitute precursors of cyclopropanones commonly encountered as high energy intermediates in the Favorskii rearrangement, eventually affording ring-opened carboxylic acid derivatives in the presence of protic nucleophiles.[5]

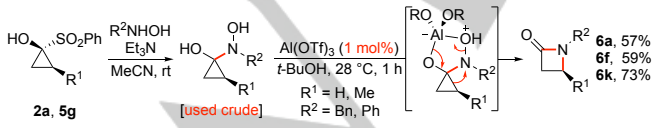
Synthesis of β-lactams by formal [3+1] cycloaddition. With general access to a wide variety of highly reactive cyclopropanone precursors, we sought to apply these substrates in strain-releasing rearrangements. Considering the biological relevance of β-lactam derivatives,[25] a particularly attractive transformation we were prompted to study is the formal [3+1] cycloaddition of cyclopropanones with nitrene equivalents to afford β-lactams. An analogous Schmidt-type rearrangement had previously been reported by Aubé and co-workers using (1-ethoxycyclopropoxy)trimethylsilane in the presence of organoazides and BF_3•OEt_2,[26] although only unsubstituted achiral β-lactam derivatives could be obtained in low to moderate yield.[27,28] In that work, the relatively harsh conditions required for equilibration to cyclopropanone likely led to multiple decomposition pathways. Moreover, we sought to avoid organoazides in order to improve the applicability of the method on a larger scale. After evaluating various other nitrene equivalents,[11] it was found that simple hydroxylamines or their corresponding ethers could play the same role when the reaction was run in presence of a Lewis acid (Scheme 4). Indeed, treatment of a chosen hydroxylamine with the 1-sulfonylcyclopropanol substrate leads to smooth formation of a stable hemiaminal intermediate under mild basic conditions, which then rearranges *in situ* to the corresponding β-lactam following addition of $Al(OTf)_3$. Interestingly, the direct use of unprotected hydroxylamines as nitrene equivalents is unprecedented and might be applicable in other types of reactions involving nitrene precursors. Importantly, the corresponding hydrochloride salts and *O*-alkyl hydroxylamines could also be used in the reaction with similar efficiency (see **6a** in parentheses). A number of sterically and electronically distinct *N*-alkyl and *N*-aryl hydroxylamines were found to be compatible in the reaction when **2a** was used as substrate, leading to a variety of unsubstituted β-lactams (**6a–6i**), including an *N*-capped phenylalanine building block (**6e**). Gratifyingly, the reaction was found to be particularly efficient when performed from chiral 2-substituted cyclopropanone precursors, leading to high yields of the corresponding 4-substituted β-lactams, either using *N*-alkyl- or *N*-aryl hydroxylamines (**6j–6m**). Sterically hindered cyclopropanone equivalent **5j** was also found to be

compatible in the transformation, providing access to congested β-lactam **6n** in moderate yield. Bicyclic cyclopropanone precursor **5n** led to formation of ring-fused lactam **6o**, albeit in lower yield likely due to competitive ring-opening of the hemiaminal intermediate to a hydroxamic acid, similar to what is observed in the Favorskii rearrangement.[5]



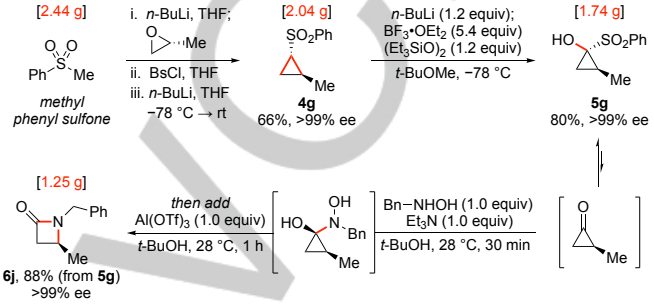
Scheme 4. Scope of accessible β-lactams by formal [3+1] cycloaddition of cyclopropanone equivalents with hydroxylamines. All yields correspond to yields of isolated product on a 1 mmol scale. [a] Yield obtained from the corresponding *O*-benzyl-protected hydroxylamine. [b] Yield obtained from the corresponding hydroxylamine hydrochloride salt, using 2.2 equiv Et_3N. [c] Yield obtained starting from **5b** (0.29 mmol) instead of **5a**.

In an effort to increase the sustainability and cost-efficiency of this transformation, we sought to evaluate the viability of a catalytic version. Although direct application of our previous conditions with a substoichiometric amount of Lewis acid did not yield any of the β-lactam product,[11] it was found that similar efficiency could be realized when the reaction was performed in a two-step manner using only 1 mol% of $Al(OTf)_3$, where the hemiaminal intermediate was used crude after aqueous workup (Scheme 5). Considering the high nucleophilicity of sulfinate anions,[12] we believe that the leaving group liberated in the first step is capable of poisoning the Lewis acid catalyst, thus forming various aluminum species of type $Al(PhSO_2)_x(OR)_{3-x}$ too electron-rich to catalyze the subsequent rearrangement. Therefore, performing an aqueous workup after the first step eliminates all sulfinate salts initially formed and allows for the use of a catalytic amount of Lewis acid in the subsequent step.



Scheme 5. Catalytic version of the formal [3+1] cycloaddition developed with hydroxylamines. All yields correspond to yields of isolated product on a 1 mmol scale.

To assess the stereospecificity of our approach as well as its applicability on a larger scale, we synthesized gram quantities of enantiopure β-lactam **6j** in three steps starting from methyl phenyl sulfone (Scheme 6). Using method B and commercially available (*R*)-propylene oxide (see Scheme 3), chiral sulfonylcyclopropane **4g** was obtained in reasonable yield and subjected to our α-hydroxylation procedure, furnishing enantiopure cyclopropanone equivalent **5g** in 80% isolated yield. Gratifyingly, directly submitting this chiral 1-sulfonylcyclopropanol to our formal [3+1] cycloaddition conditions afforded 1.25 gram of chiral β-lactam **6j** in 88% yield and >99% ee, ultimately confirming the stereospecific nature of the 1,2-shift occurring during the ring expansion.



Scheme 6. Asymmetric, gram-scale synthesis of chiral cyclopropanone equivalent **5g** and β-lactam **6j** from methyl phenyl sulfone. All yields correspond to yields of isolated product on the scale indicated. Enantiomeric excesses were determined by HPLC analysis using a chiral stationary phase.

Conclusion

In summary, we report the first enantioselective synthesis of 1-sulfonylcyclopropanols, which constitute versatile precursors to highly energetic chiral cyclopropanone derivatives. Kinetic studies revealed the modular nature of these compounds with respect to their equilibration to cyclopropanones, where both the electronic and steric properties of the sulfinate group can readily be tuned to control their overall reactivity as cyclopropanone equivalents. Such a tunability should prove highly beneficial in future reaction development, allowing different sets of reaction conditions to be compatible with these cyclopropanone surrogates. To showcase their applicability in the synthesis of biologically relevant compounds, a mild and stereospecific formal [3+1] cycloaddition with readily available hydroxylamines was developed, efficiently affording a variety of chiral β-lactam derivatives. All synthetic methods developed herein were shown to proceed with similar efficiency on gram scale, and the use of an enantioenriched cyclopropanone equivalent led to complete transfer of the stereochemical information to the final β-lactam product. To the best of our knowledge, this work constitutes the first general enantioselective approach to cyclopropanone derivatives.[10] Considering the importance of strained ketone rearrangements in synthesis[1] and the tremendous potential of cyclopropanones as reactive intermediates,[4] this work should find applicability in the elaboration of complex, biologically relevant molecules. The development of various other transformations using 1-sulfonylcyclopropanols as cyclopropanone surrogates is currently underway in our laboratories and will be reported in due course.

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Keywords: Cyclopropanone • β-Lactam • α-Hydroxylation • Ring expansion • Formal [3+1] Cycloaddition

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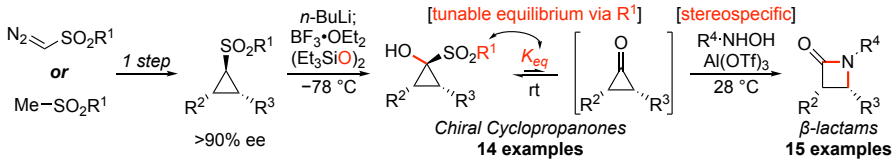

The first general approach to the formation of enantioenriched cyclopropanone equivalents is reported via the α-hydroxylation of sulfonylcyclopropanes, giving access to a wide variety of highly reactive and modular reagents suitable for ring-expansion processes, as exemplified here in the formation of chiral β-lactams via formal [3+1] cycloaddition using simple hydroxylamines as nitrene sources.