JOC*Note*

Enantioselective Synthesis of γ-Aryl-γ-butyrolactones by Sequential Asymmetric Epoxidation, Ring Expansion, and Baeyer−Villiger Oxidation

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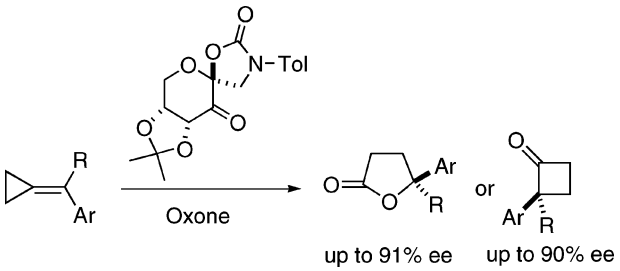
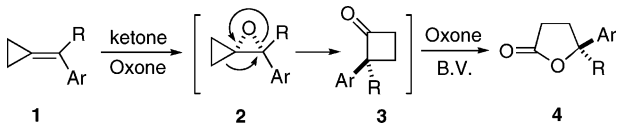


This paper describes an enantioselective synthesis of γ-butyrolactones, using the *N*-tolyl-substituted oxazolidinone-containing ketone as catalyst and Oxone as oxidant via a sequential asymmetric epoxidation of benzylidenecyclopropanes, ring expansion, and Baeyer−Villiger oxidation. Up to 91% ee was obtained. Optically active cyclobutanones can also be obtained by suppressing the Baeyer−Villiger oxidation with use of more ketone catalyst and less Oxone.

Optically active γ-butyrolactones are a useful class of chiral building blocks for the synthesis of biologically important molecules. A number of methods have been reported for the preparation of chiral γ-lactones.[1] Earlier, Ihara and co-workers[2] reported that chiral γ-aryl-γ-butyrolactones were obtained in 37% to 72% ee by asymmetric epoxidation of trisubstituted benzylidenecyclopropane derivatives (R = H) using fructose-derived ketone **5** and Oxone, followed by in situ epoxide rearrangement and Baeyer−Villiger oxidation (Schemes 1 and 2).[3−5]

SCHEME 1



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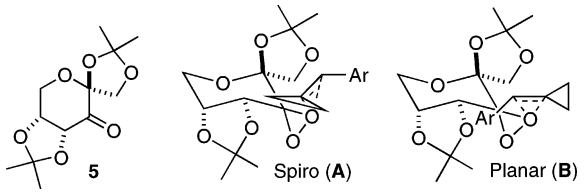
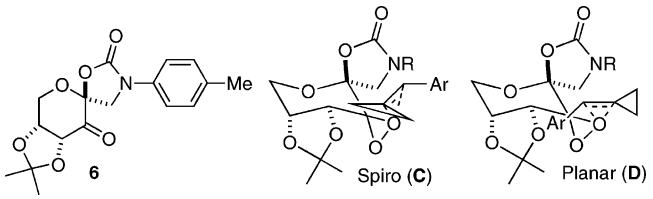


SCHEME 3



The low ee values obtained for this class of olefin are likely due to a significant competition from planar transition state **B** (Scheme 2).[6] Our studies on *N*-aryl-substituted oxazolidinone-containing ketones have shown that there is an attractive interaction between the aryl group of the olefin and the oxazolidinone moiety of the ketone catalyst,[7,8] which should favor the desired spiro transition state **C** over a competing planar transition state such as **D** (Scheme 3). This has already been observed in the case of benzylidenecyclobutane derivatives,[9] so higher ee values should be expected for benzylidenecyclopropane derivatives with ketone **6**[10] than with ketone **5**.

(1) For examples on the synthesis of optically active γ-butyrolactones, see: (a) Gutman, A. L.; Zuobi, K.; Bravdo, T. *J. Org. Chem.* **1990**, *55*, 3546. (b) Brown, H. C.; Kulkarni, S. V.; Racherla, U. S. *J. Org. Chem.* **1994**, *59*, 365. (c) Nair, V.; Prabhakaran, J. *J. Chem. Soc., Perkin Trans. 1* **1996**, 593. (d) Nair, V.; Prabhakaran, J.; George, T. G. *Tetrahedron* **1997**, *53*, 15061. (e) Fukuzawa, S-I.; Seki, K.; Tatsuzawa, M.; Mutoh, K. *J. Am. Chem. Soc.* **1997**, *119*, 1482. (f) Mikami, K.; Yamaoka, M. *Tetrahedron Lett.* **1998**, *39*, 4501. (g) Merlic, C. A.; Walsh, J. C. *J. Org. Chem.* **2001**, *66*, 2265. (h) Ramachandran, P. V.; Pitre, S.; Brown, H. C. *J. Org. Chem.* **2002**, *67*, 5315. (i) Movassaghi, M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 2456. (j) Kamal, A.; Sandbhor, M.; Shaik, A. *Tetrahedron: Asymmetry* **2003**, *14*, 1575.

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(3) For leading references on the rearrangement of oxaspiropentanes and oxaspirohexanes, see: (a) Trost, B. M.; Bogdanowicz, M. J. *J. Am. Chem. Soc.* **1972**, *94*, 4777. (b) Trost, B. M.; Bogdanowicz, M. J. *J. Am. Chem. Soc.* **1973**, *95*, 5321. (c) Trost, B. M.; Scudder, P. H. *J. Am. Chem. Soc.* **1977**, *99*, 7601. (d) Crandall, J. K.; Conover, W. W. *J. Org. Chem.* **1978**, *43*, 3533.

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(5) For leading references on asymmetric dihydroxylation of cyclopropylidene derivatives and subsequent rearrangement, see: (a) Krief, A.; Ronvaux, A.; Tuch, A. *Bull. Soc. Chim. Belg.* **1997**, *106*, 699. (b) Krief, A.; Ronvaux, A.; Tuch, A. *Tetrahedron* **1998**, *54*, 6903. (c) Nemoto, H.; Miyata, J.; Hakamata, H.; Fukumoto, K. *Tetrahedron Lett.* **1995**, *36*, 1055. (d) Nemoto, H.; Miyata, J.; Hakamata, H.; Nagamochi, M.; Fukumoto, K. *Tetrahedron* **1995**, *51*, 5511. (e) Diffendal, J. M.; Filan, J.; Spoors, P. G. *Tetrahedron Lett.* **1999**, *40*, 6137. (f) Miyata, J.; Nemoto, H.; Ihara, M. *J. Org. Chem.* **2000**, *65*, 504.

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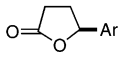
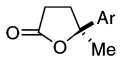
TABLE 1. Asymmetric Epoxidation, Epoxide Rearrangement, and Baeyer−Villiger Oxidation[a]

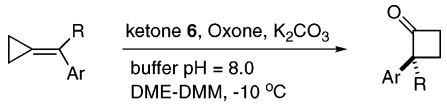
entry	lactones	T (°C)	time (h)	yield (%)[b]	ee (%)	config.[g]
						
1	Ar = *o*-MePh	-10 to 0	8	54	80[c]	(-)
2	*p*-MeOPh	-10 to 0	8	49	89[d]	(-)-(*S*)[1a,j,12a]
3	*p*-MePh	-10 to 0	8	68	90[e]	(-)-(*S*)[1a,12a]
4	*p*-*t*-BuPh	-10	12	52	91[e]	(-)
5	2-Nap	-10	12	48	91[e]	(-)
						
6	Ar = Ph	-10 to 0	8	50	84[f]	(-)-(*S*)[1d-f,12b]
7	*o*-MeOPh	-10	8	73	71[c]	(-)
8	*m*-MeOPh	-10 to 0	8	48	87[c]	(-)
9	*p*-MeOPh	-10 to 0	8	56	82[c]	(-)
10	*p*-MePh	-10	8	64	79[c]	(-)-(*S*)[12c]
11	*p*-ClPh	-10 to 0	8	45	84[c]	(-)
12	*p*-BrPh	-10	8	54	86[c]	(-)
13	2-Nap	-10 to 0	8	54	87[c]	(-)-(*S*)[12b]

[a] All epoxidations were carried out with substrate (0.5 mmol), ketone **6** (0.1 mmol), Oxone (1.6 mmol), and K_2CO_3 (6.72 mmol) in DME/DMM (3:1, v/v) (7.5 mL) and buffer (0.1 M K_2CO_3-AcOH in 4×10^{-4} M aqueous EDTA, pH 9.3) (5 mL). For entries 1, 2, 3, 6, 8, 9, 11, and 13, the reaction was carried out at −10 °C for 6 h, then 0 °C for 2 h. [b] Isolated yield. [c] The enantioselectivity was determined by chiral HPLC (chiralcel OJ). [d] The enantioselectivity was determined by chiral HPLC (chiralcel AD). [e] The enantioselectivity was determined by chiral HPLC (chiralcel OD). [f] The enantioselectivity was determined by chiral GC (chiraldex B-DM). [g] The absolute configurations were determined by comparing the measured optical rotations with the reported ones (ref 12). The absolute configurations of the remaining lactones were tentatively assigned by analogy based on mechanistic considerations.

The epoxidation of a variety of benzylidenecyclopropanes with ketone **6** was thus investigated. As shown in Table 1, γ-aryl-γ-butyrolactones can be obtained in reasonable overall yields and good ee values (up to 91% ee) for the three-step transformation. Tetrasubstituted benzylidenecyclopropanes can also be effectively epoxidized and transformed into γ-aryl-γ-methyl-γ-butyrolactones in good ee (Table 1, entries 6−13).[9b] Further studies with selected examples showed that the Baeyer−Villiger oxidation can be suppressed by using additional ketone **6** and less Oxone at lower reaction pH, giving synthetically useful 2-aryl cyclobutanones in good ee (Scheme 4).[2b,4,5,11]

Generally, the ee values obtained for γ-butyrolactones are slightly lower than the ee values obtained for 2-aryl cyclopentanones from asymmetric epoxidation of benzylidenecyclobutanes and epoxide rearrangement.[9] The lower enantioselectivity observed in the current study could be due to a less enantioselective epoxidation of benzylidenecyclopropanes and/or less stereoselective epoxide rearrangement under the epoxidation conditions.

SCHEME 4



Ar = *p*-*t*-BuPh, R = H, **6** (0.75 eq.), Oxone (0.72 eq.), K_2CO_3 (1.70 eq.), 68%, 90% ee
Ar = *p*-MePh, R = Me, **6** (0.66 eq.), Oxone (0.64 eq.), K_2CO_3 (1.50 eq.), 51%, 85% ee

In summary, the readily available glucose-derived oxazolidinone-containing ketone **6** is an effective catalyst for a variety of benzylidenecyclopropanes. Optically active γ-aryl-γ-butyrolactones and γ-aryl-γ-methyl-γ-butyrolactones can be obtained in reasonable yields and good enantioselectivities (up to 91% ee) via in situ epoxide rearrangement and Baeyer−Villiger oxidation. Chiral cyclobutanones can also be obtained by suppressing the Baeyer−Villiger oxidation with more ketone catalyst and less Oxone. Further expansion of the substrate scope of ketone **6** and the development of more effective ketone catalysts are currently underway.

Experimental Section

Representative Procedure for Asymmetric Synthesis of γ-Butyrolactones (Table 1, entry 5). To a solution of the freshly prepared olefin (0.090 g, 0.50 mmol) and ketone **6** (0.033 g, 0.10 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) (5.0 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, 8.0 mL) (0.984 g, 1.60 mmol) and a solution of K_2CO_3 (0.84 M in 4×10^{-4} M aqueous EDTA, 8.0

(9) For asymmetric epoxidation of trisubstituted and tetrasubstituted benzylidenecyclobutane derivatives with ketone **6**, see: (a) Shen, Y.-M.; Wang, B.; Shi, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 1429. (b) Shen, Y.-M.; Wang, B.; Shi, Y. *Tetrahedron Lett.* **2006**, *47*, 5455.

(10) For the synthesis of ketone **6** see: (a) ref. 8a. (b) Zhao, M.-X.; Goeddel, D.; Li, K.; Shi, Y. *Tetrahedron* **2006**, *62*, 8064.

(11) The enantioselectivity was determined by chiral GC (chiraldex B-DM). The absolute configuration of 2-methyl-2-tolylcyclobutanone was determined by comparing the measured optical rotation with the reported one (ref 4a). The absolute configuration of 2-(*p*-*tert*-butylphenyl)cyclobutanone was tentatively assigned based on mechanistic considerations.

(12) (a) Sudhir, T.; Patil, A. V. K. *Chirality* **2004**, *16*, 336. (b) Pirkle, W. H.; Spence, P. L. *J. Chromatogr. A* **1997**, *775*, 81. (c) Xu, X.-X.; Dong, H.-Q. *J. Org. Chem.* **1995**, *60*, 3039.

mL) (0.928 g, 6.72 mmol) were added separately and simultaneously via a syringe pump over a period of 12 h. The reaction mixture was quenched with EtOAc, extracted with EtOAc, washed with brine, dried (Na_2SO_4), filtered, concentrated, and purified by flash chromatography [hexane-EtOAc (20/1 to 4/1 to 2/1) was used as eluent] to give the lactone as a white solid (0.051 g, 48% yield, 91% ee). Mp 98−100 °C; $[\alpha]^{25}_D$ −19.0 (*c* 1.1, $CHCl_3$) (91% ee); IR (film) 1771 cm^{-1}; ^1H NMR (300 MHz) δ 7.89−7.81 (m, 4 H), 7.53−7.39 (m, 3 H), 5.70−5.66 (m, 1 H), 2.77−2.67 (m, 3 H), 2.34−2.25 (m, 1 H); ^{13}C NMR (75 MHz) δ 176.9, 136.7, 133.1, 133.0, 128.7, 128.0, 127.7, 126.5, 126.4, 124.3, 122.9, 81.3, 30.9, 29.0. Anal. Calcd for $C_{14}H_{12}O_2$: C, 79.22; H, 5.70. Found: C, 79.46; H, 5.88.

Procedure for the Synthesis of (*S*)-2-(*p*-*tert*-Butylphenyl)-cyclobutanone (Scheme 4). To a solution of the freshly prepared olefin (0.093 g, 0.5 mmol) and ketone **6** (0.125 g, 0.375 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 8.0) (5.0 mL) with stirring. After the mixture was cooled to −10 °C (bath temperature) via NaCl-ice bath, a solution of Oxone (0.202 M in 4 × 10^{-4} M aqueous EDTA, 1.77 mL) (0.220 g, 0.36 mmol) and a solution of K_2CO_3 (0.479 M in 4 × 10^{-4} M aqueous EDTA, 1.77 mL) (0.117 g, 0.85 mmol) were added separately and simultaneously via a syringe pump over a period of 4 h. Then the reaction mixture was immediately quenched with hexane, extracted with hexane, dried (Na_2SO_4), filtered, concentrated, and purified by flash chromatography [Iatrobeads 6RS-8060; hexane-EtOAc (1/0 to 20/1) was used as eluent] to give the cyclobutanone product as a colorless oil (0.069 g, 68% yield, 90% ee). $[\alpha]^{25}_D$ +38.1 (*c* 1.1 $CHCl_3$) (90% ee); IR (film) 1784 cm^{-1}; ^1H NMR (400 MHz) δ 7.38 (d, J = 8.4 Hz, 2 H), 7.20 (d, J = 8.4 Hz, 2 H), 4.56−4.50 (m, 1 H), 3.30−3.18 (m, 1 H), 3.10−2.98 (m, 1 H), 2.60−2.48 (m, 1 H), 2.31−2.19 (m, 1 H), 1.32 (s, 9 H); ^{13}C NMR (100 MHz) δ 208.5, 150.1, 133.7, 126.9, 125.8, 64.5, 45.0, 34.7, 31.5, 17.9; HRMS calcd for $C_{14}H_{18}O$ (M^+) 202.1358, found 202.1353.

Procedure for the Synthesis of (*S*)-2-Methyl-2-*p*-tolylcyclobutanone (Scheme 4). To a solution of the freshly prepared olefin (0.080 g, 0.5 mmol) and ketone **6** (0.110 g, 0.33 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 8.0) (5.0 mL) with stirring. After the mixture was cooled to −10 °C (bath temperature) via NaCl-ice bath, a solution of Oxone (0.202 M in 4 × 10^{-4} M aqueous EDTA, 1.56 mL) (0.194 g, 0.32 mmol) and a solution of K_2CO_3 (0.479 M in 4 × 10^{-4} M aqueous EDTA, 1.56 mL) (0.103 g, 0.75 mmol) were added separately and simultaneously via a syringe pump over a period of 4 h. Then the reaction mixture was immediately quenched with hexane, extracted with hexane, dried (Na_2SO_4), filtered, concentrated, and purified by flash chromatography [hexane-EtOAc (1/0 to 20/1) was used as eluent] to give the cyclobutanone as a colorless oil (0.044 g, 51% yield, 85% ee). $[\alpha]^{25}_D$ −58.2 (*c* 1.0, $CHCl_3$) (85% ee); IR (film) 1775 cm^{-1}; ^1H NMR (300 MHz) δ 7.26 (d, J = 8.1 Hz, 2 H), 7.16 (d, J = 8.1 Hz, 2 H), 3.23−2.99 (m, 2 H), 2.56−2.46 (m, 1 H), 2.34 (s, 3 H), 2.19−2.10 (m, 1 H), 1.54 (s, 3 H); ^{13}C NMR (100 MHz) δ 212.7, 139.6, 136.6, 129.5, 125.7, 68.0, 42.8, 26.5, 25.7, 21.2. Anal. Calcd for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 82.88; H, 7.99.

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Supporting Information Available: The characterization of γ-butyrolactones and cyclobutanones as well as the data for the determination of the enantiomeric excess of γ-butyrolactones and cyclobutanones. This material is available free of charge via the Internet at http://pubs.acs.org.

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