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Thermal [2 + 2]-Cycloaddition of Ketenes with Chiral Enol Ethers: Route to Densely Substituted Cyclobutanones

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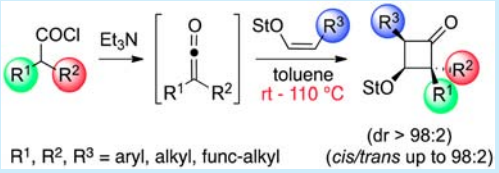
Supporting Information

ABSTRACT: Access to chiral polysubstituted cyclobutanones by [2 + 2]-cycloaddition of ketenes with chiral acyclic enol ethers is reported. A wide variety of easily accessible di- and monosubstituted ketenes were found to react with a very high degree of stereoselectivity with chiral, Stericol derived, acyclic enol ethers. This combination of simple reagents provides straightforward entry to highly substituted enantioenriched cyclobutanones.

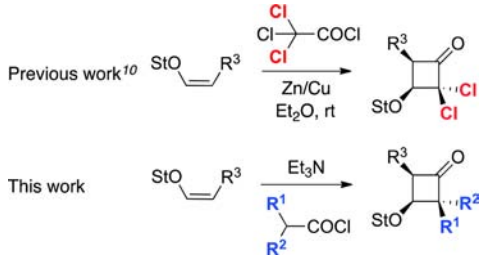


Substituted cyclobutanes are highly valuable building blocks due to both their occurrence in natural products and their potential as synthetic intermediates. Through ring contraction, ring expansion, or ring opening, cyclobutanes offer direct access to a wide range of carbo- and heterocycles.[1] The development of versatile and stereoselective methods for the construction of cyclobutanes is therefore of great interest. Among the various strategies,[2] thermal [2 + 2]-cycloaddition of ketenes with olefins offers unique entry to functionalized cyclobutanones. This process is highly regio- and stereoselective in most cases,[3] as a result of a concerted asynchronous mechanism.[4] The synthesis of enantioenriched cyclobutanes has found partial solutions with a few remarkable examples of enantioselective photochemical [2 + 2]-cycloadditions[5] and polarized non-concerted [2 + 2]-cycloadditions.[6] However, general access to enantioenriched cyclobutanones is still desirable. So far, no catalytic asymmetric version of the ketene [2 + 2]-cycloaddition has been reported.[7] The diastereoselective version of this cycloaddition therefore remains a privileged route for the synthesis of enantioenriched cyclobutanones.

Diastereoselective [2 + 2]-cycloaddition of ketenes with chiral cyclic olefins has already led to valuable synthetic applications, whereas diastereoselective cycloaddition with acyclic olefins relies on dichloroketene and chiral enol ethers.[8] The combination of Stericol (2,4,6-triisopropylphenylethanol, StOH)[9] derived enol ethers and dichloroketene has indeed led to the synthesis of a variety of enantioenriched 2,3-disubstituted cyclobutanones obtained in excellent diastereoselectivities.[10] These cyclobutanones have often been used as key intermediates in the total synthesis of natural products.[11] However, [2 + 2]-cycloaddition with chiral enol ethers has so far been limited to highly reactive dichloroketene.

In this study, we present the first diastereoselective [2 + 2]-cycloaddition of easily accessible chiral enol ethers with a wide array of symmetrical, unsymmetrical, and monosubstituted alkyl and aryl ketenes, leading to polysubstituted chiral cyclobutanones (Scheme 1).

Scheme 1. General [2 + 2]-Cycloaddition of Chiral Enol Ethers



Dichloroketene is highly reactive in [2 + 2]-cycloadditions with olefin, probably among the most reactive ketenes.[3,12] Direct transposition of the reaction conditions employed with dichloroketene with less reactive alkyl or phenyl ketenes was highly improbable. The need for significant thermal initiation for the cycloaddition could alter both the level of diastereoselectivity and the stability of the enol ether. Exploration of the [2 + 2]-cycloaddition was realized with chiral enol ether **1a**, in combination with dimethyl, diphenyl and bis(silyloxydimethyl) ketene **2a**–**c**, chosen as model ketenes. These symmetrical disubstituted ketenes represent a good diversity in term of both reactivity and steric hindrance. The ketenes were generated by a base mediated dehydrohalogenation of the corresponding acyl chlorides, which were either commercially available or easily prepared from dimethyl malonate by sequential alkylation, saponification, decarboxylation, and exposure to oxalyl chloride. Dimethyl and diphenylketene (**2a** and **2b**) have been used in [2 + 2]-cycloadditions, but never with chiral acyclic enol ethers, whereas the silyloxyketene **2c** is reported here for the first time. The effect of the solvent and temperature were first investigated to explore their influence on

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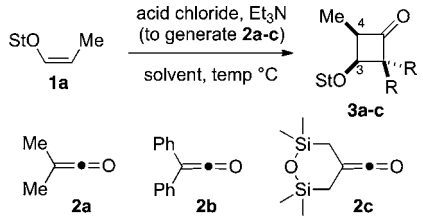
Table 1. Optimization of Reaction Conditions for the [2 + 2]-Cycloaddition of Alkyl and Aryl Ketenes 2a−c with Chiral Enol Ether 1a



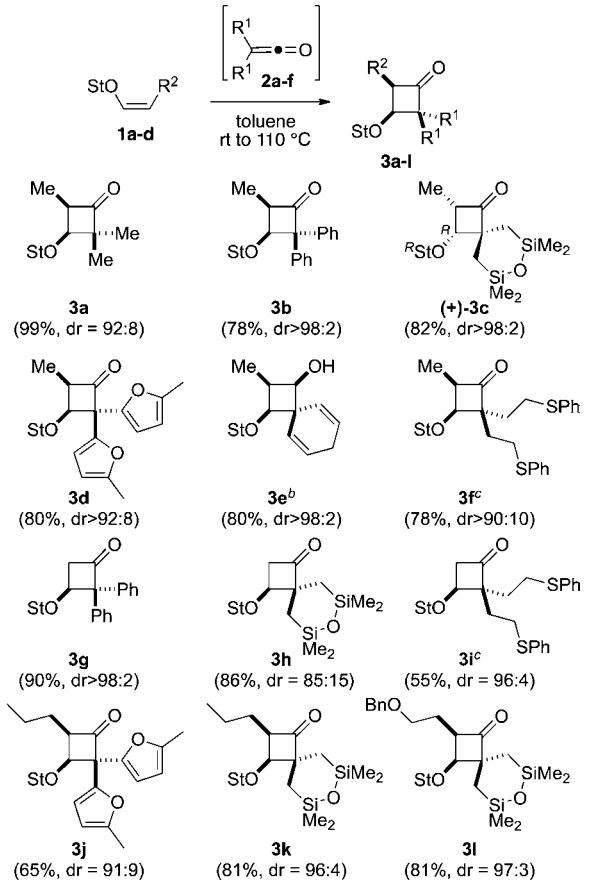
entry	ketene	solvent	temp (°C)	conv[a]	yield (%)[a]	dr
1	**2a**	Et_2O	rt	0	0	
2			reflux	10	0	
3	**2b**		rt	68	68	
4			reflux	75	56	
5	**2c**		rt	100	10	
6			reflux	100	92	97:3
7	**2a**	CH_2Cl_2	rt	100	100	92:8
8			reflux	100	100	92:8
9	**2b**		rt	100	56	
10			reflux	100	32	
11	**2c**		rt	100	100	93:7
12			reflux	100	100	93:7
13	**2a**	toluene	rt	24	24	
14			reflux	100	100	92:8
15	**2b**		35	100	80	98:2
16			reflux	92	53	
17	**2c**		rt	95	95	97:3
18			reflux	100	58	93:7
19			70	100	90	97:3

[a]Determined by NMR with anthracene as internal standard.

the efficiency of the cycloaddition and on the diastereoselectivity. Both the conversion of the enol ether and the formation of the expected cyclobutanones were determined by NMR using an internal standard.

In diethyl ether, either at room temperature or at reflux, no cycloaddition product was observed with dimethylketene **2a** (Table 1, entries 1 and 2). In this solvent, the more reactive diphenylketene led to the corresponding cyclobutanone with moderate conversion at 20 °C (Table 1, entry 3), and with partial degradation of enol ether **1a** at reflux (Table 1, entry 4). With ketene **2c** at room temperature, enol ether **1a** was fully consumed, but little cyclobutanone was observed (Table 1, entry 5), whereas a good yield of **3c** was observed at reflux (Table 1, entry 6). In dichloromethane, cycloaddition with dimethyl ketene **2a** and silyloxyketene **2c** was much more efficient, regardless of the temperature, as witnessed by the good conversions and yields (Table 1, entries 7, 8, 11, and 12). However, with diphenylketene **2b** the result was quite disappointing, with a low yield of cyclobutanone **3b** (Table 1, entries 9 and 10). In this case, an opened product arising from a nonconcerted reaction has been isolated in a notable amount.[13] In dichloromethane, cycloaddition with ketene **2a,c** is favored, but with diphenyl ketene **2b**, the reaction leads to a side product through extra stabilization of the partial positive charge in the transition state. Finally, toluene was found to be a good choice for all ketenes (Table 1, entries 13−19): either at room temperature for diphenylketene **2b** or at reflux for the less reactive dimethylketene **2a** and silyloxyketene **2b**. In each case, the conversion and estimated yields were excellent, over 90%.

Scheme 2. Scope of [2 + 2]-Cycloaddition with Symmetrical Ketenes 2a−f[a]



[a]Ketenes are generated *in situ* from the corresponding acid chloride; in parentheses, diastereoisomeric ratio of the isolated product. [b]Obtained by direct reduction with $NaBH_4$ of the unstable transient cyclobutanone. [c]Reaction in dichloromethane.

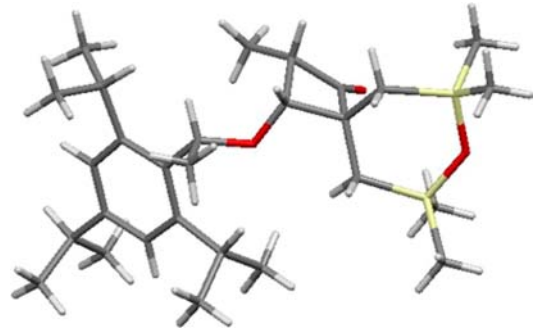


Figure 1. X-ray crystal structure of cyclobutanone (+)-**3c**.

Strikingly, the diastereoselectivity of the cycloaddition, namely the facial control of the acyclic enol ether, was excellent with each ketene, ranging from 92:8 to 98:2. The stereochemical double bond information was also retained, affording only the *cis* C3−C4 cyclobutanones from *Z* enol ethers. In addition, all three cyclobutanones **3a−c** were isolated as single diastereoisomers by simple flash chromatography (Scheme 2). Such a facial discrimination with chiral acyclic enol ethers at temperatures ranging from room temperature to 110 °C, with very little erosion of selectivity, is unprecedented in [2 + 2]-cycloadditions. It offers a general and simple route for the

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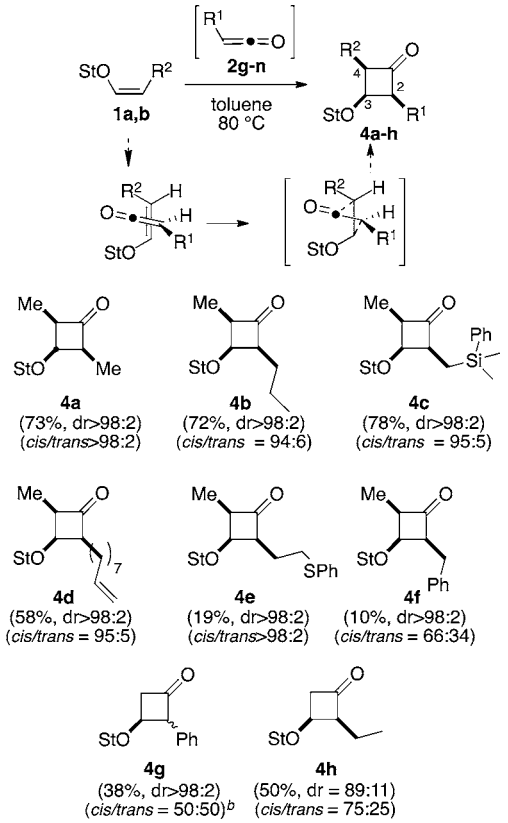
Scheme 3. Scope of [2 + 2]-Cycloaddition with Monosubstituted Ketenes 2g−n[a]



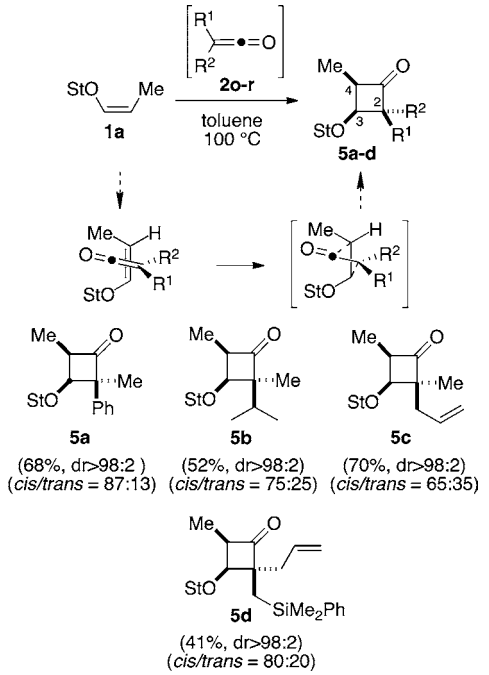
[a]Ketenes are generated *in situ* from the corresponding acid chloride; yield of isolated products. [b]The α-keto-benzylic center was too acidic to prevent its epimerization.

synthesis of enantioenriched cyclobutanones starting from a wide range of ketenes.

With the reaction conditions in hand, a variety of disubstituted ketenes (**2a−f**) were next reacted with Stericol derived enol ethers (**1a−d**) (Scheme 2). The diastereopure cyclobutanones **3a−c** could be secured in excellent yields. X-ray analysis of the crystalline, enantioenriched (ee >99.5%), cyclobutanone (+)-**3c** also confirmed the facial attack of the chiral enol ether affording the (*R*)-C3 chiral center starting from (*R*)-Stericol (Figure 1). With enol ether **1a**, difuryl,[14] cyclohexadienyl, and di(phenylthio)ethyl ketenes afforded cyclobutanones **3d−f** in very high yield and again excellent diastereoselectivity. Cyclobutanones **3d,e,j** were however much more prone to epimerization at C4: changing triethylamine to a combination of a catalytic kinetic base (DIPEA) and a thermodynamic base (proton sponge)[15] proved very effective to retain the *cis*-cyclobutanones. With nonsubstituted enol ether **1b**, cycloaddition proved as efficient in terms of yield but slightly less diastereoselective. This decrease can be explained by a more flexible conformation of the enol ether due to decreased allylic strains. A single isomer of cyclobutanone **3g** was however isolated. With a propyl side chain (**2c**), and eventually with a benzyl ether on the side chain of the enol ether (**2d**), cyclobutanones **3j−l** were again obtained very selectively.

Symmetrical disubstituted ketenes **2a−f** thus react very selectively with a variety of Stericol derived chiral enol ethers, regardless of the temperature required to compensate for the

Scheme 4. Scope of [2 + 2]-Cycloaddition with Unsymmetrical Disubstituted Ketenes 2o−r[a]



[a]Ketenes are generated *in situ* from the corresponding acid chloride. Only the major diastereoisomer is depicted.

innate difference of reactivity of the ketenes. It next seemed very appealing to extend this reaction to monosubstituted ketenes, known for their high dimerization tendency. With enol ether **1a** and methylketene **2g** in toluene at room temperature, no cyclobutanone was isolated. At 80 °C, in a sealed tube (to prevent the most-certain volatility of methylketene), slow addition of propionyl chloride to a solution of the enol ether and triethylamine afforded the desired cyclobutanone **4a** in 73% yield, as a single all *cis* diastereoisomer. The *cis*/*cis* product (dr (St-C3) > 98:2 and *cis*/*trans* (C3−C4) > 98:2) shows again the excellent facial discrepancy of the enol ether. The C3−C4 selectivity is explained by the perpendicular approach of the ketene through its least crowded face with the carbonyl of the ketene "inside" the *Z*-enol ether (Scheme 3).[4]

A variety of monosubstituted ketenes **2g−n** were then engaged in the [2 + 2]-cycloaddition with enol ethers **1a,b** affording the cyclobutanones **4a−h** (Scheme 3). For instance, cyclobutanones **4a−d** were isolated in good yield, showing the compatibility of ketene cycloaddition with alkylsilanes and simple alkenes (**4c,d**, Scheme 3). With ketene **2e** bearing a thioether, the yield was much lower, most probably due to the thioether interaction with the ketene. With benzyl ketene **2f**, a surprisingly low yield of cyclobutanone **4f** was observed. Finally, nonsubstituted enol ether **1b** also led to cyclobutanones **4g−h** with a slight decrease in selectivity (Scheme 3).

The ketene scope exploration was next enlarged to disubstituted unsymmetrical ketenes with the aim to control the newly formed quaternary stereocenter. Cycloadditions with enol ethers involving disubstituted unsymmetrical ketenes is poorly reported in the literature.[4f,7a,16] With all four ketenes **2a−d**, cyclobutanones **5a−d** were obtained in fair to good yields, much higher than those previously reported on achiral enol ethers.[16] Notably, cyclobutanone **5d** holds high synthetic

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potential by selective functionalization of the side chains. In each case, enol ether facial selectivity was excellent (dr >98:2, Scheme 4). Stereochemical control of the quaternary center, the C2−C3 *cis*/*trans* ratio ranging from 65:35 to 87:13, results from the ketene facial approach, which relies on the relative steric hindrance of the R^1/R^2 group on the ketene. The C2−C3 relative configuration of cyclobutanones **5a** and **5d** was assigned through NOE, and deduced from these examples for **5b** and **5c**.

To conclude, we have developed an efficient diastereoselective synthesis of polysubstituted cyclobutanones. Through the unprecedented [2 + 2]-cycloaddition of a wide variety of ketenes with chiral acyclic enol ethers, 24 new cyclobutanones have been synthesized, with good to excellent diastereoselectivity, showing the versatility of the approach. Given the scarcity of methods for the synthesis of enantioenriched cyclobutanones, this work represents easy and effective access to this class of molecules.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01058.

Detailed experimental procedures and full characterization for new compounds (PDF)
Crystallographic data (CIF)

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Notes

The authors declare no competing financial interest.

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