Acids Direct 2-Styrylcyclobutanone into Two Distinctly Different Reaction Pathways

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ABSTRACT



Two structurally distinct carbocycles were selectively obtained by the reactions of 2-(*o*-styryl)cyclobutanones promoted by ytterbium salts. Treatment of the cyclobutanones with YbCl₃ in 1,4-dioxane at 100 °C afforded 2-(2-chloroethyl)naphthalenes. On the other hand, the reaction with Yb(OTf)₃ in chlorobenzene at 130 °C gave 9,10-dihydrobenzocycloocten-7(8*H*)-ones.

The acid-promoted addition of an olefin to a carbonyl compound, as in the Prins reaction and the carbonyl-ene reaction, provides a valuable method for carbon—carbon bond formation.¹ In this context, cyclization reactions have been extensively studied because carbo- and heterocyclic motifs contained in a wide array of biologically active natural products can be efficiently constructed in a stereoselective manner.

We previously reported that treatment of 2-(o-styryl)cyclobutanones with a catalytic amount of rhodium produces eight-membered ring ketones.² The reaction takes place through insertion of rhodium(I) between the carbonyl carbon and the adjacent α -carbon³ and subsequent intramolecular olefin insertion process.^{3c} During the course of careful investigation of the reaction conditions, we found that two distinctly different reaction pathways, both promoted by

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simple Brønsted and Lewis acids, can operate with 2-(o-styryl)cyclobutanone.

First, HCl gas was bubbled into an ethanol solution of 2-methyl-2-(*o*-styryl)cyclobutanone (**1a**) at 75 °C for 3 h (Scheme 1). Formation of a much less polar substance was observed by a TLC analysis. Chromatographic isolation



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afforded 2-(β -naphthyl)ethyl chloride **2a-Cl** in 73% yield. The formation of **2a-Cl** is explained by assuming the following sequence. Protonation of the carbonyl group induces an intramolecular electrophilic attack on the pendant vinyl group.⁴ Elimination of the β -proton quenches the resultant benzylic cation, yielding tertiary alcohol **3**. Protonation of the hydroxy group then assists the removal of water, setting up an equilibrium with the nonclassical cyclobutyl cation **4**.⁵ A chloride anion attacks the cation in such a way to accompany concomitant aromatization, furnishing the naphthalene derivative **2a-Cl**.⁶ Release of the ring strain together with aromatic stabilization provides the driving force for this transformation.

On the other hand, when **1a** was heated in *m*-xylene at 140 °C for 18 h in the presence of molecular sieves (4 Å), the benzene-fused eight-membered ring ketone **5a** was produced in 25% yield (Scheme 2).^{7,8} It is likely that the



Lewis acidic character of the molecular sieves was responsible for activating the carbonyl group and promoting electrophilic cyclization, since no thermal reaction occurred in their absence. Loss of a proton then generates tricyclic intermediate **6**, as is the case with the HCl-promoted reaction. Intermediate **6**, in the absence of an appropriate nucleophile, undergoes thermal electrocyclic ring-opening of the 1,3-

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(8) 9,10-Dihydrobenzocycloocten-7(8*H*)-one skeleton is similar to that obtained by the rhodium-catalyzed reaction of 2-(o-styryl)cyclobutanone (ref 2). Under rhodium catalysis, however, no reaction occurred with **1a** having an additional methyl group at the α -position, presumably because the rhodium insertion was hampered due to the increased steric congestion.

cyclohexadiene moiety with disrotatory motion of the substituents to furnish the eight-membered ring intermediate $7.^{9,10}$ The strain of the four-membered ring is released by this sequence. Protonation at the benzylic position results in rearomatization to furnish the eight-membered ring ketone **5a**.

Encouraged by these distinctly contrasting results, a variety of Lewis acids were examined, with the selected results listed in Table 1. The use of $ZnBr_2$ afforded a mixture of products



	Me Lewis aci	Me x → + 2a-X			Me 0 5a	
	Lewis acid	conditions			% yield ^a	
entry	(equiv)	solvent	temp	time	2a (X)	5a
1	$ZnBr_{2}\left(1.05 ight)$	<i>m</i> -xylene	140 °C	6 h	40 (Br)	27
2	YbCl3 (2.0)	<i>m</i> -xylene	140 °C	3 h	14 (Cl)	72
3	YbCl ₃ (2.0)	PhCl	130 °C	1 h	44 (Cl)	48
4	YbCl ₃ (2.0)	dioxane	100 °C	1 h	90 (Cl)	b
5	Yb(OTf)3 (0.2)	<i>m</i> -xylene	140 °C	3 h	$\leq 5 (OH)$	73
6	Yb(OTf)3 (0.2)	PhCl	130 °C	$0.5~{ m h}$	b	87
7	$Yb(OTf)_3(0.2)$	dioxane	100 °C	3 h	24 (OH)	38

^a Determined by ¹H NMR of the crude reaction mixture. ^b Not detected.

2a-Br (40%) and **5a** (27%) (entry 1). The reactions with AlCl₃ (-10 °C) and Cu(OTf)₂ (140 °C) resulted in lower conversion. With SnCl₄ (-78 °C) and BF₃•OEt₂ (-78 °C), a complex mixture of products was obtained. Gratifying activities were finally found with ytterbium(III) salts. In the case of YbCl₃, the product distribution was largely influenced by the solvent employed (entries 2-4).¹¹ Whereas a mixture of **2a-Cl** and **5a** was obtained in *m*-xylene and in chlorobenzene, **2a-Cl** was produced exclusively in 90% yield using 1,4-dioxane. On the other hand, the use of Yb(OTf)₃ as the catalyst (20 mol %) favored the formation of the eightmembered ring ketone **5a**. In particular, **5a** was obtained as the sole product when the reaction was carried out in chlorobenzene at 130 °C (entry 6).

Thus, appropriate selection of Lewis acid and solvent dramatically alters the reaction pathway. A polar solvent favors the formation of a nonclassical cation, and opening of the four-membered ring predominates in the presence of a nucleophilic halide anion. On the other hand, the use of a less polar solvent disfavors the ionic pathway, and the absence of a suitable nucleophile steers the reaction course to an alternative electrocyclic pathway to open the sixmembered ring.

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Other examples of the selective synthesis of either 2 or 5 from 1 using the corresponding optimized reaction conditions A or B are given in Table 2. Cyclobutanones 1a and 1b



^{*a*} Conditions A: **1** and 2.0 equiv of YbX₃ (X = Cl or Br) were heated in refluxing 1,4-dioxane. Conditions B: **1** and 0.2 equiv of Yb(OTf)₃ were heated in refluxing PhCl. ^{*b*} Isolated yield by preparative TLC. ^{*c*} Reaction was carried out in refluxing Bu₂O.

having a substituent at the 2-position furnished naphthalenes 2-Cl and ketones 5, respectively, in high yield.¹² In addition to the chlorides, bromides 2a-Br and 2b-Br were successfully prepared using YbBr₃ in place of YbCl₃. The reactions of cyclobutanones 1c and 1d having a hydrogen at the 2-position also worked well to give the corresponding products with a high selectivity by simply choosing the reaction conditions. Cyclobutanone 1e with an isopropenyl group afforded the corresponding chloride 2e-Cl on treatment with YbCl₃. On the other hand, the reaction under conditions B also gave the naphthalene derivative 2e-OH instead of an eight-membered ring ketone. We assume that 2e-OH was produced by hydrolysis of 2-(β -naphthyl)ethyl triflate, initially formed via a nonclassical cation corresponding to 4. The different reactivity of 1e relative to 1a under conditions B is explained by assuming that the additional methyl group renders the cation stable enough to induce the attack even by the less nucleophilic triflate anion. A phenyl group could also participate in the YbCl₃-promoted reaction as the electrophilic site, although less efficiently. However, the attempted cyclization of 1f with Yb(OTf)₃ gave a complex mixture. The thermal electrocyclic ring-opening process is likely to be energetically disfavored because the two phenyl rings need to be dearomatized simultaneously.

In summary, two structurally distinct carbocycles 2 and 5 have been selectively synthesized from 2-(o-styryl)cyclobutanones 1 by simply choosing the acidic reaction conditions. These results demonstrate that cyclobutanones having a pendant unsaturated functionality are highly versatile compounds that are amenable to Lewis acids as well as to transition metal catalysts.¹³

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Supporting Information Available: Experimental procedures and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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⁽¹²⁾ **2a-Cl** was obtained in 81% yield with 1.0 equiv of YbCl₃, and **4a** was obtained in 80% yield with 0.1 equiv of Yb(OTf)₃.

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