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Asymmetric Synthesis of Functionalized, Monocyclic Chlorocyclobutenes

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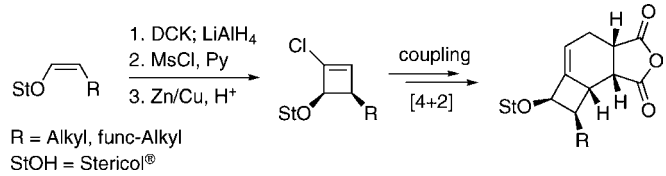
ABSTRACT



The selective synthesis of a variety of stereopure monocyclic chlorocyclobutenes is described. These derivatives could be coupled with Grignard reagents; two dienes from coupling with vinylmagnesium bromide reacted smoothly with maleic anhydride to yield illudol-related [4 + 2] cycloadducts.

The synthesis of functionalized monocyclic cyclobutenes has received relatively little attention over the years[1] despite their potential as building blocks in organic synthesis.[2] As far as halocyclobutenes (vinylic) derivatives are concerned, the situation is particularly striking: there are few reports[1a−e,h,3] on the preparation of functionalized monocyclic halocyclobutenes; moreover, such compounds have invariably been prepared in racemic form (as have been the vast majority of cyclobutenes synthesized to date[4]). Monocyclic halocyclobutene derivatives should be readily susceptible to further elaboration, especially through coupling reactions, and thus a general enantioselective approach to these compounds would be of particular interest.

We wondered whether it might be possible to transform the dichlorocyclobutanones stemming from the diastereoselective cycloaddition of dichloroketene (DCK) to chiral enol ethers[5] into chlorocyclobutenes and under conditions mild enough to avoid electrocyclic ring opening of the products once obtained. Our plan, drawing on an earlier isolated report,[3a] was to convert cyclobutanones **II** into the dichlorocyclobutanol derivatives **III** (R^2 = electron-withdrawing group); a mild and selective reductive elimination might then furnish the chlorocyclobutenes **IV** (Figure 1).

(1) Other than enol and squaric acid derivatives. For some methods of preparation, see: (a) Caserio, M. C.; Simmons, H. E., Jr.; Johnson, A. E.; Roberts, J. D. *J. Am. Chem. Soc.* **1960**, *82*, 3103–3106. (b) Sullivan, R.; Lacher, J. R.; Park, J. D. *J. Org. Chem.* **1964**, *29*, 3664–3668. (c) Steinmetz, R.; Hartmann, W.; Schenck, G. O. *Chem. Ber* **1965**, *98*, 3854–3873. (d) Snider, B. B.; Roush, D. M.; Rodini, D. J.; Gonzalez, D.; Spinell, D. *J. Org. Chem.* **1980**, *45*, 2773–2785. (e) Goodman, M. M.; Shoup, T. *PCT Int. Appl. WO 9717092 A1 19970515*, 1997. (f) Gourdel-Martin, M.-E.; Huet, F. *J. Org. Chem.* **1997**, *62*, 2166–2172. (g) Takahashi, T.; Shen, B.; Nakajima, K.; Xi, Z. *J. Org. Chem.* **1999**, *64*, 8706–8708. (h) Hamura, T.; Kakinuma, M.; Tsuji, S.; Matsumoto, T.; Suzuki, K. *Chem. Lett.* **2002**, 748–749. (i) Liu, Y.; Liu, M.; Song, Z. *J. Am. Chem. Soc.* **2005**, *127*, 3662–3663. (j) Fürstner, A.; Aïssa, C. *J. Am. Chem. Soc.* **2006**, *128*, 6306–6307. (k) Shi, M.; Liu, L.-P.; Tang, J. *J. Am. Chem. Soc.* **2006**, *128*, 7430–7431. (l) Debleds, O.; Campagne, J.-M. *J. Am. Chem. Soc.* **2008**, *130*, 1562–1563. (m) Tian, G.-Q.; Yuan, Z.-L.; Zhu, Z.-B.; Shi, M. *Chem. Commun.* **2008**, 2668–2670. (n) Xu, H.; Zhang, W.; Shu, D.; Werness, J. B.; Tang, W. *Angew. Chem., Int. Ed.* **2008**, *47*, 8933–8936. (o) Masarwa, A.; Fürstner, A.; Marek, I. *Chem. Commun.* **2009**, 5760–5762. (p) Barluenga, J.; Riesgo, L.; Lopez, L. A.; Rubio, E.; Tomas, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 7569–7572. (q) Lopez-Carillo, V.; Echavarren, A. *J. Am. Chem. Soc.* **2010**, *132*, 9292–9294.

(2) For reviews on cyclobutane derivatives, see: (a) *The Chemistry of Cyclobutanes*; Rappoport, Z., Liebman, J. F., Eds.; John Wiley & Sons, Ltd.: West Sussex, England, 2005; Vols. 1 and 2. (b) Lee-Ruff, E.; Mladenova, G. *Chem. Rev.* **2003**, *103*, 1449–1483.

(3) For the synthesis of some polycyclic halocyclobutenes, see: (a) Hassner, A.; Fletcher, V. R. *Tetrahedron Lett.* **1970**, *58*, 5053–5056. (b) Ohkita, M.; Ando, K.; Tsuji, T. *Chem. Commun.* **2001**, 2570–2571. (c) Fürstner, A.; Schlecker, A.; Lehmann, C. *Chem. Commun.* **2007**, 4277–4279. (d) Allen, A.; Villeneuve, K.; Cockburn, N.; Fatila, E.; Riddell, N.; Tam, W. *Eur. J. Org. Chem.* **2008**, 4178–4192.

(4) For some routes to enantioenriched cyclobutenes, see: (a) Villeneuve, K.; Tam, W. *Angew. Chem., Int. Ed.* **2004**, *43*, 610–613. (b) Shibata, T.; Takami, K.; Kawachi, A. *Org. Lett.* **2006**, *8*, 1343–1345. (c) Ishihara, K.; Fushimi, M. *J. Am. Chem. Soc.* **2008**, *130*, 7532–7533, and refs 1o, 2b, and 3a.

(5) Darses, B.; Greene, A. E.; Coote, S. C.; Poisson, J.-F. *Org. Lett.* **2008**, *10*, 821–824.

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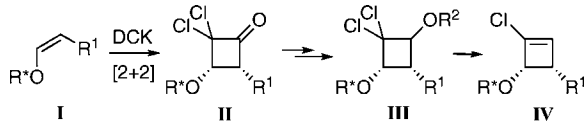
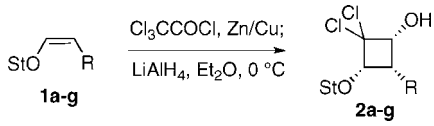
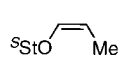
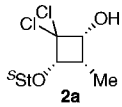
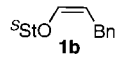
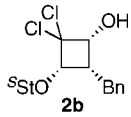
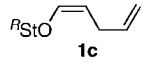
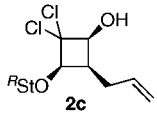
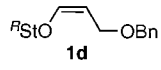
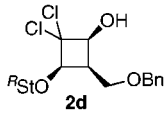
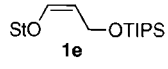
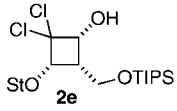
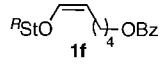
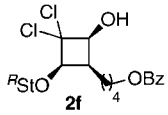
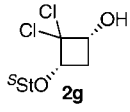


Figure 1. Chlorocyclobutenes **IV** from enol ethers **I**.

We began our study with chiral enol ether **1a** (Table 1).[6] Reaction of this ether with dichloroketene, generated from trichloroacetyl chloride with zinc−copper couple, led to the rather unstable corresponding dichlorocyclobutanone (dr ca. 95:5). The crude cycloadduct, on treatment with sodium borohydride, afforded a complex mixture of products, from which cyclobutanol **2a** could be isolated in low yield (22% for 2 steps). The use of Dibal-H did not improve the results. Fortunately, however, lithium aluminum hydride at 0 °C was more rewarding, affording the cyclobutanol **2a** in 73% yield; better yet, direct addition of the supernatant from the cycloaddition reaction mixture to an ethereal solution of $LiAlH_4$ at 0 °C led to cyclobutanol **2a** in 88% yield for the 2 steps (entry 1). Alcohol **2a** was obtained as a single isomer, all *cis*, resulting from hydride attack on the less hindered face of the molecule.[7]

Table 1. Cyclobutanols Synthesis[a]



entry	enol ether	cyclobutanol[b]	yield %[c]
1	 **1a**	 **2a**	88
2	 **1b**	 **2b**	83
3	 **1c**	 **2c**	66
4	 **1d**	 **2d**	85
5	 **1e**	 **2e**	71[d]
6	 **1f**	 **2f**	73
7	 **1g**	 **2g**	62

[a] ^{S}StOH = (*S*)-(−)-1-(2,4,6-triisopropylphenyl)ethanol. ^{R}StOH = (*R*)-(+)-1-(2,4,6-triisopropylphenyl)ethanol. [b] Cl_3CCOCl, Zn/Cu, Et_2O, 20 °C, then $LiAlH_4$, Et_2O, 0 °C. [c] After flash chromatography (in all cases, dr >98:2). [d] Cl_3CCOCl, Zn/Cu, Et_2O, 20 °C, then $NaBH_4$, EtOH, 0 °C.

This optimized procedure was next applied to a variety of Stericol-derived enol ethers (**1b**−**g**, Table 1). It proved efficient with the benzyl-, allyl-, and benzyloxymethyl-substituted enol ethers **1b**−**d** (entries 2−4), affording the corresponding cyclobutanols in 66−85% yields for the 2 steps. Unexpectedly, the same procedure when applied to the triisopropylsilyloxymethyl enol ether **1e** led to cleavage of the silyl ether to give the corresponding diol in low yield (36%). Fortunately, with this substrate sodium borohydride gave a satisfactory result, producing cyclobutanol **2e** in 71% yield (2 steps). Enol ether **1f** underwent surprisingly clean conversion into cyclobutanol **2f** under the general conditions, without detectable reduction of the benzoyloxy group (entry 6). Finally, the "naked" enol ether **1g** produced cyclobutanol **2g**, albeit in slightly lower yield (62%), also under the general conditions. In every case, the cyclobutanol **2** was isolated as a single diastereoisomer.

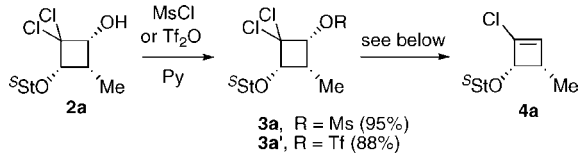
With this effective procedure in hand, selective reductive elimination in the dichlorocyclobutanols **2** was next addressed beginning with **2a**. This alcohol was first transformed into the corresponding mesylate **3a** and triflate **3a′** (95% and 88% yields, respectively).[8] These substrates were then subjected to a number of reductive elimination procedures, which indicated zinc metal to be the most promising reducing agent (Table 2). Addition of an ethereal solution of mesylate **3a** to a suspension of zinc−copper couple in acidic methanol, followed by heating at 55 °C under microwave irradiation, led to chlorocyclobutene **4a** in 80% yield (entry 1). Also formed, however, was a small amount of diene (ring-opened product). By conducting the same reaction in refluxing ether−methanol without microwave irradiation, though, the problem of electrocyclic ring opening could be suppressed and **4a** obtained in somewhat better yield (Table 2, entry 2). Finally, the cleanest and most efficient conversion was produced with a suspension of zinc−copper couple in

(6) All enol ethers used in this work were obtained from Stericol [1-(2,4,6-triisopropylphenyl)ethanol] through the dichloroenol and ynol ethers, following a procedure similar to that described in. (a) Kann, N.; Bernardes, V.; Greene, A. E. *Org. Synth* **1997**, *74*, 13–22. For the mechanism of the formation of ynol ethers from dichloroenol ethers, see: (b) Darses, B.; Milet, A.; Philouze, C.; Greene, A. E.; Poisson, J.-F. *Org. Lett.* **2008**, *10*, 4445–4447.

(7) The relative stereochemistry in **2a** has been assigned from considerable antecedent for the face of the cycloaddition and by NOE experiments for the face of the reduction.

(8) Reductive elimination was also attempted directly on **2a** with chromium perchlorate; however, a mixture of products containing only a minor amount of cyclobutene **4a** was produced.

Table 2. Chlorocyclobutene **4a** from Alcohol **2a**



entry	substrate	dechlorination conditions	yield of **4a** (%)[a]
1	**3a**	Zn/Cu, MeOH/NH_4Clsat, Et_2O, μ-wave, 55 °C	80
2	**3a**	Zn/Cu, MeOH/NH_4Clsat, Et_2O, reflux	84
3	**3a**	Zn/Cu, MeOH/NH_4Clsat, Et_2O, ultrasound, 35 °C	93
4	**3a**	*t*-BuLi, THF, −78 °C	86
5	**3a′**	Zn/Cu, MeOH/NH_4Clsat, Et_2O, ultrasound, 35 °C	89
6	**3a′**	*t*-BuLi, THF, −78 °C	94

[a] Yield from **3a** or **3a′** after chromatography.

ether−methanol in the presence of ammonium chloride at 35 °C under sonication, which afforded chlorocyclobutene **4a** in an excellent 93% yield (88% for the 2 steps, entry 3).

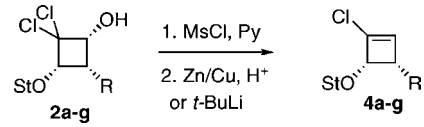
Alternative conditions for avoiding the formation of the ring-opened diene were also examined. Since α-deprotonation appeared unlikely, chlorine−lithium exchange with *tert*-butyllithium at low temperature seemed possible. The addition of 2 equiv of *tert*-butyllithium to mesylate **3a** in THF at −78 °C indeed led to the desired product in high yield (entry 4).

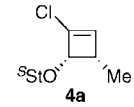
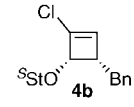
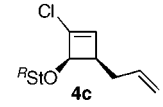
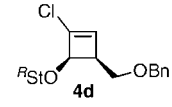
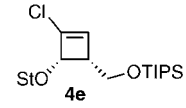
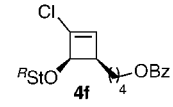
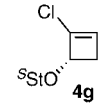
With the triflate derivative **3a′**, both methods (Zn/Cu and *t*-BuLi) afforded **4a** in yields similar to those above (entries 5 and 6); however, since formation of the mesylate was more efficient than that of the triflate and the derivative was more stable, mesylates were subsequently used.

Thus, two complementary reductive elimination methods for the formation of chlorocyclobutenes have been developed, one using zinc metal that requires near ambient temperature and the other employing *tert*-butyllithium at −78 °C.

These optimized methods were next applied to alcohols **2b**−**g** (Table 3). The benzyl-substituted chlorocyclobutene **4b** could be obtained from alcohol **2b** in 78% overall yield (2 steps, entry 2; 65% from the enol ether). Similarly, the allyl- and benzyloxymethyl-substituted cyclobutanols **2c** and **2d** afforded the corresponding cyclobutenes **4c** and **4d** in high yields (entries 3 and 4). The mesylate from cyclobutanol **2e**, however, under the Zn−Cu reductive elimination conditions successful in the above examples, led to a 3.3:1 mixture of chlorocyclobutene **4e** and ring-opened diene. As expected, though, the chlorine−lithium exchange procedure generated **4e** in excellent yield, without a trace of ring-opened product (entry 5). The mesylate from cyclobutanol **2f** could be transformed uniquely into chlorocyclobutene **4f**, again by using Zn−Cu (90%, entry 6), but that derived from the less-substituted cyclobutanol **2g** was better converted into the thermally sensitive chlorocyclobutene **4g** with *tert*-butyllithium at −78 °C (82%, entry 7).

Table 3. Chlorocyclobutenes **4a**−**g** from Alcohols **2a**−**g**

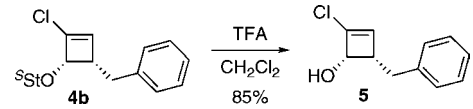


entry	cyclobutanol	mesylate[a]	chlorocyclobutene	yield[a]
1	**2a**	95	 **4a**	93[b]
2	**2b**	89	 **4b**	88[b]
3	**2c**	95	 **4c**	94[b]
4	**2d**	94	 **4d**	87[b]
5	**2e**	95	 **4e**	89[c]
6	**2f**	82	 **4f**	90[b]
7	**2g**	85	 **4g**	82[c]

[a] Yield of isolated product after flash chromatography. [b] Zn−Cu, Et_2O, MeOH/NH_4Clsat, ultrasound, 35 °C. [c] *t*-BuLi (2 equiv), THF, −78 °C.

Importantly, the chiral control group can be readily and selectively cleaved in these chlorocyclobutenes, leaving a synthetically useful hydroxyl, as illustrated in Scheme 1.

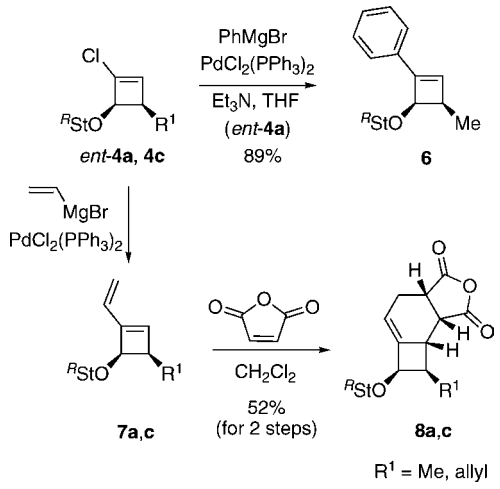
Scheme 1. Stericol Cleavage



Significant also is that these vinylic choride derivatives are good Kumada−Corriu coupling[9] partners: reaction of *ent*-**4a** with phenylmagnesium bromide in the presence of

$PdCl_2(PPh_3)_2$ gave the phenyl-substituted cyclobutene **6** in excellent yield (89%) and those of *ent*-**4a** and **4c** with vinylmagnesium bromide yielded the vinyl-substituted cyclobutenes **7a** and **7c** (Scheme 2). These dienes were prone

Scheme 2. Elaboration of Chlorocyclobutenes **4a,c**



to ring opening, however, and thus immediately subjected to reaction with maleic anhydride to afford the [4 + 2] endo cycloadducts **8a** and **8c**, respectively, in 52% overall yield in each case. It should be noted that this sequence of reactions constitutes a potential approach to the illudol family of natural products.

In conclusion, we have described the first general, asymmetric entry to (poly)functionalized monocyclic chlorocyclobutenes. The cyclobutenes are formed in good overall yields and are sufficiently stable toward ring opening to allow Kumada−Corriu coupling with aryl and vinyl Grignard reagents. We expect that there will be other applications of this chemistry.

Acknowledgment. We thank Dr. J. Einhorn (UJF) for his interest in our work, the CNRS and the French Ministry of Research for financial support (UMR 5250), and the French Ministry of Research for a fellowship (to B.D.).

Supporting Information Available: Complete characterization data and ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) For examples of vinylic chloride coupling reactions, see: (a) Ramiandrasoa, P.; Bréhon, B.; Thivet, A.; Alami, M.; Cahiez, G. *Tetrahedron Lett.* **1997**, *14*, 2447–2450. (b) Tan, Z.; Negishi, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 762–765. (c) Lemay, A. B.; Vulic, K. S.; Ogilvie, W. W. *J. Org. Chem.* **2006**, *71*, 3615–3618.