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Enantioselective synthesis of 2-alkyl-2-aryl cyclopentanones by asymmetric epoxidation of tetrasubstituted cyclobutylidene olefins and epoxide rearrangement

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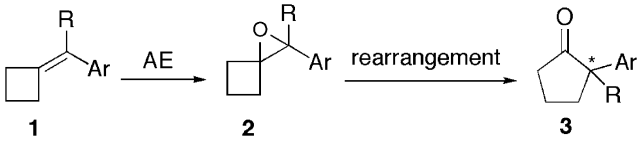
Abstract—This letter describes a highly enantioselective epoxidation of tetrasubstituted benzylidenecyclobutanes using glucose-derived ketone as catalyst and oxone as oxidant. The Et_2AlCl promoted rearrangement of the resulting epoxides provides 2-alkyl-2-aryl cyclopentanones with high ees.

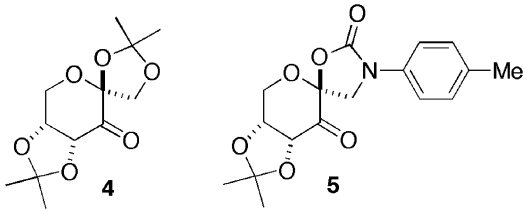
The generation of chiral all-carbon quaternary stereocenters is of great interest in organic synthesis.[1] Optically active 2-alkyl-2-aryl cyclopentanones are potentially useful intermediates for the synthesis of natural products.[2] A number of approaches have been developed for the synthesis of 2-alkyl-2-aryl disubstituted cycloalkanones, including asymmetric alkylation of α-aryl cycloalkanones,[3,4] enzymatic resolution,[5] and epoxide rearrangement.[6] High enantioselectivities have also recently been achieved by the Pd-catalyzed asymmetric α-arylation of alkyl-substituted cycloalkanones in which the α′-methylene carbon is blocked,[7] and by the chelation-controlled Heck arylation of enol ethers.[8]

Recently, we reported that 2-aryl cyclopentanones can be obtained with high ees by the asymmetric epoxidation of benzylidenecyclobutanes (R = H) and subsequent epoxide rearrangement (Scheme 1).[9–11] Based on these observations, we decided to investigate whether 2-alkyl-2-aryl cyclopentanones can also be obtained by this approach. However, the feasibility of this route requires highly enantioselective asymmetric epoxidation of unfunctionalized tetrasubstituted olefins, which is a challenging problem.[12] Herein we wish to report our studies on this subject.



Scheme 1.

Tetrasubstituted cyclobutylidene olefins were readily prepared from ketones and 4-bromobutyltriphenylphosphonium bromide using *t*-BuOK in THF in a manner similar to the reported procedure.[13] Asymmetric epoxidation of 1-cyclobutylidene-1-phenylethane with ketone **4** (Scheme 2) gave only 58% ee.[14] Encouragingly, the ee increased to 84% when ketone **5** was used (Table 1, entry 1).[15] Further studies showed that the epoxidation could also be extended to a variety of phenyl substituted olefins (Table 1, entries 2–9), and up to 91% ee was obtained.[16] Generally, higher ees were obtained for the olefins having substituents on the phenyl group, which



Scheme 2.

Keywords: Asymmetric epoxidation; 2-Alkyl-2-aryl cyclopentanone; Chiral dioxirane; Epoxide rearrangement; Chiral quaternary carbon; Tetrasubstituted olefin.
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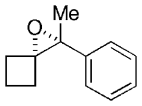
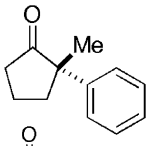
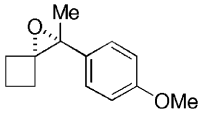
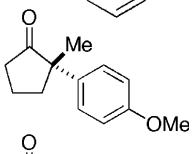
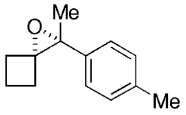
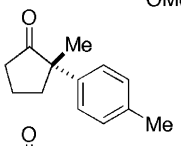
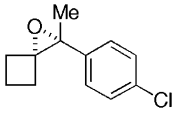
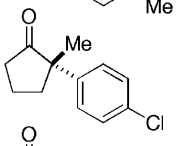
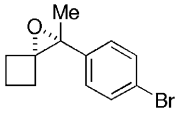
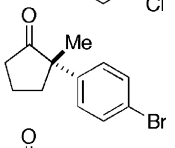
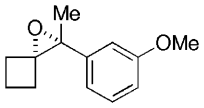
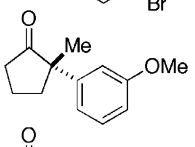
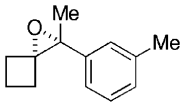
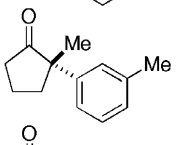
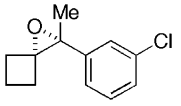
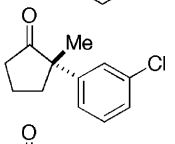
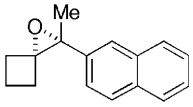
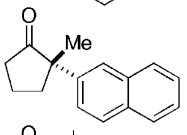
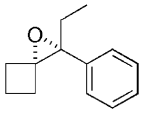
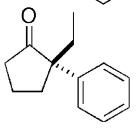
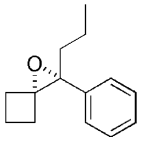
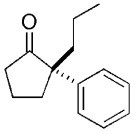
Table 1. Asymmetric epoxidation and epoxide rearrangement[a,b]

Entry	Epoxide[c]	Yield (ee) (%) (**2**)	Ketone[d]	Yield (ee) (%) (**3**)
1		94[e] (84)[h]		93[g] (84)[h]
2		95[e] (87)[i]		92[g] (88)[h]
3		86[f] (88)[h]		78[g] (88)[h]
4		77[g] (89)[h]		98[g] (90)[h]
5		78[g] (91)[h]		99[g] (90)[h]
6		98[f] (88)[h]		73[g] (87)[j]
7		96[e] (87)[h]		93[g] (88)[h]
8		79[g] (88)[h]		99[g] (89)[h]
9		nd		65[g] (90)[j]
10		67[g] (77)[h]		88[g] (77)[j]
11		48[g] (70)[h]		99[g] (70)[i]

[a] All epoxidations were carried out with substrate (0.5 mmol), ketone **5** (0.1 mmol), oxone (0.8 mmol), and K_2CO_3 (3.36 mmol) in DME/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.

[b] All rearrangements were carried out with epoxide (1.0 equiv) and Et_2AlCl (0.25 equiv) in $PhCH_3$ at −78 °C for 15–30 min unless otherwise noted. For entry 10, 0.5 equiv Et_2AlCl was used (60 min); for entry 11, 0.75 equiv Et_2AlCl was used (25 min).

[c] The absolute configuration was tentatively assigned based on the spiro reaction mode. The absolute configurations of entries 1 and 5 were determined using the VCD spectra by BioTools.

[d] The cyclopentanone products were purified by silica gel column. For entries 3, 6, and 9, the yield is the two-step overall yield after purification. The absolute configuration was tentatively assigned based on the mechanistic consideration. For entries 1 and 5, the absolute configuration was determined using the VCD spectra by BioTools. For entries 1, 3, and 6, the configuration was determined by comparing the measured optical rotations with the reported ones (Refs. 2b and 8).

[e] Crude yield.

[f] Conversion as determined by GC.

[g] Isolated yield.

[h] The enantioselectivity was determined by chiral GC (Chiraldex B-DM).

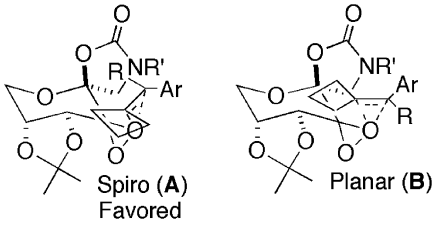
[i] The enantioselectivity was determined by chiral HPLC (Chiralcel OJ).

[j] The enantioselectivity was determined by chiral HPLC (Chiralpak AD).

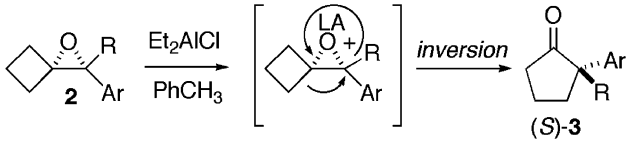
is consistent with an earlier observation that substituents on the phenyl group of *cis*-β-methylstyrene have positive effects on the enantioselectivity of the epoxidation.[15b] The epoxidation is likely to proceed mainly via spiro transition state **A** (Scheme 3). Based on this model, this transition state will be disfavored as the size of the R group increases, thus giving lower ees, which was observed when the methyl group was replaced by ethyl and *n*-propyl groups (Table 1, entries 10 and 11).

Some of the epoxide products were purified by column chromatography on silica gel, but some underwent rearrangement on silica gel, thus they were used directly for the subsequent rearrangement without purification. When the epoxide rearrangement was carried out with Et_2AlCl in toluene, little ee was lost during the rearrangement, giving 2-methyl-2-aryl cyclopentanones in high ees (Table 1).[17] The absolute configurations of the epoxides and rearranged products of entries 1 and 5 were determined using vibrational circular dichroism (VCD; BioTools).[18] It was found that the epoxide is of an *R* configuration and the rearranged cyclopentanone has an *S* configuration. For entries 1, 3, and 6, the *S* configuration of the cyclopentanone was further confirmed by comparing the measured optical rotations with the reported ones.[2b,8] Thus, the rearrangement proceeds in a concerted fashion with inversion of configuration (Scheme 4).[9]

In summary, we have shown that 1-cyclobutylidene-1-phenylethane derivatives can be epoxidized with readily available glucose-derived ketone **5** in high enantioselectivity. The resulting epoxides can be rearranged to 2-methyl-2-aryl cyclopentanones with inversion of configuration using Et_2AlCl in high ees. While a similar asymmetric epoxidation of trisubstituted cyclobutylidene olefins and epoxide rearrangement has recently been reported by us,[9] the results described herein show that chiral dioxiranes[19] have the potential to epoxidize certain tetrasubstituted olefins in a high degree of enantioselectivity, which is very encouraging, considering the fact that highly enantioselective epoxidation of unfunctionalized tetrasubstituted olefins is a challenging problem.[12] Further studies with substrate scope and design of new ketone catalysts for this class of olefin will be pursued.



Scheme 3.



Scheme 4.

Acknowledgements

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Supplementary data

Experimental procedures for asymmetric epoxidation and epoxide rearrangement, the characterization of epoxides and cyclopentanones, the data for the determination of ees of epoxides and cyclopentanones, and VCD spectra (26 pages). Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.05.175.

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16. *Representative procedure for asymmetric epoxidation* (*Table 1, entry 4*). To a solution of the olefin (0.096 g, 0.5 mmol) and ketone **5** (0.033 g, 0.1 mmol) in DME–DMM (3:1, v/v) (7.5 mL) was added buffer (0.1 M K_2CO_3–AcOH in 4×10^{-4} M aqueous EDTA, pH 9.3) (5 mL) with stirring. After the mixture was cooled to −10 °C (bath temperature) via NaCl–ice bath, a solution of oxone (0.20 M in 4×10^{-4} M aqueous EDTA, 4.0 mL) (0.492 g, 0.80 mmol) and a solution of K_2CO_3 (0.84 M in 4×10^{-4} M aqueous EDTA, 4.0 mL) (0.464 g, 3.36 mmol) were added separately and simultaneously via a syringe pump over a period of 8 h. The reaction mixture was quenched with hexane, extracted with hexane, washed with brine, dried (Na_2SO_4), filtered, concentrated, and purified by flash chromatography [the silica gel was buffered with 1% Et_3N in organic solvent; hexane–EtOAc (1/0 to 50/1) was used as eluent] to give the epoxide as a colorless oil (0.080 g, 77% yield, 89% ee).
Entry 1, −10 °C, 8 h; entry 2, −10 °C, 4 h; entry 3, −10 °C, 6 h; entry 5, 0 °C, 8 h; entry 6, −10 °C, 4 h; entry 7, −10 °C, 8 h; entry 8, −10 °C, 8 h; entry 9, −10 °C, 8 h; entry 10, −10 °C, 8 h; entry 11, 0 °C, 10 h.
17. *Representative procedure for the epoxide rearrangement with Et_2AlCl* (*Table 1, entry 1*). To a solution of the epoxide (0.035 g, 0.2 mmol) (84% ee) in dry toluene (2 mL) at −78 °C was added a solution of Et_2AlCl (1.0 M in hexane, 50 μL, 0.05 mmol). Upon stirring at −78 °C to completion (about 15 min), the reaction was 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 (0.032 g, 93% yield, 84% ee).
Entries 2, 3, 6, 7, and 9, 0.25 equiv Et_2AlCl, 15 min; entries 4 and 5, 0.25 equiv Et_2AlCl, 20 min; entry 8, 0.25 equiv Et_2AlCl, 30 min; entry 10, 0.5 equiv Et_2AlCl, 60 min; entry 11, 0.75 equiv Et_2AlCl, 25 min.
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