Synthetic Methods

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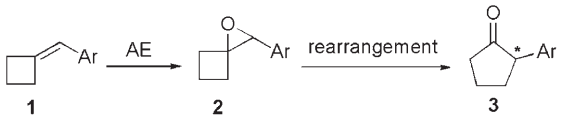
Enantioselective Synthesis of 2-Aryl Cyclopentanones by Asymmetric Epoxidation and Epoxide Rearrangement**

*Yu-Mei Shen, Bin Wang, and Yian Shi**

Optically active 2-aryl cycloalkanones are a class of useful molecules for organic synthesis and have received extensive attention. A number of effective approaches have been developed for the synthesis of 2-alkyl-2-aryl disubstituted cycloalkanones,[1–7] including the Pd-catalyzed asymmetric α-arylation of alkyl substituted cycloalkanones,[1] the allylic alkylation of 2-aryl cycloalkanones,[2] and the chelation-controlled Heck arylation of enol ethers.[3] In the preparation of monosubstituted 2-aryl cycloalkanones, high *ee* values have also been obtained for 2-aryl cyclohexanones and cycloheptanones through the asymmetric protonation of the corresponding silyl enol ethers and enolates.[7] Thus far, monosubstituted 2-aryl cyclopentanones are still a challenge to obtain, presumably because of facile racemization under the reaction conditions. Herein, we wish to report our preliminary efforts on the asymmetric epoxidation of benzylidenecyclobutane and subsequent epoxide rearrangement (Scheme 1).[8–12]



Scheme 1. Asymmetric epoxidation of benzylidenecyclobutane (**1**) and subsequent epoxide rearrangement. AE = asymmetric epoxidation.

The initial epoxidation of benzylidenecyclobutane with fructose-derived ketone **4**, which has been shown to be effective for a variety of *trans*- and trisubstituted olefins,[13] gave only 42% *ee*. The low *ee* value obtained with **4** could be attributed to the severe competition of the planar transition state **B** with the favored spiro transition state **A** (Scheme 2). Our recent studies with oxazolidinone-containing ketones have shown that there is an attractive interaction between the

[*] Y.-M. Shen, B. Wang, Prof. Dr. Y. Shi
Department of Chemistry
Colorado State University
Fort Collins, CO 80523 (USA)
Fax: (+1) 970-491-1801
E-mail: yian@lamar.colostate.edu

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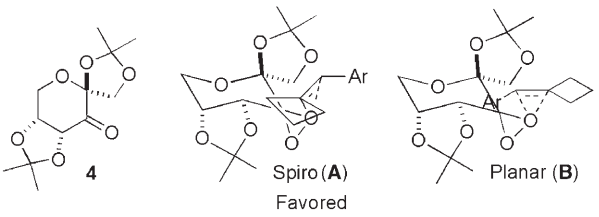
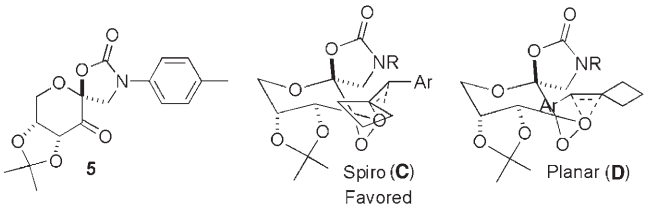


Scheme 2. Transition states of ketone **4**.

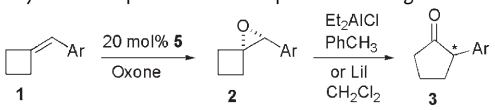
aryl group of the olefin and the oxazolidinone moiety of the ketone catalyst.[14] These studies indicate that the desired spiro transition state **C** could be further favored by such an attraction (Scheme 3), thus resulting in higher enantioselectivity. The *ee* value of the epoxide increased to 90% when the epoxidation was carried out with 20 mol% ketone **5** at −10°C (Table 1, entry 1). High enantioselectivities were also obtained for a variety of other substituted benzylidenecyclobutanes (Table 1).[15]

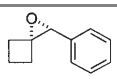
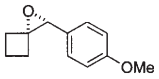
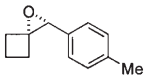
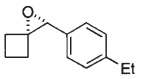
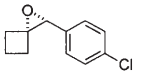
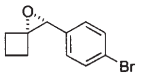
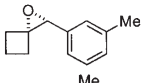
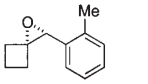
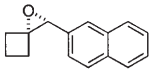


Scheme 3. Transition states of ketone **5**.

With optically active epoxides in hand, the Lewis acid catalyzed epoxide rearrangement was explored. The stereoselectivity of the rearrangement was found to be highly sensitive to the Lewis acid and solvent. After optimization, the rearrangement was effectively achieved with Et_2AlCl in toluene at −78°C. The cyclopentanone product was obtained cleanly after careful work up,[16] and high *ee* values were generally maintained (Table 1). The rearrangement with Et_2AlCl is likely to go through a concerted process with inversion of the configuration (pathway a; Scheme 4). Slightly more enantioselectivity is lost for epoxides with electron-donating groups, such as the 4-MeO moiety (Table 1, entry 2), during the rearrangement. This lowered enantioselectivity could be because of the competition from a stepwise S_N1-type process via a carbocation which is stabilized by electron-donating groups. To probe the reaction mechanism further, the rearrangement was then carried out with LiI.[17] The opposite enantiomer of the rearrangement product was obtained under these conditions (Table 1), and good *ee* values were also obtained in most cases. The rearrangement with LiI is likely to go via intermediate **6** with double inversion (pathway b; Scheme 4). The low *ee* value obtained with the 4-MeO substituted epoxide (Table 1, entry 2) could be because of the competition from pathway a and/or the S_N1-type process. To support the above mechanistic pathways further, the configurations of the 4-Cl substituted epoxide (Table 1, entry 5) and the corresponding rearranged cyclopentanone product with Et_2AlCl were determined by using vibrational circular dichroism (VCD; BioTools).[18] It is shown that the epoxide has an *R* configuration and the rearranged cyclopentanone has an *S* configuration. The configuration of the rearranged cyclopentanone was also determined for entry 1 by comparison with the measured optical-rotation value of the lactone product (obtained from the Baeyer–Villiger

Table 1: Asymmetric epoxidation and epoxide rearrangement.[a–c]



Entry	Epoxide	Yield of (**2**) [%] (*ee*)[d]	Conditions	Yield of **3** [%] (*ee*)[e]
1		93 (90)	Et_2AlCl LiI	90 (90) (*S*) 81 (90) (*R*)
2		95 (91)	Et_2AlCl LiI	98 (82) (*S*) 81 (40) (*R*)
3		84 (93)	Et_2AlCl LiI	82 (88) (*S*) 91 (92) (*R*)
4		67 (94)	Et_2AlCl LiI	99 (91) (*S*) 86 (92) (*R*)
5		78 (96)	Et_2AlCl LiI	89 (94) (*S*) 87 (84) (*R*)
6		80 (96)	Et_2AlCl LiI	94 (93) (*S*) 87 (84) (*R*)
7		80 (95)	Et_2AlCl LiI	82 (92) (*S*) 92 (93) (*R*)
8		77 (86)	Et_2AlCl LiI	83 (84) (*S*) 90 (80) (*R*)
9		88 (95)	Et_2AlCl LiI	94 (96) (*S*) 84 (87) (*R*)

[a] All epoxidations were carried out with the substrate (0.5 mmol), **5** (0.1 mmol), oxone (0.8 mmol), and K_2CO_3 (3.36 mmol) in dimethoxyethane (DME)/dimethoxymethane (DMM) (3:1, v/v; 7.5 mL) and buffer (0.1 M K_2CO_3/AcOH, pH 9.3; 5 mL) at −10 or 0°C for 4–12 h, except for entry 9, in which the reaction was carried out in DME/DMM (1:1, v/v; 9.4 mL) and buffer (3.1 mL) at 0°C for 8 h. The epoxides in entries 4, 5, 6, 8, and 9 were purified by column chromatography on silica gel (buffered with Et_3N). [b] All rearrangements were carried out with epoxide (1.0 equiv) and Et_2AlCl (0.25 or 1.0 equiv) in $PhCH_3$ at −78°C for 0.25–3 h. The ketone products were not purified by column chromatography on silica gel and were clean as judged by NMR spectroscopy. [c] All rearrangements were carried out with LiI (1.0–3.0 equiv) in CH_2Cl_2 at room temperature for 5–30 min, except for entry 2, in which the reaction was carried out at 0°C. [d] The *ee* value (%) of the epoxide was determined by chiral GC (Chiraldex B-DM), except for entry 2, for which the *ee* value was determined by chiral HPLC (Chiralcel AD). The absolute configuration was tentatively assigned based on the spiro reaction mode. The absolute configuration of entry 5 was determined by using the VCD spectra (BioTools). [e] The *ee* value (%) of the cyclopentanone was determined by chiral HPLC (Chiralcel AD). The absolute configuration was tentatively assigned based on the mechanistic consideration. The absolute configuration was determined for entry 1 by comparison of the measured optical-rotation value of the lactone product (obtained from the Baeyer–Villiger oxidation of the ketone with *m*CPBA) with the reported value.[20] The absolute configuration of entry 5 was determined by using the VCD spectra (BioTools).

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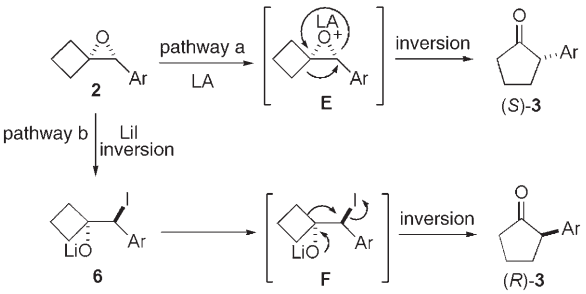

Scheme 4. Possible reaction pathways for the epoxide rearrangement. LA = Lewis acid.

oxidation of the ketone with *meta*-chloroperoxybenzoic acid (*m*CPBA)[19]) with the reported value.[20]

In conclusion, we have shown that benzylidenecyclobutanes can undergo epoxidation with the readily available glucose-derived ketone **5** in high enantioselectivity. The resulting epoxides can be rearranged to 2-aryl cyclopentanones with either inversion or retention of configuration using Et_2AlCl or LiI. High *ee* values have been obtained for cyclopentanones in most cases. This two-step process provides a viable entry to optically active 2-aryl cyclopentanones, which until now could not be readily obtained.

Experimental Section

Representative procedure for asymmetric epoxidation (Table 1, entry 5): Buffer (0.1 M K_2CO_3/AcOH in aqueous ethylenediaminetetraacetate (EDTA; 4×10^{-4} M), pH 9.3; 5 mL) was added to a solution of **1** (0.089 g, 0.5 mmol) and **5** (0.033 g, 0.1 mmol) in DME/DMM (3:1 v/v; 7.5 mL). After the mixture was cooled to −10 °C by using a NaCl/ice bath, a 0.20 M solution of oxone (0.492 g, 0.80 mmol) in aqueous EDTA (4×10^{-4} M, 4.0 mL) and a solution of 0.84 M K_2CO_3 (0.464 g, 3.36 mmol) in aqueous EDTA (4×10^{-4} M, 4.0 mL) were added separately yet simultaneously by a syringe pump over a period of 10 h. The reaction mixture was quenched and extracted with hexane, washed with brine, dried over Na_2SO_4, filtered, concentrated, and purified by flash column chromatography (the silica gel was buffered with 1% Et_3N in organic solvent; hexane/EtOAc as the eluent) to give the epoxide as a colorless oil (0.076 g, 78% yield, 96% *ee*).

Representative procedure for the epoxide rearrangement with Et_2AlCl (Table 1, entry 1): A solution of Et_2AlCl (1.0 M in hexane; 50 μL, 0.05 mmol) was added to a solution of the epoxide (90% *ee*; 0.032 g, 0.2 mmol) in dry toluene (2 mL) at −78 °C. The reaction mixture was stirred at −78 °C until completion (about 3 h) and quenched with saturated aqueous $NaHCO_3$ (0.10 mL) at −78 °C. Upon warming up to 0 °C, the reaction mixture was diluted with hexane, washed with brine, dried over Na_2SO_4, filtered, and concentrated to give the ketone product as a colorless oil (0.029 g, 90% yield, 90% *ee*).[21]

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[16] It was found that α-aryl cyclopentanones readily underwent racemization on silica gel; the ketone products were not purified by column chromatography on silica gel and were clean as judged by NMR spectroscopy.

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[21] Experimental procedures for the asymmetric epoxidation and epoxide rearrangement, the characterization of the epoxides and cyclopentanones, the determination of the *ee* values of the epoxides and cyclopentanones, and the VCD spectra are given in the Supporting Information.

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