Enantioselective Synthesis of Alkylidenecyclobutanones via Formal Vinylidene Insertion into Cyclopropanone Equivalents

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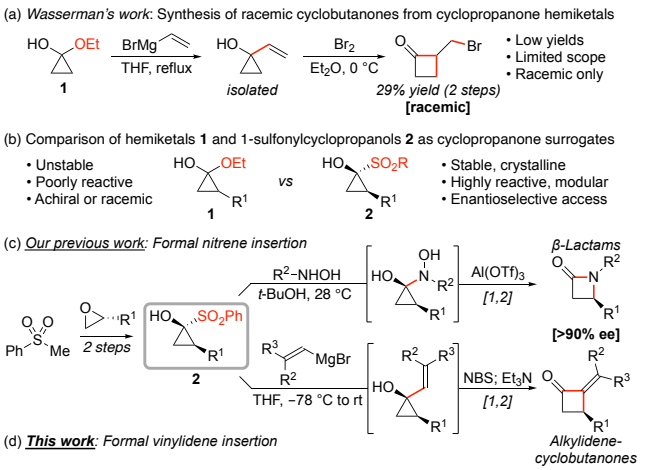
ABSTRACT: 1-Sulfonylcyclopropanols are employed here as efficient cyclopropanone equivalents in a formal vinylidene insertion process, providing the first general synthetic route to enantioenriched alkylidenecyclobutanones. The addition of an alkenyl-Grignard reagent to the cyclopropanone leads to an alkenylcyclopropanol capable of electrophilic activation by NBS, triggering a regio- and stereospecific 1,2-migration and the formation of a brominated cyclobutanone intermediate prone to elimination. The parent β-amino ketone can also be accessed by one-pot aza-Michael addition to the resulting product, and activation of the alkenylcyclopropanol intermediate with other electrophiles such as HCl or *m*CPBA led to the controlled formation of a variety of chiral cyclobutanones and γ-lactones via alternative pathways.

The ring expansion or ring-opening of strained cyclic compounds constitutes a key strategy in organic synthesis for the elaboration of complex molecules.[1] The relevance of cyclobutanone derivatives in this regard cannot be understated,[2] with countless strain-releasing transformations now available to synthetic chemists, thus allowing rapid access to a range of structurally complex and diverse scaffolds.[3] More particularly, alkylidenecyclobutanones[4,5] have been employed as privileged substrates in stereospecific ring-opening or rearrangements[4a-b] and constitute divergent substrates leading to functionalized cyclobutanones via conjugate addition of heteronucleophiles[4c,5o-p] or organometallic reagents,[4d-e,5t] conjugate reduction[4f-h,5c,q-r] or hydroformylation reactions.[4i] Moreover, these species have been employed as unique precursors of oxatetramethyleneethane intermediates via photoinduced electron transfer.[4j-l] While they can be accessed in racemic form by a variety of approaches including the [2+2] cycloaddition of ketenes with allenes,[5a-f] the carbonylation or oxidation of alkylidenecyclopropanes,[5g-k] the rearrangement of 1-alkynylcyclopropanols[5l-n] or by classical condensation or cyclization strategies,[5o-z] the general enantioselective access to alkylidenecyclobutanones still remains elusive. An interesting approach to racemic cyclobutanones reported by Wasserman and co-workers involves the electrophilic activation and ring expansion of 1-vinylcyclopropanol, which in turn can be synthesized by vinyl Grignard addition to hemiketal **1**, used as a cyclopropanone surrogate (Scheme 1a).[6,7] While cyclobutanone derivatives are relatively stable to isolation and storage, cyclopropanones are often highly unstable and prone to multiple decomposition pathways,[1d,8,9] and it is thus often more convenient to form them *in situ* via elimination from a surrogate such as **1** (Scheme 1b).[8d,10] Due in part to the poor leaving group ability of alkoxides, hemiketals **1** require harsh conditions to equilibrate to the cyclopropanone and often lead to low yields of the desired rearranged products, as exemplified here in a racemic cyclobutanone synthesis (29% overall yield, see Scheme 1a).[6a] Recently, our group reported an expedient synthesis of optically active 1-sulfonylcyclopropanols **2**,[11] which constitute stable yet highly reactive and modular surrogates of cyclopropanone derivatives.[12] This approach is in fact the first general enantioselective route to cyclopropanone equivalents, and later allowed us to access enantioenriched 4-substituted β-lactams using a formal nitrene insertion reaction with simple *N*-substituted hydroxylamines as reagents (Scheme 1c).[11]

Scheme 1. Reactivity of various cyclopropanone equivalents and application in (3+1) ring expansion processes.

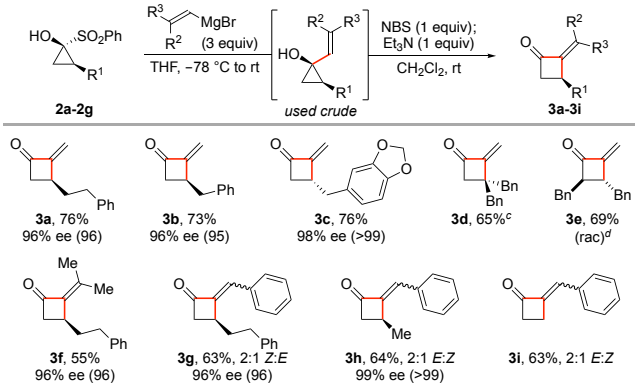


Cognizant of the superior reactivity of surrogates **2** towards the addition of organometallic reagents to afford chiral tertiary cyclopropanols,[12a] we envisioned that they would constitute privileged substrates for the production of optically active cyclobutanones via an analogous stereospecific ring expansion pathway. Herein we report the first general route to enantioenriched alkylidenecyclobutanones via a formal vinylidene insertion process into chiral cyclopropanones starting from readily accessible 1-sulfonylcyclopropanols **2** as surrogates (Scheme 1d). The addition of an alkenyl nucleophile to substrates **2** followed by appropriate electrophilic activation with *N*-bromosuccinimide (NBS) was found to trigger a fully regio- and stereospecific 1,2-migration, leading to a bromocyclobutanone prone to elimination. A number of chiral alkylidenecyclobutanones could be obtained through variation of the alkenyl nucleophile and cyclopropanone substituents, and alternative activation of the allylic alcohol with HCl or *m*CPBA

led to the controlled formation of chiral saturated cyclobutanones and γ-lactones instead. Other applications of this chemistry documented here include the synthesis of β-aminocyclobutanones via *in situ* aza-Michael addition, the use of a β-bromo alkylidenecyclobutanone as a cross-coupling partner, and the stereospecific formation of α-quaternary cyclobutanones. Considering the relevance of chiral cyclobutanones and alkylidenecyclobutanones as strained building blocks in synthesis,[2,4] this work should find broad applicability in the elaboration of complex and biologically relevant molecules.

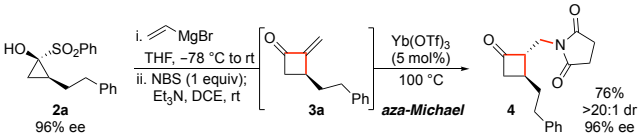
Our preliminary studies focused on the addition of vinylmagnesium bromide to substrate **2a** to yield the corresponding 1-vinylcyclopropanol, and identified the use of an excess organometallic reagent at –78 °C as crucial to the overall reaction efficiency.[13] We also observed that NBS was a superior electrophile to trigger the subsequent ring expansion, presumably via an hydroxycyclopropylbromonium species, leading to quantitative NMR yields of the ring-expanded bromocyclobutanone from the crude 1-vinylcyclopropanol intermediate. This brominated product was found to be highly sensitive to elimination by mild base,[14] which prompted us to pursue a one-pot sequence to alkylidenecyclobutanones **3**. To our delight, optimal conditions for the overall process from **2a** were rapidly identified, involving the sequential stoichiometric addition of NBS and Et_3N at room temperature to the crude 1-vinylcyclopropanol intermediate, affording **3a** in 76% isolated yield from 1-sulfonylcyclopropanol **2a** with complete regio- and stereospecificity (Scheme 2). Using our previously developed two-step sequence to enantioenriched cyclopropanone equivalents from methyl phenyl sulfone[11] and in order to explore the scope of accessible alkylidenecyclobutanones, diverse chiral substrates **2a-2g** were synthesized and submitted to our formal vinylidene insertion sequence. When employing vinylmagnesium bromide as nucleophile, chiral methylenecyclobutanones **3a-3e** were obtained in moderate to good overall yields and high enantiomeric purity, tolerating either monosubstituted (**3a-3c**), *gem*-disubstituted (**3d**) or 2,3-disubstituted (**3e**) substrates with similar efficiency. In the case of **3d**, additional time and heat was required for the elimination to proceed, presumably due to increased steric hindrance during deprotonation. The use of commercially available 2-methyl-1-propenylmagnesium bromide as nucleophile led to tetrasubstituted olefin **3f** in moderate yield. Employing freshly prepared *trans*-β-styrenylmagnesium bromide efficiently gave access to β-phenyl alkylidenecyclobutanones **3g-3i** in various *E*:*Z* ratios, where alkene isomerization was found to occur during chromatography.[5l,13] Gratifyingly, all products **3a-3i** were obtained as single regioisomers without the need for purification of the vinylcyclopropanol intermediates, and no significant loss of stereochemical information was observed in any case, confirming the stereospecificity of the 1,2-migration occurring upon olefin bromination. Interestingly, the alkylidenecyclobutanone initially produced can be directly employed as an electrophile in an aza-Michael reaction in one-pot, leading to the clean formation of a β-aminoketone such as **4** (Scheme 3). Upon heating and addition of a catalytic amount of $Yb(OTf)_3$ as Lewis acid, the succinimide liberated as byproduct during olefin activation can act as a nucleophile in the final step to directly afford a protected β-amino cyclobutanone **4** with high efficiency. A single *trans* diastereomer of the cyclobutanone is obtained in the process, likely due to thermodynamic keto-enol equilibration occurring under these conditions.[5q,7f]

Scheme 2. Scope of accessible alkylidenecyclobutanones by formal vinylidene insertion into cyclopropanone equivalents[a,b]



[a]Isolated yields from **2a-2g**. [b]Enantiomeric excesses were determined by HPLC analysis using a chiral stationary phase (ee of starting material **2** in parentheses). [c]Heated to reflux for 18 h after addition of Et_3N. [d]Racemic substrate **2e** was used.

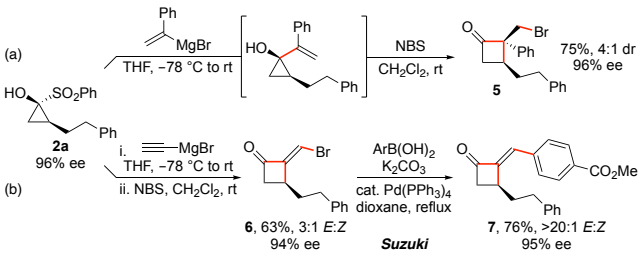
Scheme 3. Direct synthesis of enantioenriched β-aminoketone 4 by one-pot aza-Michael addition of the succinimide byproduct[a,b]



[a]Isolated yield from **2a**. [b]Enantiomeric excess was determined by HPLC analysis using a chiral stationary phase

The addition of a 1-substituted alkenyl-metal reagent such as α-styrenylmagnesium bromide as initial nucleophile in this transformation efficiently leads to an enantioenriched α-quaternary β-bromocyclobutanone (e.g. **5**), which cannot undergo further elimination to an alkene following olefin activation and 1,2-migration (Scheme 4a). When ethynylmagnesium bromide was employed instead, the 1-alkynylcyclopropanol initially formed underwent an analogous rearrangement upon activation with NBS, directly affording β-brominated alkylidenecyclobutanone **6** (Scheme 4b). This compound can then be effectively employed as a substrate in a Suzuki cross-coupling reaction to furnish an ester-functionalized alkylidenecyclobutanone **7**. Such a sequence should prove particularly useful as an alternative route to alkylidenecyclobutanones when functional group compatibility is an issue, either during the initial Grignard addition or the electrophilic alkene activation step.

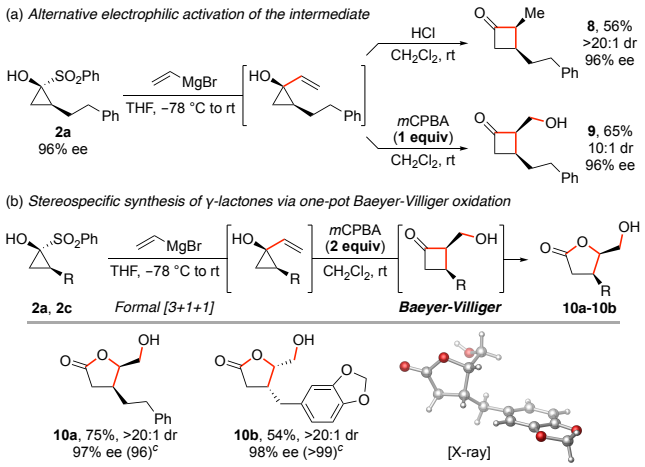
Scheme 4. Synthesis and application of brominated cyclobutanones 5 and 6 via the addition of α-styrenylmagnesium bromide (a) or ethynylmagnesium bromide (b) as initial nucleophiles[a,b]



[a]Isolated yields. [b]Enantiomeric excesses were determined by HPLC analysis using a chiral stationary phase.

The stereospecific 1,2-migration of the ring expansion sequence can also be triggered by the addition of electrophiles other than NBS to the crude 1-vinylcyclopropanol intermediate, directly leading to the corresponding saturated chiral cyclobutanones in moderate to good overall yields (Scheme 5).[6a,10a-b] For example, treatment of this intermediate with a few drops of concentrated HCl in CH_2Cl_2 at room temperature led to enantioenriched α-methylated *cis*-cyclobutanone **8** as a single diastereomer, following protonation of the vinyl group and 1,2-migration (Scheme 5a, top). Stoichiometric addition of *m*CPBA instead led to epoxidation of the allylic alcohol, initiating a stereospecific 1,2-migration and affording *cis*-β-hydroxycyclobutanone **9** in good overall yield (Scheme 5a, bottom). During this process, we observed the formation of a small amount of γ-lactone **10a**, presumably arising from Baeyer-Villiger oxidation of product **9**, even when only one equivalent *m*CPBA was added for the epoxidation step. This result highlights the fact that β-hydroxycyclobutanone **9** constitutes a particularly reactive ketone in such a strain-releasing esterification, and prompted us to investigate a one-pot double ring expansion sequence in the presence of two equivalents *m*CPBA, directly affording optically active *cis*-γ-lactones **10a-10b** in good overall yields (Scheme 5b).[15] This diastereoselective formal [3+1+1] sequence should prove highly useful considering the relevance of chiral γ-lactones as synthetic fragments in the formation of biologically active compounds.[16]

Scheme 5. Alternative activation of the vinylcyclopropanol intermediate with HCl or *m*CPBA (a) and stereospecific synthesis of γ-lactones via one-pot Baeyer-Villiger oxidation (b)[a,b]



[a]Isolated yields from **2a** or **2c**. [b]Enantiomeric excesses were determined by HPLC analysis using a chiral stationary phase. [c]ee of starting material **2a** or **2c** in parentheses.

In summary, the first general synthesis of enantioenriched alkylidenecyclobutanones is reported via a formal vinylidene insertion into cyclopropanone derivatives, starting from readily accessible 1-sulfonylcyclopropanols as versatile surrogates.[11,12] The addition of an alkenyl nucleophile followed by electrophilic activation of the resulting crude allylic alcohol with NBS triggers a stereospecific ring expansion occurring in a fully regioselective manner, favoring migration of the most substituted (stereogenic) carbon of the cyclopropyl group. Other activating agents such as HCl or *m*CPBA efficiently led to the formation of chiral saturated *cis*-cyclobutanones instead, which can be further expanded to *cis*-γ-lactones *in situ* by Baeyer-Villiger oxidation in the presence of *m*CPBA. An alternative divergent route to functionalized alkylidenecyclobutanones is also documented, involving the synthesis of an enantioenriched β-bromo alkylidenecyclobutanone capable of subsequent Suzuki cross-coupling in good efficiency. Moreover, the one-pot synthesis of a protected β-aminocyclobutanone is demonstrated via aza-Michael addition, and the stereospecific formation of an α-quaternary cyclobutanone is achieved through the use of a 1-substituted alkenyl-metal reagent as initial nucleophile. Considering the prevalence of chiral cyclobutanones[2] and alkylidenecyclobutanones[4] as strained synthetic intermediates and of chiral γ-lactones in medicinal chemistry,[16] this work should find general applicability in the elaboration of complex and biologically relevant molecules.

ASSOCIATED CONTENT

Supporting Information

Experimental details and spectroscopic data. The Supporting Information is available free of charge on the ACS Publications website.
Crystallographic data for compound **10b**:
$C_{13}H_{14}O_5$ (CIF)

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Author Contributions

The manuscript was written through contributions of all authors.

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Notes

The authors declare no competing financial interest.

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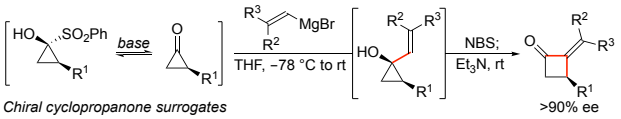
TOC GRAPHIC



Chiral cyclopropanone surrogates

>90% ee