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Acids Direct 2-Styrylcyclobutanone into Two Distinctly Different Reaction Pathways

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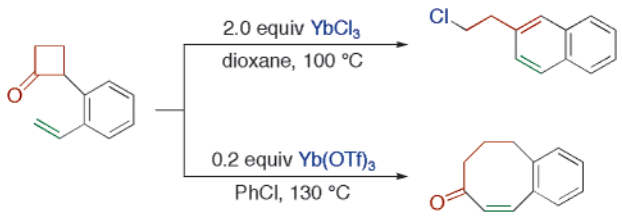
ABSTRACT



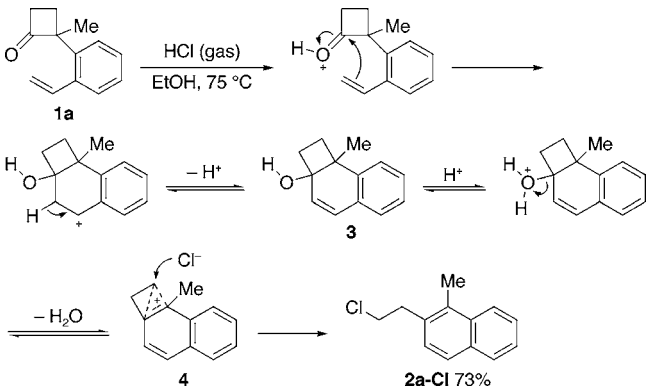
Two structurally distinct carbocycles were selectively obtained by the reactions of 2-(*o*-styryl)cyclobutanones promoted by ytterbium salts. Treatment of the cyclobutanones with $YbCl_3$ in 1,4-dioxane at 100 °C afforded 2-(2-chloroethyl)naphthalenes. On the other hand, the reaction with $Yb(OTf)_3$ 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-carbon[3] 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 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

Scheme 1



(1) (a) Snider, B. B. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I. Eds.; Pergamon: Oxford, 1991; Vol. 2, p 527. (b) Mikami, K.; Terada, M.; Narisawa, S.; Nakai, T. *Synlett* **1992**, 255.

(2) Matsuda, T.; Fujimoto, A.; Ishibashi, M.; Murakami, M. *Chem. Lett.* **2004**, *33*, 876.

(3) (a) Suggs, J. W.; Jun, C.-H. *J. Am. Chem. Soc.* **1984**, *106*, 3054. (b) Murakami, M.; Amii, H.; Ito, Y. *Nature* **1994**, *370*, 540. (c) Murakami, M.; Itahashi, T.; Ito, Y. *J. Am. Chem. Soc.* **2002**, *124*, 13976.

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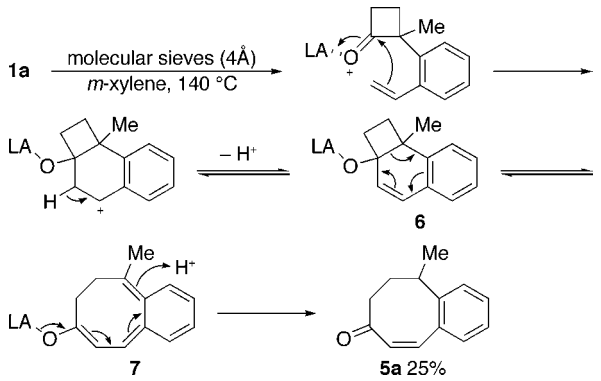
afforded 2-(β-naphthyl)ethyl chloride **2a-Cl** in 73% yield. The formation of **2a-Cl** is explained by assuming the following sequence. Protonation of the carbonyl group induces an intramolecular electrophilic attack on the pendant vinyl group.[4] Elimination of the β-proton quenches the resultant 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

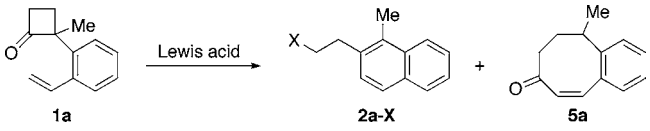
Scheme 2



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-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

Table 1. Effect of Reaction Conditions on the Reaction of 2-(*o*-Styryl)cyclobutanone **1a**



entry	Lewis acid (equiv)	conditions: solvent	temp	time	% yield[a]: **2a** (X)	**5a**
1	$ZnBr_2$ (1.05)	*m*-xylene	140 °C	6 h	40 (Br)	27
2	$YbCl_3$ (2.0)	*m*-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)	*m*-xylene	140 °C	3 h	<5 (OH)	73
6	$Yb(OTf)_3$ (0.2)	PhCl	130 °C	0.5 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 $AlCl_3$ (−10 °C) and $Cu(OTf)_2$ (140 °C) resulted in lower conversion. With $SnCl_4$ (−78 °C) and $BF_3{\cdot}OEt_2$ (−78 °C), a complex mixture of products was obtained. Gratifying activities were finally found with ytterbium(III) salts. In the case of $YbCl_3$, 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 eight-membered 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 six-membered ring.

(4) For a related electrophilic aromatic substitution, see: Bernard, A. M.; Floris, C.; Frongia, A.; Piras, P. P. *Synlett* **2002**, 796.

(5) (a) Koch, W.; Liu, B.; DeFrees, D. J. *J. Am. Chem. Soc.* **1988**, *110*, 7325. (b) Saunders, M.; Laidig, K. E.; Wiberg, K. B.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1988**, *110*, 7652. (c) Holman, R. W.; Plocica, J.; Blair, L.; Giblin, D.; Gross, M. L. *J. Phys. Org. Chem.* **2001**, *14*, 17.

(6) For recent examples of acid-promoted dehydrative aromatization reactions, see: (a) Kumar, S. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3157. (b) Kabalka, G. W.; Ju, Y.; Wu, Z. *J. Org. Chem.* **2003**, *68*, 7915. For a review, see: (c) Bradsher, C. K. *Chem. Rev.* **1987**, *87*, 1277.

(7) For the syntheses of eight-membered ring ketones from cyclobutanones, see: (a) Wender, P. A.; Correa, A. G.; Sato, Y.; Sun, R. *J. Am. Chem. Soc.* **2000**, *122*, 7815. (b) Oh, H.-S.; Lee, H.-I.; Cha, J. K. *Org. Lett.* **2002**, *4*, 3707. (c) Dowd, P.; Zhang, W. *Chem. Rev.* **1993**, *93*, 2091. (d) Mehta, G.; Singh, V. *Chem. Rev.* **1999**, *99*, 881. See also: (e) Paquette, L. A. *Eur. J. Org. Chem.* **1998**, 1709. (f) Hamura, T.; Kawano, N.; Tsuji, S.; Matsumoto, T.; Suzuki, K. *Chem. Lett.* **2002**, 1042.

(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.

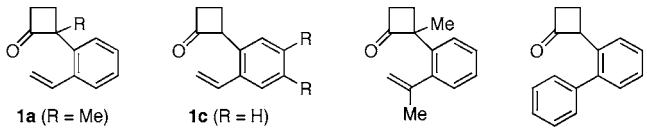
(9) For the disrotatory 6π electrocyclic ring-opening of bicyclo[4.2.0]-octane ring system, see: (a) Wang, T.-Z.; Paquette, L. A. *J. Org. Chem.* **1986**, *51*, 5232. (b) Takeda, T.; Fujiwara, T. *Synlett* **1996**, 481.

(10) For a related ring-expansion, see: Suginome, H.; Itoh, M.; Kobayashi, K. *J. Chem. Soc., Perkin Trans. 1* **1988**, 491.

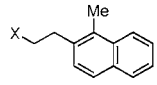
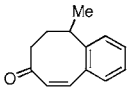
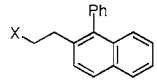
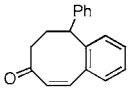
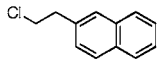
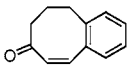
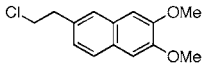
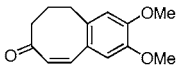
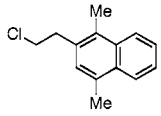
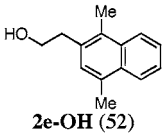
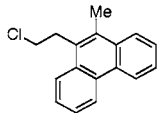
(11) Use of other lanthanide salts such as $SmCl_3$ and $CeCl_3$ led to poor reactivities compared with $YbCl_3$.

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**

Table 2. Lewis Acid-Promoted Reactions of **1**[a]



1a (R = Me) **1b** (R = Ph) **1c** (R = H) **1d** (R = OMe) **1e** **1f**

1	conditions A		conditions B	
	product	**2-X** (%)[b]	product	**5** (%)[b]
1a		**2a-Cl** (83) **2a-Br** (86)		**5a** (82)
1b		**2b-Cl** (79) **2b-Br** (94)		**5b** (90)
1c		**2c-Cl** (68)		**5c** (64)
1d		**2d-Cl** (65)		**5d** (85)
1e		**2e-Cl** (51)	 **2e-OH** (52)	
1f		**2f-Cl** (49)[c]	–	

[a] Conditions A: **1** and 2.0 equiv of YbX_3 (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 Bu_2O.

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 $YbBr_3$ in place of $YbCl_3$. 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 $YbCl_3$. 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 $YbCl_3$-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]

Acknowledgment. S.K. thanks fellowship support from the Japan Society of Promotion of Science for Young Scientists.

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 $YbCl_3$, and **4a** was obtained in 80% yield with 0.1 equiv of $Yb(OTf)_3$.

(13) For synthetic applications of cyclobutane derivatives, see: (a) Lee-Ruff, E.; Mladenova, G. *Chem. Rev.* **2003**, *103*, 1449. (b) Namyslo, J. C.; Kaufmann, D. E. *Chem. Rev.* **2003**, *103*, 1485.