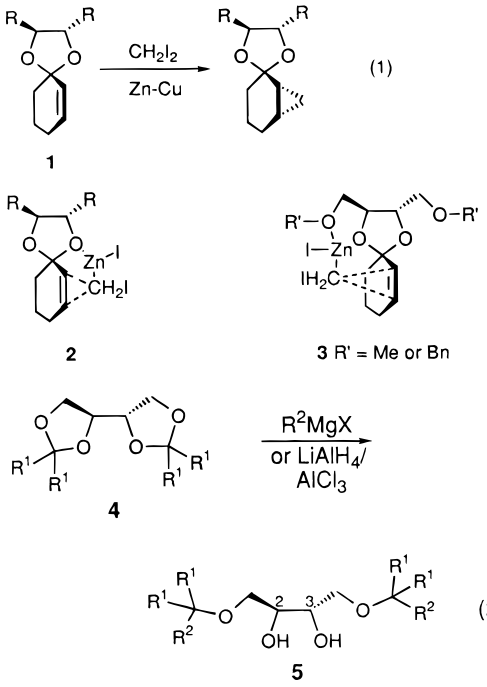
Diastereoselective Simmons−Smith Cyclopropanation of α,β-Unsaturated Cycloalkenones Using Tunable Diol as Chiral Auxiliary

Sue-Min Yeh,[1a] Li-Hsing Huang,[1b] and Tien-Yau Luh*

Department of Chemistry, National Taiwan University, Taipei, Taiwan 106, Republic of China

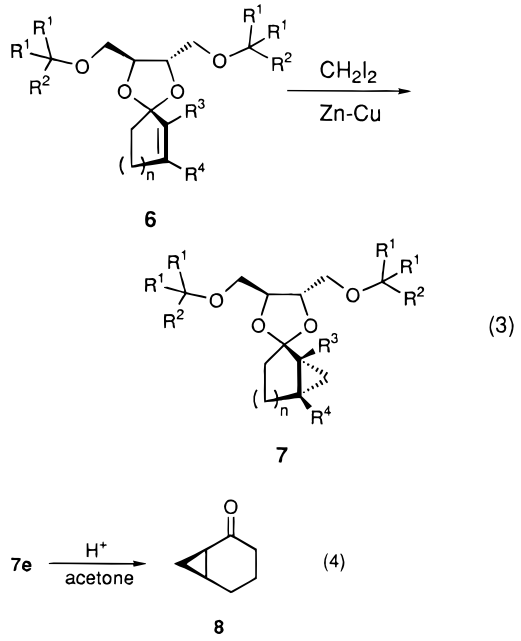
Received January 29, 1996

Diastereoselective cyclopropanation of α,β-unsaturated ketones or related compounds has recently received much attention.[2−8] Chiral ketals of α,β-unsaturated carbonyl compounds (**1**) are commonly used to furnish diastereoselective Simmons−Smith cyclopropanation (eq 1).[2,3] The



oxygen atom of the ketal moiety plays a key role (such as the formation of **2**) to direct the selectivity of this reaction. However, other heteroatom substituent on the chiral auxiliary (for example, R = CH_2OMe, eq 1) may compete with the oxygen atom of the ketal group to form the chelation complex with zinc (such as the formation of **3**), resulting in relatively poor stereoselectivity in the overall reaction.[3] We recently reported a convenient synthesis of various tunable C_2-chiral diols **5** from reaction of bisketals of L-threitol **4** with different kinds of the Grignard reagent (eq 2).[9] Diols 2*S*,3*S*-**5** might demonstrate certain unique properties to serve as a ligand in asymmetric reactions because the size of the alkoxy substituents can easily be tuned by changing the Grignard reagent or by varying the ketal moiety. We felt that an increase in the size of the R′ group in **3** may reduce the possibility for the formation of the corresponding chelation complex and thereby may enhance the diastereoselectivity of the cyclopropanation reaction. In this paper, we have tested this conjecture by studying the effect of the variation of the alkoxy substituent on the diastereoselective cyclopropanation of chiral ketals of cyclic enones **6**.

The reactions of enones with diols 2*S*,3*S*-**5** in the presence of a catalytic amount of TsOH afforded the corresponding ketals **6**. Treatment of **6** with CH_2I_2 in the presence of Zn−Cu couple in refluxing ether afforded the corresponding 2-bicyclo[*m*.1.0]alkanone (*m* = 3−5) acetal derivatives **7** (eq 3). The diastereoselectivity was



determined by ^1H NMR and by HPLC. Representative results are summarized in Table 1. Acid-catalyzed hydrolysis of **7e** in acetone gave **8** (eq 4).[3] The optical rotation of **8** was compared with the literature data,[2] and the stereochemical assignment for **7** was thus obtained.

As can be seen from Table 1, the ring size and the substituent on the starting enones do not affect significantly the diastereoselectivity of the cyclopropanation. The diastereoselectivity of the cyclopropanation reaction depends on the size of the *tert*-alkoxy substituent, the bulkier one giving the better selectivity (cf. entries 1−3 and 5). Apparently, the bulky alkoxy group would prohibit the formation of the corresponding complex **3** and the diastereoselectivity is directed by the ketal oxygen atom via intermediate **2**.

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S0022-3263(96)00181-8 CCC: $12.00

Table 1. Reactions of 6 with CH_2I_2 in the Presence of Cu−Zn Couple

entry	6	R^1	R^2	R^3	R^4	*n*	% yield of **7**	de %
1	**a**	Me	Me	H	H	2	61	62
2	**b**	Me	Et	H	H	2	69	66
3	**c**	Et	Me	H	H	2	77	79
4	**d**	Me	iPr	H	Me	2	74	87
5	**e**	Me	iPr	H	H	2	76	>98
6	**f**	Me	iPr	H	H	3	90	>98
7	**g**	Me	iPr	Me	H	1	81	>98

In summary, our results demonstrate a useful practice of employing the tunable chiral auxiliary **5** in asymmetric Simmons−Smith cyclopropanation. Further applications of these chiral diols in asymmetric synthesis are in progress.

Experimental Section

Preparation of 6. To a well-stirred solution of enone (1 equiv) in dry benzene (40 mL) were added **5** (1 equiv) and PPTS (1 mol %). The mixture was refluxed overnight, cooled, diluted with ether, washed with saturated $NaHCO_3$ and brine, and dried ($MgSO_4$). The organic solution was evaporated in vacuo to give the residue, which was chromatograted (1% EtOAc in hexane) to give **6**.

6a: 70%, $[\alpha]^{32}_D$ +4.3° (*c* 0.18); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.16 (s, 18 H), 1.70−1.97 (m, 6 H), 3.42−3.57 (m, 4 H), 3.83−3.97 (m, 2 H), 5.61 (d, *J* = 10.1, Hz, 1 H), 5.87 (dt, *J* = 10.1, 3.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.6, 24.8, 27.4, 34.8, 63.2, 73.1, 76.4, 78.9, 106.4, 128.8, 132.2; HRMS calcd for $C_{18}H_{32}O_4$ 312.2301, found 312.2309.

6b: 73%, $[\alpha]^{30}_D$ +0.22° (*c* 0.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.83 (t, *J* = 7.4 Hz, 6 H), 1.10 (s, 12 H), 1.46 (q, *J* = 7.5 Hz, 4 H), 1.70−1.97 (m, 6 H), 3.39−3.52 (m, 4 H), 3.39−3.99 (m, 2 H), 5.62 (d, *J* = 10.1 Hz, 1H), 5.88 (dt, *J* = 10.1, 3.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 8.2, 20.7, 24.9, 27.4, 32.6, 34.8, 62.8, 75.0, 78.0, 78.8, 106.3, 128.9, 132.2; HRMS calcd for $C_{20}H_{36}O_4$ 340.2614, found 340.2617.

6c: 68%, $[\alpha]^{32}_D$ −7.7° (*c* 0.31, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.80 (t, *J* = 7.5 Hz, 12 H), 1.03 (s, 6 H), 1.43 (q, *J* = 7.5 Hz, 8 H), 1.69−2.0 (m, 6 H), 3.34−3.51 (m, 4 H), 3.92−4.04 (m, 2 H), 5.62 (dt, *J* = 10.1, 1.9 Hz, 1 H), 5.88 (dt, *J* = 10.1, 3.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 7.5, 7.8, 20.7, 22.0, 24.5, 24.8, 26.0, 29.7, 32.3, 34.8, 37.0, 62.2, 62.4, 76.9, 77.9, 78.5, 78.9; HRMS calcd for $C_{22}H_{40}O_4$ 368.2927, found 368.2928.

6d: 50%, $[\alpha]^{32}_D$ +4.4° (*c* 0.07, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.85 (dd, *J* = 6.9, 0.9 Hz, 12 H), 1.05 (d, *J* = 11.4 Hz, 12 H), 1.65 (s, 3H), 1.46 (q, *J* = 7.5 Hz, 4 H), 1.70−1.88 (m, 6 H), 3.39−3.57 (m, 4 H), 3.89−3.99 (m, 2 H), 5.38 (s, 1 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 17.5, 20.8, 22.0, 23.4, 30.0, 34.5, 35.6, 35.8, 62.2, 62.4, 77.2, 77.4, 77.7, 78.9, 107.1, 123.8, 141.0; HRMS calcd for $C_{23}H_{42}O_4$ 382.3083, found 382.3087.

6e: 53%, $[\alpha]^{32}_D$ +1.67° (*c* 0.04 , $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.85 (d, *J* = 6.8 Hz, 12 H), 1.05 (s, 12 H), 1.46 (q, *J* = 7.5 Hz, 4 H), 1.70−1.97 (m, 6 H), 3.39−3.99 (m, 4 H), 3.89−4.01 (m, 4 H), 5.62 (dt, *J* = 10.1, 11.8 Hz, 1 H), 5.88 (dt, *J* = 10.1, 3.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 17.5, 20.7, 22.0, 24.8, 34.9, 35.6, 62.2, 62.4, 77.3, 77.4, 77.9, 78.9, 106.2, 129.0, 132.3; HRMS calcd for $C_{22}H_{40}O_4$ 368.2927, found 368.2929. Anal. Calcd for $C_{22}H_{40}O_4$: C, 71.68; H, 10.95; O, 17.37. Found: C, 71.66; H, 10.95; O, 17.39.

6f: 45%, $[\alpha]^{30}_D$ −3.1° (*c* 0.11, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.85 (d, *J* = 6.8 Hz, 12 H), 1.04 (s, 12 H), 1.57−1.97 (m, 8 H), 2.10−2.18 (m, 2 H), 3.37−3.55 (m, 4 H), 3.86−3.97 (m, 4 H), 5.64−5.85 (m, 2 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 17.4, 22.0, 23.4, 26.7, 27.5, 35.7, 37.3, 38.8, 42.2, 62.2, 62.6, 77.2, 77.3, 77.9, 78.2, 78.3, 79.0, 110.2, 132.8, 135.2; HRMS calcd for $C_{23}H_{42}O_4$ 382.3083, found 382.3076.

6g: 46%, $[\alpha]^{34}_D$ −2.0° (*c* 0.33, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.86 (d, *J* = 6.7 Hz, 12 H), 1.06 (s, 12 H), 1.66 (m, 3 H), 1.71−1.85 (m, 2 H), 2.02−2.08 (m, 2 H), 2.20−2.26 (m, 2 H), 3.43−3.56 (m, 4 H), 3.87−4.0 (m, 2 H), 5.64 (m, 1 H); ^{13}H NMR ($CDCl_3$, 75 MHz) δ 10.7, 14.1, 17.5, 22.0, 27.9, 35.6, 36.4, 61.9, 62.1, 77.2, 77.4, 78.1, 79.4, 120.6, 131.2; HRMS calcd for $C_{22}H_{40}O_4$ 368.2927, found 368.2933.

Preparation of 7. To a suspension of a freshly prepared Zn−Cu couple (400−700 mg/mmol of **6**) in Et_2O (5 mL) under nitrogen were added a small crystal of iodine and CH_2I_2 (3 equiv). The mixture was refluxed for 30 min, and **6** (1 equiv) in ether (5 mL) was added. The mixture was refluxed for 16 h, cooled to 0 °C, and quenched with saturated $NaHCO_3$. After stirring at rt for 30 min, the grayish black precipitate was filtered and the filter cake was washed with ether. The combined organic solution was dried ($MgSO_4$). Solvent was removed in vacuo to give the residue, which was chromatographed on silica gel (1% EtOAc in hexane) to give **7**. Diastereomeric pure isomer was obtained by preparative HPLC on silica gel.

1*R*,6*S*-**7a**: $[\alpha]^{23}_D$ −13.0° (*c* 3.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.26 (q, *J* = 5.5 Hz, 1 H), 0.66 (dt, *J* = 5.5, 9.0 Hz, 1 H), 1.15 (s, 9 H), 1.17 (s, 9 H), 1.22−1.60 (m, 7 H), 1.74−1.90 (m, 1 H), 3.40−3.61 (m, 4 H), 3.82−4.01 (m, 2 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 9.4, 12.3, 19.9, 22.4, 27.4, 32.7, 63.2, 63.3, 73.0, 77.2, 77.9, 78.6, 109.9; HRMS calcd for $C_{19}H_{34}O_4$ 326.2457, found 326.2464.

1*R*,6*S*-**7b**: $[\alpha]^{23}_D$ −15.3° (*c* 1.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.25 (q, *J* = 5.3 Hz, 1 H), 0.66 (dt, *J* = 5.3, 9.0 Hz, 1 H), 0.84 (t, *J* = 7.4 Hz, 6 H), 1.10−1.65 (m, embodied two singlets at 1.10 and 1.11 due to four methyl groups, 23 H), 1.74−1.86 (m, 1 H), 3.36−3.58 (m, 4 H), 3.85−4.03 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.2, 9.4, 12.3, 19.9, 20.0, 22.5, 24.9, 32.7, 32.8, 62.7, 62.9, 75.0, 77.2, 78.0, 78.6, 109.8; HRMS calcd for $C_{19}H_{34}O_4$ 354.2770, found 354.2777.

1*R*,6*S*-**7c**: $[\alpha]^{23}_D$ −23.1° (*c* 3.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.25 (q, *J* = 5.4 Hz, 1 H), 0.66 (dt, *J* = 5.4, 9.0 Hz, 1 H), 0.79 (t, *J* = 7.5 Hz, 6 H), 0.80 (t, *J* = 7.5 Hz, 6 H), 1.02 (s, 3 H), 1.04 (s, 3 H), 1.15 (ddd, *J* = 5.5, 8.8, 15.0 Hz, 1 H), 1.22−1.60 (m, 14 H), 1.80 (dt, *J* = 6.2, 12.6 Hz, 1 H), 3.34−3.53 (m, 4 H), 3.91−4.03 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 7.8, 7.9, 9.3, 12.3, 19.8, 19.9, 22.0, 22.1, 22.5, 29.7, 32.7, 62.2, 62.4, 76.8, 76.9, 78.1, 78.5, 109.7; HRMS calcd for $C_{23}H_{42}O_4$ 382.3083, found 382.3090.

1*R*,6*S*-**7d**: $[\alpha]^{23}_D$ −18.2° (*c* 9.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.38 (dd, *J* = 9.5, 5.0 Hz, 1H), 0.46 (t, *J* = 5.0 Hz, 1H), 0.84 (d, *J* = 6.9 Hz, 6H), 0.86 (d, *J* = 6.6 Hz, 6H), 1.03 (s, 6H), 1.05 (s, 3H), 1.06 (s, 6H), 1.18−1.29 (m, 2H), 1.45−1.83 (m, 5H), 3.36−3.56 (m, 4H), 3.88−3.95 (m, 1H), 3.90−4.10 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 15.1, 17.5, 18.1, 19.0, 22.0, 22.6, 26.9, 28.6, 29.6, 31.6, 33.5, 35.6, 35.7, 62.3, 77.2, 77.3, 77.4, 79.0, 109.5; HRMS calcd for $C_{24}H_{44}O_4$ 396.3240, found 396.3238.

1*R*,6*S*-**7e**: $[\alpha]^{23}_D$ −21.9° (*c* 18.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.26 (q, *J* = 5.3 Hz, 1 H), 0.66 (dt, *J* = 5.3, 9.0 Hz, 1 H), 0.84 (d, *J* = 7.0 Hz, 12 H), 1.04 (s, 6 H), 1.05 (s, 6 H), 1.10−1.90 (m, 10 H), 3.38−3.60 (m, 4 H), 3.90−4.04 (m, 2 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 9.3, 12.3, 17.5, 19.8, 20.0, 22.0, 22.5, 32.8, 35.7, 62.3, 62.4, 77.3, 78.0, 78.5, 109.6; HRMS calcd for $C_{23}H_{42}O_4$ 382.3083, found 382.3092.

1*R*,7*S*-**7f**: $[\alpha]^{23}_D$ −20.7° (*c* 5.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.44 (q, *J* = 5.0 Hz, 1 H), 0.57 (dt, *J* = 5.0, 8.8 Hz, 1 H), 0.84 (d, *J* = 6.7 Hz, 12 H), 1.05 (s, 12 H), 1.00−2.08 (m, 12 H), 3.39−3.57 (m, 4 H), 3.77−3.90 (m, 2 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 9.5, 14.9, 17.5, 22.0, 22.1, 24.5, 27.9, 29.4, 35.6, 35.9, 40.7, 62.3, 62.7, 77.1, 77.3, 79.4, 111.2; HRMS calcd for $C_{24}H_{44}O_4$ 396.3240, found 396.3241.

1*R*,5*S*-**7g**: $[\alpha]^{23}_D$ −13.5° (*c* 6.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.35 (dd, *J* = 5.1, 7.6 Hz, 1 H), 0.64 (t, *J* = 4.6 Hz, 1 H), 0.83 (d, *J* = 7.0 Hz, 6 H), 0.84 (d, *J* = 7.0 Hz, 6 H), 1.04 (s, 6 H), 1.07 (s, 6 H), 1.13 (s, 3 H), 1.24−1.89 (m, 7 H), 3.38−3.59 (m, 4 H), 3.85−3.95 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 14.3, 17.5, 17.6, 22.0, 22.9, 24.1, 26.9, 32.2, 35.6, 61.9, 62.2, 77.2, 77.4, 77.6, 78.9, 119.5; HRMS calcd for $C_{23}H_{42}O_4$ 382.3083, found 382.3074.

Hydrolysis of 7e. An acetone solution (20 mL) of **7e** (0.91 g, 2.4 mmol) and p-TsOH·H_2O (0.16 g, 0.8 mmol) was stirred at rt for 5 h. The mixture was then treated with K_2CO_3, filtered, and dried ($MgSO_4$). The solvent was carefully removed by distillation and the residue was purified by chromatography to give **8** (0.17 g, 64%). An analytical sample was obtained by preparative vapor phase chromatography (6 ft, 30% SE30, 35−120 °C): $[\alpha]^{24}_D$ = +14.6° (*c* 1.3, $CDCl_3$, lit.[10] $[\alpha]^{25}_D$ +15.3°,

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$CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 0.99−1.21 (m, 2 H), 1.52−1.72 (m, 4 H), 1.87−2.10 (m, 3H), 2.20−2.33 (m, 1 H).

Acknowledgment. This work is supported by the National Science Council of the Republic of China. S.-M.Y. thanks the Li-Ching Foundation for a scholarship.

Supporting Information Available: ^1H NMR spectra for compounds **6a**−**g** and **7a**−**g** (14 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO960181G