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Regioselective Carbon–Carbon Bond Cleavage in the Oxidation of Cyclopropenylcarbinols

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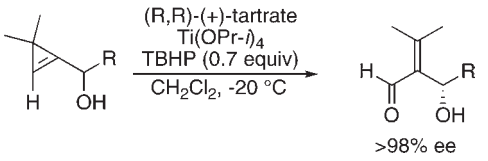
ABSTRACT



The strained double bond of cyclopropenylcarbinols undergoes a facile oxidation reaction to lead to unsaturated carbonyl derivatives. The distribution of the formed products depends on the relative stability of carbon-centered radical species, and the Sharpless kinetic resolution leads to enantiomerically pure Baylis–Hillman enal adducts.

Following his landmark discovery on the enantioselective epoxidation reaction of allylic alcohols,[1] Sharpless reported the application of the Ti(OPr-*i*)$_4$/diisopropyl tartrate catalyst system for the kinetic resolution of secondary allylic alcohols[2] (SKR). The broad scope of the reaction combined with the readily accessible catalyst components led to a rapid adoption of the SKR by organic chemists, and to date, it has certainly been one of the most often used kinetic resolution reactions involving synthetic catalysts.[3] Therefore, when we had to prepare enantiomerically enriched cyclopropenylcarbinol species **1**, we just considered them as particularly strained allylic alcohols and the SKR was logically the method of choice. We were indeed pleased to observe that, despite the very reactive nature of the strained double bond, a very efficient kinetic resolution occurs at −20 °C and the non-oxidized cyclopropenylcarbinols **1** were obtained with very high enantiomeric excess and yields (97–99% ee and 40–47% yield of isolated products, Scheme 1).[4] The latter could then be used as starting materials for the preparation of enantiomerically enriched alkylidenecyclopropanes[5,6] and beyond that to a large variety of synthetically important fragments possessing challenging acyclic all-carbon quaternary stereogenic centers.[7] The oxidized product,

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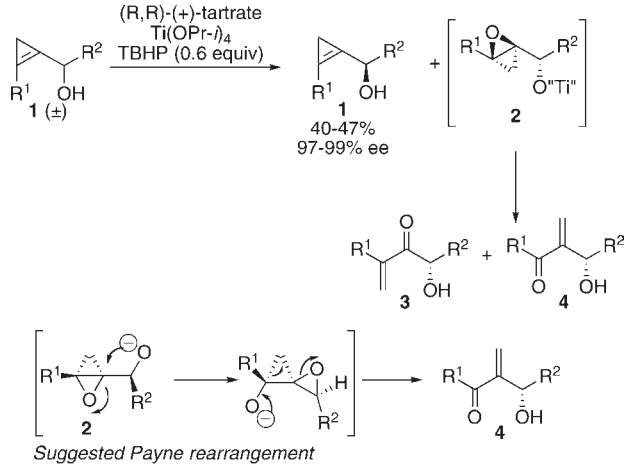
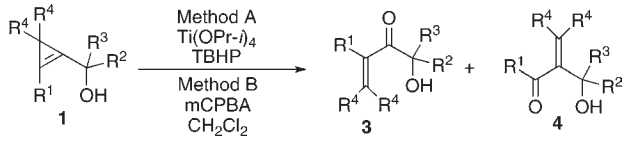
Scheme 1. Sharpless Kinetic Resolution (SKR) of Cyclopropenyl Alcohol: Expected Formation of Baylis–Hillman Adduct **4**



namely, the putative chiral 2-oxabicyclo[1.1.0]butane (OBB) **2**, leads through a hypothetical cleavage of the two peripheral σ-bonds[8] to the two enantiomerically enriched α,β-unsaturated ketols **3** and **4** in equal amounts (each in 22–25% yield of isolated product).[4] Oxabicyclo[1.1.0]-butane species **2** have been postulated for more than 45 years as intermediates in various oxidation,[9] thermal,[10] or photochemical reactions,[11] but they have never been isolated nor spectroscopically detected. Although we were also not able to isolate such intermediates, the formation of enantiomerically enriched products **1** led us to suggest that the corresponding oxabicyclobutanes **2** were formed as reactive intermediates through the SKR reaction.[4] However, high-level ab initio calculations have shown that high activation barriers characterize unimolecular as well as acid-catalyzed fragmentation of oxabicyclobutanes, and these should therefore be thermodynamically stable molecules.[12] Moreover, we were intrigued that the two enones **3** and **4** were obtained in an exact equimolar amount in the rearrangement process; this result was particularly striking as titanium alcoholate in **2** should have promoted a selective ring-opening reaction into **4** through an initial Payne rearrangement and subsequent skeletal reorganization (Scheme 1).[13]

To understand better the mechanism of formation of the two enones, we first checked that this process was a general one for a large variety of alkyl-substituted cyclopropenylcarbinol species **1** using either the classical Sharpless epoxidation (method A) or the simplest peracid epoxidation reaction (*m*CPBA, method B) as summarized in Table 1. Whatever the method used (Sharpless epoxidation, method A, or peracid oxidation, method B, Table 1, entries 1–4), cyclopropenylcarbinols **1a,b** always gave the two enones **3** and **4** in equimolar amount and in good isolated yield. As similar results were obtained with the two methods, we initially concentrated on the peracid oxidation reaction for a rapid screening, and we found that, for R^1 = alkyl, whatever the substitutions of the cyclopropenylcarbinols (R^2, R^3 = alkyl, hydrogen, aryl; and R^4 = hydrogen or alkyl), the two isomeric enones were always formed in a 1:1 ratio (Table 1, entries 1–8). We have also performed DFT calculations for the transformation of

Table 1. Epoxidation Reaction of Cyclopropenylcarbinols **1**



entry	R^1	R^2	R^3	R^4	method	dr [a] **3**:**4**	yield (%)[b]
1 (**1a**)	Me	Ph	H	H	A	1:1	98
2 (**1a**)	Me	Ph	H	H	B[c]	1:1	96
3 (**1b**)	Me	Ph	H	Me	A	1:1	70
4 (**1b**)	Me	Ph	H	Me	B	1:1	65
5 (**1c**)	Me	Ph	Ph	H	B	1:1	88
6 (**1d**)	Me	Me	Me	H	B	1:1	80
7 (**1e**)	Me	$(CH_2)_2Ph$	H	H	B	1:1	89
8 (**1f**)	Me	$(CH_2)_2Ph$	Me	Me	B	1:1	65
9 (**1g**)	Ph	Me	Me	H	B	1:0	84
10 (**1g**)	Ph	Me	Me	H	A	1:0	80
11 (**1h**)	Ph	Ph	Ph	H	B	1:0	82
12[d](**1i**)	Ph	Ph	H	H	B	1:0	90
13 (**1j**)	Ph	$(CH_2)_2Ph$	H	H	B	1:0	79
14 (**1k**)	Ph	Bu	H	H	B	1:0	72
15 (**1l**)	Ph	iPr	H	H	B	1:0	77
16(**1m**)	Ph	iBu	H	H	B	1:0	72
17 (**1n**)	Me_3Si	*p*BrPh	H	Me	B	1:0	94
18 (**1o**)	$PhMe_2Si$	*p*BrPh	H	Me	B	1:0	91
19 (**1p**)	Ph_2MeSi	*p*BrPh	H	Me	B	1:0	81
20 (**1q**)	H	Ph	H	Me	B	0:1	65
21 (**1r**)	H	*p*MeOPh	H	Me	B	0:1	66
22 (**1r**)	H	*p*MeOPh	H	Me	A	0:1	65
23 (**1s**)	H	*i*Pr	H	Me	B	0:1	60
24 (**1t**)	H	$(CH_2)_2Ph$	H	Me	B	0:1	61
25 (**1t**)	H	$(CH_2)_2Ph$	H	Me	A	0:1	67

[a] Diastereomeric ratio determined by ^{1}H NMR. [b] Combined isolated yields for all isomers after column chromatography (based on **1**). [c] Same results were obtained in either THF or toluene at −40 °C or rt. [d] As aryl-substituted (R^1 = Ph) secondary cyclopropenylcarbinol derivatives (R^3 = H) are unstable when neat, the oxidation reaction was performed only with *m*CPBA directly on the crude reaction mixture in solution.

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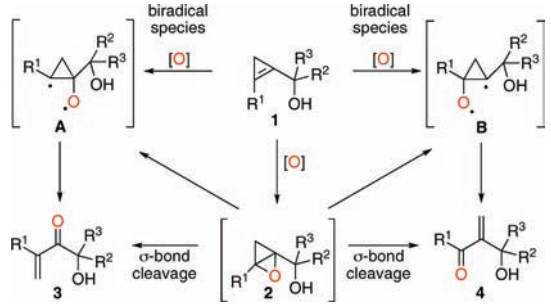
oxabicyclo[1.1.0]butane **2** into enones and found, for all substrates, that the barrier for enone **3** is lower than that for enone **4** (> 3 kcal/mol).[14] These results suggest that the two enones should not be formed in equimolecular amount in the reaction, which is opposite to our experimental results. Oxidation of the double bond could also proceed through an unsymmetrical transition state that could lead to the formation of a biradical intermediate.[15] If formation of a biradical species was occurring, the equimolar formation of the two-biradical species **A** and **B** would consequently lead to the equimolar formation of the two enones **3** and **4**, respectively (Scheme 2). If correct, if one could design a system leading to a single biradical entity, the reaction should now be selective and lead to a single enone.

Scheme 2. Possible Explanations for the Formation of Enones **3** and **4**



Therefore, by using the conjugative resonance stabilization of radicals (i.e., formation of benzyl radicals), the oxidation reaction of cyclopropenylcarbinol should lead to a complete and selective reaction.

To check this hypothesis, cyclopropenylcarbinol **1g**[7e] was prepared (R^1 = Ph, R^2 = R^3 = Me, R^4 = H) and oxidized with *m*CPBA, and to our delight, a *single* isomer **3g** was obtained in good yield (Table 1, entry 9). The same isomer was formed when the Sharpless epoxidation conditions were used (Table 1, entry 10), illustrating that, in both cases, the exclusive formation of intermediate **A** (R^1 = Ph) leads quantitatively to enone **3**. This transformation has a broad scope and is insensitive to the nature of substituents R^2 and R^3 (aryl, primary and secondary alkyl groups, Table 1, entries 11−16). However, the exclusive formation of **3** does not preclude the initially formed oxabicyclobutane **2**, which would undergo heterolytic opening of the epoxide moiety either (1) to the biradical intermediate **A** or (2) to a 1,3-zwitterionic intermediate with a cationic center on the cyclopropane ring (not shown in Scheme 2). By a subsequent ring opening of this zwitterionic species into the corresponding oxy-substituted allyl cation, the carbonyl compound could be formed. The intermediate zwitterion would also explain the observed regioselectivity for this particular substitution pattern since the stabilizing effect of an aryl substituent (R^1 = Ph) on a tertiary carbenium ion is pronounced. To distinguish between these two possibilities (biradical vs zwitterionic), silyl-substituted cyclopropenyl carbinols **1n**−**1p** were prepared and tested in our experimental conditions. Indeed, the β-silicon effect (silicon hyperconjugation) leads to a stabilization of carbocation in a β-position,[16] and therefore, if a carbocationic species is involved, adduct **4** would be obtained. However, if a radical is involved, silicon stabilizes the radical in the α-position and **3** should be formed. When **1n**−**1p** were oxidized, a single isomer of vinyl silanes **3n**−**p** was obtained in good isolated yields (Table 1, entries 17−19), suggesting that no transient carbocationic species were involved but rather biradical species.[17] Vinyl silanes are very useful intermediates for further synthetic manipulations.[18] The formation of carbocationic species seems to be excluded, but we still cannot rule out the initial formation of OBB **2** which would undergo a subsequent heterolytic ring opening into **A** (or **B**). However, DFT calculations show that the heterolytic cleavage of oxabicyclobutane into a biradical species is much higher in energy (> 8 kcal/mol) than its direct transformation into an enone, which is not consistent with the ratio of enones **3** and **4** obtained experimentally.[14] On the other hand, a very small energy difference (1−2 kcal/mol) between biradical **A** and **B** was found for **1a** (Table 1, entry 1, R^1 = Me, R^2 = Ph, R^3 = R^4 = H) and **1d** (Table 1, entry 6, R^1 = R^2 = R^3 = Me, R^4 = H), which is in a good agreement with the 1:1 ratio of the two enones. Additionally, biradical **A** of **1g** is more stable by almost 12 kcal/mol than biradical **B** (Table 1, entry 9, R^1 = Ph, R^2 = R^3 = Me, R^4 = H).[14]

To increase structural complexity of these enones, a fundamental strategy is to utilize substrate stereochemistry to control the introduction of new stereogenic centers through the Felkin-Anh or Cram chelation models.[19] Particularly interesting is the formation of quaternary stereogenic centers in acyclic systems[20,21] and the addition of cyclopropenyllithium species[22] to α-substituted aldehydes and ketones, which led to the formation of diastereoisomerically pure cyclopropenylcarbinols **1u**−**z** in excellent yields (Scheme 3) as single diastereoisomers.[23] The simple addition of *m*CPBA to these substituted cyclopropenylcarbinols gave the corresponding enones **3u**−**z** as unique isomers in good yield. The stereochemistry was confirmed by X-ray analysis of **1z** and **3u**; the

(14) See Supporting Information.
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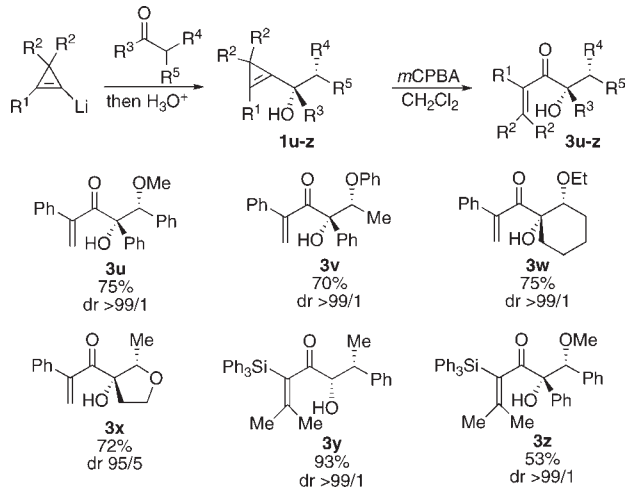
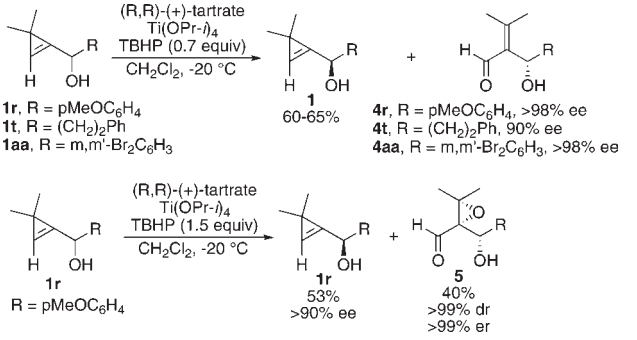
configurations of other reaction products were assigned by analogy.

Scheme 3. Oxidation of Functionalized Cyclopropenylcarbinol Derivatives **1u,z**



Having access to enones of general structure **3** via the biradical species **A**, we then wondered if enones **4** could be selectively prepared by driving the reaction through the formation of the biradical intermediate **B**. As tertiary radicals are more stable than secondary, we hypothesized that cyclopropenylcarbinol **1q**–**t** (R^1 = H) would only lead to intermediates **B** possessing a tertiary centered radical. We were delighted to see that our prediction was correct and only single isomers corresponding to the Baylis–Hillman enals[24] **4** were formed (Table 1, entries 20–25) whatever the method (A or B) used. In these cases, the biradical **B** for **1q** (Table 1, entry 20, R^1 = H, R^2 = Ph, R^3 = H, R^4 = Me) is more stable by 17 kcal/mol than biradical **A**.[14] The Sharpless kinetic resolution conditions were then used to oxidize cyclopropenylcarbinols **1r**, **1t**, and **1aa**, and the corresponding enals were obtained in very good chemical yields (45, 40, and 41% yields, respectively) and with outstanding enantioselectivities[25] along the remaining cyclopropenylcarbinols **1**, as described in Scheme 4. Even more appealing was the kinetic resolution with an excess of *t*-BuOOH (1.5 equiv, Scheme 4). In this case, epoxidation of the resulting enal was faster that the oxidation of unreacted cyclopropenylcarbinol. Epoxyalcohols **5** were obtained as single diastereoisomers and enantiomers.[25]

Scheme 4. SKR of Cyclopropenylcarbinol Leading to Enantiomerically Enriched Baylis–Hillman Adducts



In conclusion, by a judicious choice of substituent R^1 on the cyclopropenyl core, both isomers **3** and **4** could be selectively obtained, suggesting the formation of biradical intermediates **A** and **B**. Although no intermediates could be detected (the ring opening of such entities is much faster than any possible trapping experiments), the selective formation of such isomers depends on the relative stability of carbon-centered radicals and is strongly supported by high-level ab initio calculations. This mild and selective oxidation reaction was then successfully used for the preparation of complex conjugated carbonyl compounds possessing two stereogenic centers. Alternatively, the Sharpless kinetic resolution (SKR) of monosubstituted cyclopropenylcarbinol derivatives (R^1 = H) leads to enantiomerically enriched α-hydroxy enal derivatives (Baylis–Hillman adducts) with outstanding enantiomeric ratios.

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Supporting Information Available. Experimental procedures with a description of ^{1}H NMR, ^{13}C NMR, and crystallographic data (CIF) and all calculated energies. This material is available free of charge via the Internet at http://pubs.acs.org.

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(25) Enantiomeric excesses were determined on crude ^{19}F NMR after transformation into Mosher esters; see experimental part.