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Expedient Approach to Chiral Cyclobutanones: Asymmetric Synthesis of Cyclobut-G

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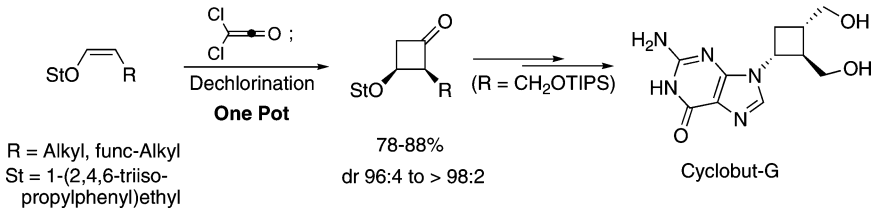
ABSTRACT



An efficient one-pot asymmetric synthesis of cyclobutanones from chiral enol ethers is described. The approach is illustrated with alkyl- and functionalized alkyl-substituted enol ethers (nine examples). A new enantioselective synthesis of cyclobut-G (Lobucavir) could thus be achieved.

Cyclobutanes are important building blocks, primarily due to their ring-expansion chemistry, which derives from substantial strain energy (essentially that of cyclopropanes).[1,2] The four-membered carbocycle is, furthermore, present in numerous natural products and synthetically derived bioactive substances.[2c,3] Not surprisingly, there are many different methods in the literature for preparing cyclobutanes, the most useful of which involve [2 + 2] cycloaddition, intramolecular nucleophilic substitution, and ring contraction/expansion reactions.[1b,4] However, current approaches are largely limited in scope, and few are able to provide enantioselection.[5] Herein, a flexible route to chiral, functionalized cyclobutanes is presented.

To date, α,α-dichloro-β-alkoxycyclobutanones generated by diastereoselective [2 + 2] thermal cycloaddition of dichloroketene (DCK) with chiral enol ethers have been directly used for the enantioselective synthesis of a variety of ring expansion products.[6−8] Given the interest in cyclobutanes and the paucity of useful approaches to enantiomerically enriched four-membered carbocycles, the possibility of obtaining the chiral cyclobutanones themselves through direct dechlorination of these fragile dichlorocyclobutanones seemed worth examining. Although dechlorination of simple dichlorocyclobutanones can be achieved with a variety of

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(2) (a) Fu, N.-Y.; Chan, S.-H.; Wong, H. N. C. In *The Chemistry of Cyclobutanes*; Rappoport, Z.; Liebman, J. F., Eds.; John Wiley & Sons, Ltd.: West Sussex, England, 2005; Vol. 1, Chapter 9. (b) Namyslo, J. C.; Kaufmann, D. E. *Chem. Rev.* **2003**, *103*, 1485−1538. (c) Bellus, D.; Ernst, B. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 797−827.

(3) (a) Hansen, T. V.; Stenstrøm, Y. Naturally Occurring Cyclobutanes. In *Organic Synthesis Theory and Applications*; Hudlicky, T., Ed.; Elsevier Science Ltd.: New York, 2001; Vol. 5, pp 1−38. (b) Taber, D. F.; Frankowski, K. J. *J. Org. Chem.* **2005**, *70*, 6417−6421 and references therein.

(4) Lee-Ruff, E. In *The Chemistry of Cyclobutanes*; Rappoport, Z.; Liebman, J. F., Eds.; John Wiley & Sons, Ltd.: West Sussex, England, 2005; Vol. 1, Chapter 8.

(5) For recent approaches limited to bicyclic adducts, see: (a) Canales, E.; Corey, E. J. *J. Am. Chem. Soc.* **2007**, *129*, 12686−12687. (b) Luzung, M. R.; Mauleon, P.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 12402−12403. See also: (c) Honda, T.; Kimura, N. *J. Chem. Soc., Chem. Commun.* **1994**, 77−78. (d) Hazelard, D.; Fadel, A. *Tetrahedron: Asymmetry* **2005**, *16*, 2067−2070.

(6) Cyclopentanones: (a) Greene, A. E.; Charbonnier, F.; Luche, M.-J.; Moyano, A. *J. Am. Chem. Soc.* **1987**, *109*, 4752−4753. (b) Kanazawa, A.; Delair, P.; Pourashraf, M.; Greene, A. E. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1911−1912.

(7) Lactones: (a) B. M. de Azevedo, M.; Murta, M. M.; Greene, A. E. *J. Org. Chem.* **1992**, *57*, 4567−4569. (b) Murta, M. M.; De Azevedo, M. B. M.; Greene, A. E. *J. Org. Chem.* **1993**, *58*, 7537−7541. (c) De Azevedo, M. B. M.; Greene, A. E. *J. Org. Chem.* **1995**, *60*, 4940−4942.

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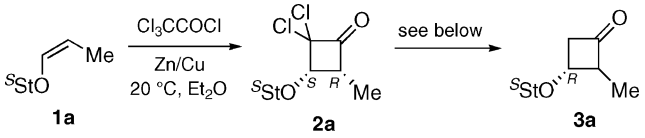
reagents (Bu_3SnH, Zn/AcOH, Zn/NH_4Cl/MeOH, Al/Hg,...),[9] the presence of an epimerizable substituent and an elimination-prone and possibly acid-sensitive alkoxyl group in these α,α-dichlorocyclobutanones made success far from certain.

To study the [2 + 2] cycloaddition/dechlorination sequence, the prototypical *cis*-enol ether **1a** was prepared[10] from (*S*)-Stericol.[11] Cycloaddition of dichloroketene occurred rapidly at room temperature with this reactive ketenophile to provide the rather unstable crude dichlorocyclobutanone **2a** as a 92:8 mixture of diastereomers (see Table 1).

Table 1. Dechlorination of Cyclobutanone **2a**



entry	dechlorination conditions	yield (%)[a,b]
1	Bu_3SnH, ACCN, toluene, 90 °C, 1 h	68 (62:38)
2	Zn/Cu, AcOH, 50 °C, 1 h	37 (100:0)
3	Zn/Cu, MeOH/NH_4Cl, reflux,12 h	59 (45:55)
4	Zn/Cu, MeOH/NH_4Cl, −20 °C, 10 min	99[c]
5	Zn/Cu, MeOH/NH_4Cl, reflux, 10 min	63 (100:0)
6	**Zn/Cu, MeOH/NH_4Cl, reflux, 10 min (one-pot)**	**91 (100:0)**[d]

[a] Overall yield from **1a** after chromatography (without separation of diastereomers). [b] *cis/trans* cyclobutanone ratio in parentheses. [c] Crude monochlorocyclobutanone (single isomer, β-Cl). [d] dr = 92:8. [S]StOH = (*S*)-(−)-1-(2,4,6-triisopropylphenyl)ethanol ((*S*)-(−)-Stericol). ACCN = 1,1′-azobis(cyclohexanecarbonitrile).

Although a large excess of Bu_3SnH in hot toluene did effect the desired transformation in acceptable yield, the product was partially isomerized and, furthermore, the use of this toxic reagent was to be avoided, if at all possible (Table 1, entry 1). Encouragingly, zinc−copper couple in warm acetic acid produced in moderate yield only the *cis*-cyclobutanone **3a**, along with some Stericol-containing products from degradation (entry 2). On replacing the acetic acid with a methanolic ammonium chloride solution, an improved yield of the dechlorinated cyclobutanone could be obtained after 12 h at reflux, however now as a 45:55 *cis*−*trans* mixture (entry 3). Brief exposure of the dichloride to the same reagents at −20 °C successfully eliminated the problem of isomerization, but at this temperature the monochlorocyclobutanone was the unique product (entry 4); at reflux temperature for only 10 min, however, the desired *cis*-cyclobutanone **3a** was cleanly produced in a respectable 63% overall yield (entry 5). Even better, this [2 + 2] cycloaddition/dechlorination sequence could be conveniently compressed into a one-pot procedure, which obviated the need to handle the sensitive dichlorocyclobutanone: after cycloaddition, a methanolic solution of NH_4Cl was merely added to the reaction mixture (containing residual zinc−copper couple), which was then refluxed for 10 min. The diastereomerically enriched (92:8) *cis*-cyclobutanone **3a** could thus be obtained in 91% overall yield (entry 6).

These optimized conditions were next applied to a variety of *cis*-enol ethers (Table 2).[12,13] The cyclobutanones were obtained in good to excellent overall yields and, in most cases, in stereopure form after simple flash chromatography. From (*S*)- and (*R*)-Stericol, the 3*R* and 3*S* configurations, respectively, were assigned in **3a**−**i** based on considerable antecedent.[6−8] Pleasingly, benzyl, allyl, and phenylpropyl substituents (entries 2−4), as well as even hydrolysis-susceptible benzoyl- and TBDMS-protected hydroxybutyl groups (entries 5,6), were compatible with the conditions of the sequence. The outcomes with the TIPS-, benzyl-, and benzoyl-protected hydroxymethyl substituents proved particularly interesting in several respects (entries 7−9).[14]

Acyclic enol ethers bearing a protected hydroxyl function in the allylic position have not, to the best of our knowledge, previously been subjected to dichloroketene cycloaddition. These molecules in the presence of dichloroketene can potentially undergo, in addition to cycloaddition, a [3,3]-sigmatropic (Bellus−Claisen) rearrangement (Figure 1), which is well precedented with allylic alcohol and thiol derivatives.[15]

Gratifyingly, the TIPS-, benzyl-, and benzoyl-protected γ-hydroxy enol ethers **1g**−**i**, on exposure to dichloroketene,

(8) Pyrrolidinones: (a) Nebois, P.; Greene, A. E. *J. Org. Chem.* **1996**, *61*, 5210−5211. (b) Kanazawa, A.; Gillet, S.; Delair, P.; Greene, A. E. *J. Org. Chem.* **1998**, *63*, 4660−4663. (c) Delair, P.; Brot, E.; Kanazawa, A.; Greene, A. E. *J. Org. Chem.* **1999**, *64*, 1383−1386. (d) Pourashraf, M.; Delair, P.; Rasmussen, M. O.; Greene, A. E. *J. Org. Chem.* **2000**, *65*, 6966−6972. (e) Rasmussen, M. O.; Delair, P.; Greene, A. E. *J. Org. Chem.* **2001**, *66*, 5438−5443. (f) Roche, C.; Delair, P.; Greene, A. E. *Org. Lett.* **2003**, *5*, 1741−1744. (g) Muniz, M. N.; Kanazawa, A.; Greene, A. E. *Synlett* **2005**, 1328−1330. (h) Ceccon, J.; Poisson, J. F.; Greene, A. E. *Synlett* **2005**, 1413−1416. (i) Roche, C.; Kadlecikova, K.; Veyron, A.; Delair, P.; Philouze, C.; Greene, A. E.; Flot, D.; Burghammer, M. *J. Org. Chem.* **2005**, *70*, 8352−8363. (j) Ceccon, J.; Greene, A. E.; Poisson, J. F. *Org. Lett.* **2006**, *8*, 4739−4742.

(9) For selected references, see: (a) Jeffs, P. W.; Molina, G.; Cass, M. W.; Cortese, N. A. *J. Org. Chem.* **1982**, *47*, 3871−3875. (b) Johnston, B. D.; Slessor, K. N.; Oehlschlager, A. C. *J. Org. Chem.* **1985**, *50*, 114−117. (c) Redlich, H.; Lenfers, J. B.; Kopf, J. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 777−778. (d) Hanna, I.; Pan, J.; Lallemand, J.-Y. *Synlett* **1991**, 511−512. (e) Paquette, L. A.; Heidelbaugh, T. M. *Synthesis* **1998**, 495−508.

(10) Kann, N.; Bernardes, V.; Greene, A. E. *Org. Synth.* **1997**, *74*, 13−22.

(11) Delair, P.; Kanazawa, A. M.; de Azevedo, M. B. M.; Greene, A. E. *Tetrahedron: Asymmetry* **1996**, *7*, 2707−2710. (*R*)- and (*S*)-Stericol [1-(2,4,6-triisopropylphenyl)ethanol] are now commercially available from Sigma-Aldrich.

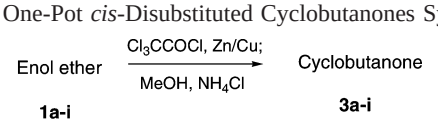
(12) The *cis*-enol ethers were prepared from Stericol (52−71% yields) by the procedure described in ref 10.

(13) General procedure for cycloaddition−dechlorination: To enol ether **1** (0.5 mmol) in degassed Et_2O (10 mL) at 20 °C was added Zn−Cu (480 mg, 7.3 mmol), followed by trichloroacetyl chloride (0.11 mL, 1.0 mmol) dropwise over 30 min. A saturated solution of ammonium chloride in methanol (20 mL) was then added, and the resulting mixture was refluxed for 10 min. The crude product was isolated in the usual way and purified by flash chromatography on silica gel to afford cyclobutanone **3**.

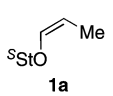
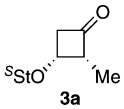
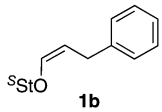
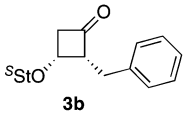
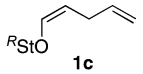
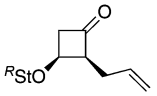
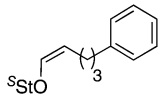
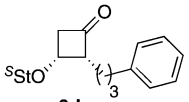
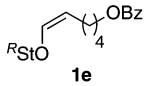
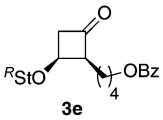
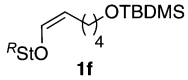
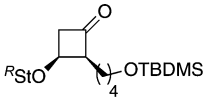
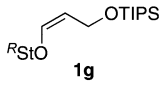
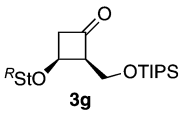
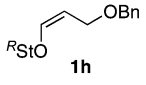
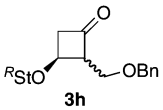
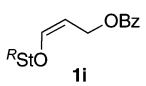
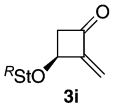
(14) Except for the cycloadditions of the benzyl- and allyl-substituted enol ethers **1b** and **1c**, these cycloadditions have not been previously reported.

(15) (a) Malherbe, R.; Bellus, D. *Helv. Chim. Acta* **1978**, *61*, 3096−3099. (b) For a minireview, see: Gonda, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 3516−3524.

Table 2. One-Pot *cis*-Disubstituted Cyclobutanones Synthesis

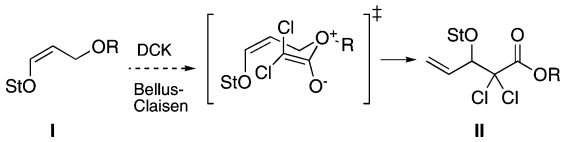


1a-i 3a-i

entry	enol ether[a]	cyclobutanone[b]	yield (dr)[c]
1	 **1a**	 **3a**	83 (>98:2) 72 (>98:2)[d]
2	 **1b**	 **3b**	85 (>98:2)
3	 **1c**	 **3c**	81 (97:3)
4	 **1d**	 **3d**	85 (96:4)
5	 **1e**	 **3e**	88 (>98:2)
6	 **1f**	 **3f**	79 (>98:2)
7	 **1g**	 **3g**	78 (>98:2)
8	 **1h**	 **3h**	73 (92:8)[e]
9	 **1i**	 **3i**	65 (92:8)

[a] ^{S}StOH = (*S*)-(−)-1-(2,4,6-triisopropylphenyl)ethanol ((*S*)-(−)-Stericol); ^{R}StOH = (*R*)-(+)-1-(2,4,6-triisopropylphenyl)ethanol ((*R*)-(+)-Stericol). [b] Cl_3CCOCl, Zn/Cu, Et_2O, 20 °C, then MeOH/NH_4Cl_{sat}, reflux, 10 min. [c] After flash chromatography; dr measured by NMR and/or HPLC (dr of crude mixtures 91:9 to 93:7). [d] 10-mmol scale. [e] 33:67 *cis*:*trans* mixture.

experienced predominantly (or exclusively) cycloaddition, as only the dechlorinated cyclobutanones could be detected in the crude reaction mixtures. Purification of the crude silyloxymethyl derivative afforded the stereopure cyclobutanone **3g** in 78% overall yield (entry 7). Curiously, the crude benzyloxymethyl cyclobutanone suffered epimerization on silica gel, alumina, or Florisil chromatography, which produced a mixture of the *cis*- and *trans*-isomers **3h** (entry 8). In contrast, the crude benzoyloxymethyl derivative underwent facile elimination on simple silica gel filtration to afford in 65% overall yield the novel methylenecyclobutanone **3i** (entry 9), a synthetically attractive intermediate that is the formal product of an unprecedented chiral allenol ether−ketene cycloaddition. The ready cycloaddition/dechlorination of these hydroxy-substituted enol ether derivatives is significant in that it allows a useful functional group to be easily introduced into the cyclobutanones in a key position (see below).



I II

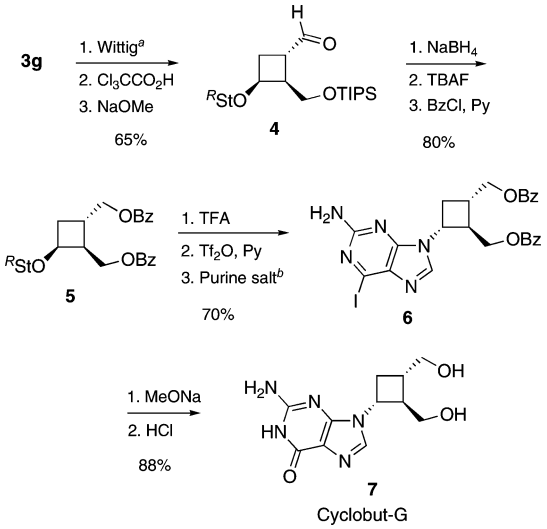
Figure 1. Potential Bellus−Claisen pathway.

To demonstrate some of the considerable potential of this asymmetric approach to cyclobutanones, a synthesis of cyclobut-G (Lobucavir)[16] was undertaken. This cyclobutyl guanine nucleoside analogue, which was developed by Bristol-Myers-Squibb in 1997, derives from oxetanocin A, an unusually potent anti-HIV oxetan.[17] Our approach began by methoxy olefination of cyclobutanone **3g**, which was followed by hydrolysis of the enol ether and isomerization of the resulting formyl group (13:1, *trans*:*cis*), to afford aldehyde **4** in 65% yield for the three steps (Scheme 1). Dibenzoate **5** was next produced from **4** by sequential carbonyl reduction, TIPS cleavage, and benzoylation of the two free hydroxyl groups (80%, three steps), and then treated with trifluoroacetic acid to generate cleanly the corresponding cyclobutanol (92%).[16a−c,18] The last step of this sequence illustrates the efficiency of Stericol cleavage to prepare the corresponding cyclobutanols. Triflation of the free hydroxyl function in this derivative was followed by nucleophilic

(16) (a) Bisacchi, G. S.; Braitman, A.; Cianci, C. W.; Clark, J. M.; Field, A. K.; Hagen, M. E.; Hockstein, D. R.; Malley, M. F.; Mitt, T.; Slusarchyk, W. A.; Sundeen, J. E.; Terry, B. J.; Tuomari, A. V.; Weaver, E. R.; Young, M. G.; Zahler, R. *J. Med. Chem.* **1991**, *34*, 1415−1421. (b) Bisacchi, G. S.; Singh, J.; Godfrey, J. D., Jr.; Kissick, T. P.; Mitt, T.; Malley, M. F.; Di Marco, J. D.; Gougoutas, J. Z.; Mueller, R. H.; Zahler, R. *J. Org. Chem.* **1995**, *60*, 2902−2905. (c) Singh, J.; Bisacchi, G. S.; Ahmad, S.; Godfrey, J. D., Jr.; Kissick, T. P.; Mitt, T.; Kocy, O.; Vu, T.; Papaioannou, C. G.; Wong, M. K.; Heikes, J. E.; Zahler, R.; Mueller, R. H. *Org. Process Res. Dev.* **1998**, *2*, 393−399. (d) Genovesi, E. V.; Lamb, L.; Medina, I.; Taylor, D.; Seifer, M.; Innaimo, S.; Colonno, R. J.; Clark, J. M. *Antiviral Res.* **2000**, *48*, 197−203. (e) Hanson, R. L.; Shi, Z.; Brzozowski, D. B.; Banerjee, A.; Kissick, T. P.; Singh, J.; Pullockaran, A. J.; North, J. T.; Fan, J.; Howell, J.; Durand, S. C.; Montana, M. A.; Kronenthal, D. R.; Mueller, R. H.; Patel, R. N. *Bioorg. Med. Chem.* **2000**, *8*, 2681−2687.

(17) (a) Hoshino, H.; Shimizu, N.; Shimada, N.; Takita, T.; Takeuchi, T. *J. Antibiot.* **1987**, *40*, 1077−1078. For additional references to this and related compounds, see: (b) Rustullet, A.; Alibés, R.; de March, P.; Figueredo, M.; Font, J. *Org. Lett.* **2007**, *9*, 2827−2830.

Scheme 1. Cyclobut-G Synthesis



[a] (Ph_3PCH_2OMe,Cl), KHMDS. [b] 2-Amino-6-iodopurine tetrabutylammonium salt.

substitution with a purine salt and hydrolysis.[16b,c] to afford cyclobut-G, which provided spectral data identical to those reported in the literature ($[\alpha]^{20}_D$ −24.7; lit.[16b] $[\alpha]^{22}_D$ −24.4).[16a,b] This approach should permit novel structural modification at several points.

In summary, a simple, efficient, and stereoselective one-pot transformation of readily available enol ethers to functionalized chiral cyclobutanes has been developed. Given the dearth of generally useful approaches to chiral cyclobutane derivatives, we expect that this new approach will find additional application. Further work in this area is planned.

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Supporting Information Available: Complete characterization data and ^1H and ^{13}C NMR spectra for cyclobutanones **3a**−**g**, **3i** and intermediates for the synthesis of Cyclobut-G. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Er = 98.3:1.7, by HPLC: Chiracel AD-H, 5 mm, hexane/isopropanol, 9:1, 1.0 mL/min. t_R = 16.0 min; t_R (enantiomer) = 18.0 min.