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DIASTEREOSELECTIVE REDUCTION OF CHIRAL *N*-TOSYL-2-BENZOYL-1,3-OXAZINE DERIVED FROM (1*R*)-(+)-CAMPHOR

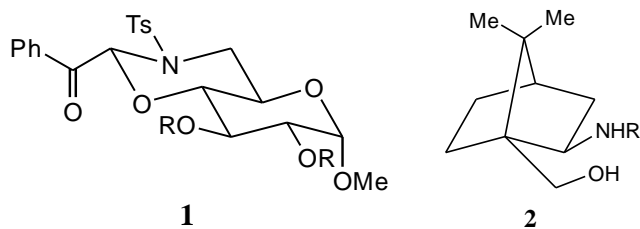
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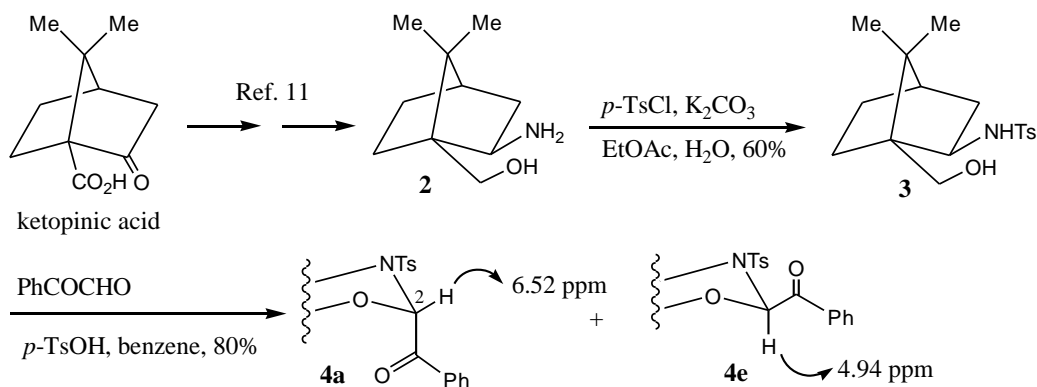
Abstract – The stereochemistry of reduction of chiral *N*-tosyl-2-benzoyl-1,3-oxazine prepared by condensation of 1,3-amino alcohol derived from (1*R*)-(+)-camphor with phenylglyoxal was investigated using various reducing agents. Based on X-ray crystallography, 2-benzoyl group in 1,3-oxazine ring was situated in the axial position. High diastereoselectivity observed in the hydride reduction can be explained by a chelate model where *N*-tosyl oxygen atom takes part in chelation rather than ring oxygen atom.

The diastereoselective addition of nucleophilic reagents to ketones having a chiral auxiliary is a useful method for obtaining optically active alcohols.¹ Chiral auxiliaries used for this purpose include enantiomerically pure amino alcohols derived from norephedrine,² (+)-pulegone³ or amino acids,⁴ 3-hydroxythiols derived from (+)-pulegone,⁵ (-)-myrtenal⁶ or (1*R*)-(+)-camphor,⁷ and 1,3-diols.⁸ We previously reported highly diastereoselective reduction of chiral *N*-tosyl-1,3-oxazines **1** derived from *D*-glucose.⁹ In this case, the high diastereoselectivity observed in the reduction with chelating reducing agents such as L-Selectride[®] (lithium tri-*sec*-butylborohydride) has been explained by invoking a Cram's chelate model, where the ring oxygen and the carbonyl oxygen take part in the chelation with metal cation. On the contrary, non-chelating agents such as diisobutylaluminum hydride (DIBAL-H) and *n*-Bu₄NBH₄ have been suggested to react according to a Felkin-Anh model.⁹



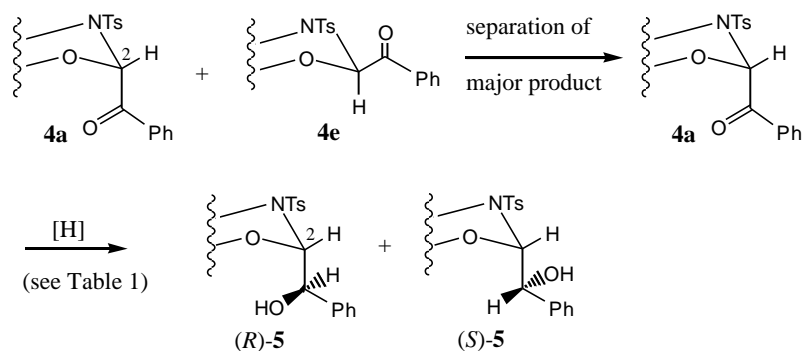
(1*R*)-(+)-Camphor has been used as a starting material for the preparation of various chiral auxiliaries or chiral catalysts.¹⁰ Chiral auxiliaries derived from camphor are known to have good crystallinity, giving some advantages in purification of product. However, 3-amino alcohols **2** which can be easily derived from camphor have not yet been used as chiral auxiliary for asymmetric reduction. As an extension of our previous work,⁹ we wish to report a highly diastereoselective reduction of camphor-based oxazine and determination of absolute configuration of newly formed stereocenter by single crystal X-ray diffraction.

N-Tosylamino alcohol **3**, a camphor-derived chiral auxiliary used for the present study was prepared according to Scheme 1. Thus, ketopinic acid derived from (+)-camphor was converted to known amino alcohol **2**.¹¹ Subsequent tosylation with *p*-TsCl gave **3** as a crystalline solid. Finally, condensation with phenylglyoxal in acidic condition gave a mixture of two phenyl ketones **4** in a ratio of 4 : 1, as judged by ¹H-NMR spectrum. Major product could be isolated in a pure form by recrystallization from EtOH.



Scheme 1. Preparation of 2-Benzoyl-1,3-oxazines **4**

Then, we studied reduction of phenyl ketone **4a** using several reducing agents, as shown in Table 1 (Scheme 2).

Scheme 2. Diastereoselective reduction of 2-benzoyl-1,3-oxazine **4a**Table 1. Diastereoselectivity in the reduction of 2-benzoyl-1,3-oxazine **4a**^a

Entry	Reagent	Solvent	Temp. (°C)	Time (h)	de (%) ^{b,c}
1	NaBH ₄	EtOH	0	18	40
2	KBH ₄	EtOH	0	18	30
3a	LiAlH ₄	THF	-70	1	72(68 ^d)
3b	LiAlH ₄	Et ₂ O	-70	1	98(98 ^d)
4a	L-Selectride [®]	Et ₂ O	-70	1	98
4b	L-Selectride [®]	toluene	-70	1	90(87 ^d)
5a	LiAlH(O- <i>t</i> -Bu) ₃	THF	-70	10	70
5b	LiAlH(O- <i>t</i> -Bu) ₃	Et ₂ O	-70	10	98
6a	LiEt ₃ BH	THF	-70	1	8
6b	LiEt ₃ BH	Et ₂ O	-70	1	64
6c	LiEt ₃ BH	toluene	-70	1	70(30 ^d , -60 ^e)
7a	NaEt ₃ BH	THF	-70	1	66(-50 ^e)
7b	NaEt ₃ BH	Et ₂ O	-70	1	95(10 ^e)
7c	NaEt ₃ BH	toluene	-70	1	96(14 ^f)
8a	DIBAL-H	THF	-70	1	10
8b	DIBAL-H	Et ₂ O	-70	1	-81
8c	DIBAL-H	toluene	-70	1	40
8d	DIBAL-H	CH ₂ Cl ₂	-70	1	53
9	<i>n</i> -Bu ₄ NBH ₄	CH ₂ Cl ₂	20	10	10

a. Determined by ¹H NMR on the crude products.

b. Minus sign indicates formation of (*S*)-isomer as the major product.

c. The number in parenthesis is the de in the presence of crown ether. The molar ratio of **4a**, reagent, and crown ether = 1 : 3 : 5.

d. In the presence of 12-Crown-4.

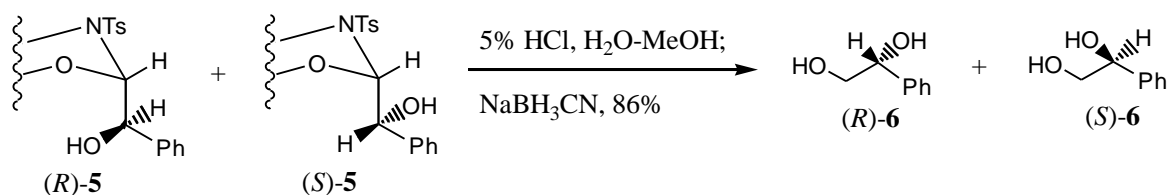
e. In the presence of 15-Crown-5.

f. In the presence of 18-Crown-6.

Diastereoselectivity could be easily determined by $^1\text{H-NMR}$ spectroscopy. For example, in entry 1, C-2 proton of the major product appeared as a doublet at δ 5.40 ($J = 3.7$ Hz) and that of the minor one appeared as a doublet at δ 5.54 ($J = 9.1$ Hz).

Either alcohol (*R*)-**5** or (*S*)-**5** (see below for the determination of the absolute configuration) was obtained as the major product, depending on the nature of reducing agents and solvents. Generally, all the chelating reducing agents used in the present case gave the (*R*)-**5** as the major product (entries 1~7). Nonchelating agents such as DIBAL-H and *n*-Bu₄NBH₄ also gave the (*R*)-isomer albeit in rather poor selectivity, except for the entry 8b. High selectivity (>98%) favoring the (*R*)-alcohol was observed when LiAlH₄, L-Selectride[®] or LiAlH(O-*t*-Bu)₃ was used as reducing agents (entries 3b, 4a, 5b).

Next, we undertook the cleavage of oxazines **5** to determine the absolute configuration of the newly formed carbinol carbon and thereby the approaching preference of the nucleophile to the carbonyl faces: alcohol **5** obtained from L-Selectride[®] reduction (entry 4b) was converted to diol **6**, $[\alpha]_{\text{D}}^{20} -35.5$ (c 1.01, EtOH) using acidic hydrolysis followed by NaBH₃CN reduction of the resulting 2-hydroxyaldehyde intermediate (Scheme 3).¹²



Scheme 3. Preparation of diol **6** by acidic hydrolysis of oxazine ring followed by reduction

Since (*R*)-**6** is known to be levorotatory ($[\alpha]_{\text{D}}^{20} -39.7$ (c 4.33, EtOH)),¹³ we can conclude that the carbinol carbon has (*R*)-configuration. The formation of (*R*)-isomer can be explained by invoking a similar chelate model as in the case of ketone **1** where ring oxygen atom takes part in chelation, assuming that benzoyl group is situated equatorially.⁹ However, chemical shift for C-2 proton of major phenyl ketone **4** appeared downfield relative to that in the minor one (6.52 vs. 4.94 ppm), which may imply that benzoyl group is situated in an axial position rather than in an equatorial one.¹⁴ To unambiguously determine the absolute configuration of C-2 on **4a** and carbinol carbon of **5**, we resorted to single crystal X-ray crystallography of **4a** and **5**.¹⁵ Figure 1 and 2 show an ORTEP drawing of ketone **4a**¹⁶ and the major product **5**¹⁷ of LiAlH₄ reduction, respectively. Figure 1 clearly shows the axial orientation of the benzoyl group in **4a**,¹⁸ as suspected based on the $^1\text{H NMR}$ data. The oxazine ring has a chair conformation, which is in contrast to the boat conformation of the similar *N*-tosyl-2-vinyl-1,3-oxazine ring.¹⁹ Figure 2 shows the (*R*)-configuration of carbinol carbon, which agrees with the optical rotation data.

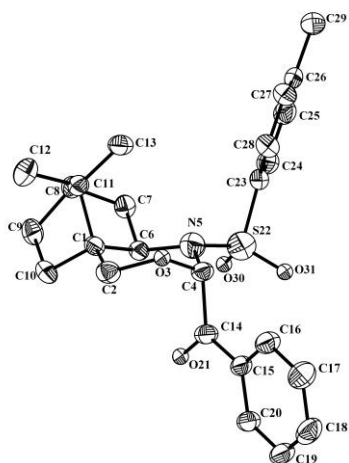


Figure 1. A view of **4a**. Vibrational ellipsoids are drawn at the 30% probability level. Hydrogen atoms are omitted for clarity.

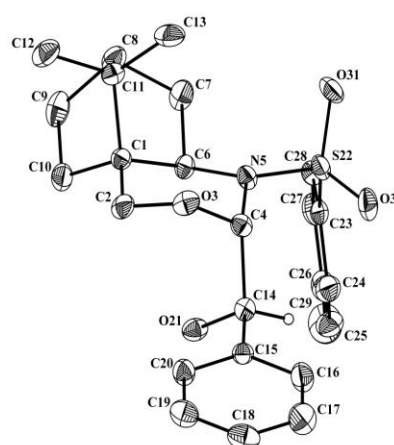
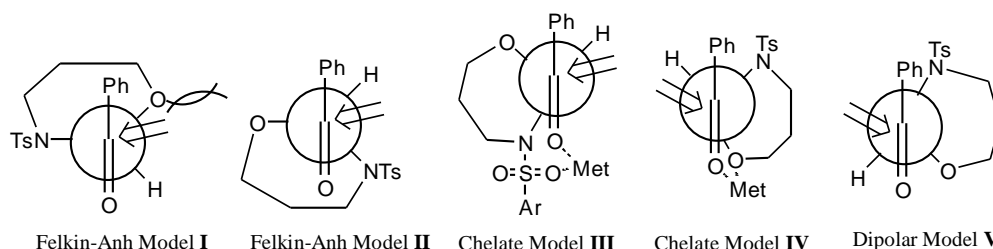


Figure 2. A view of (*R*)-**5**. Vibrational ellipsoids are drawn at the 30% probability level. Hydrogen atoms except H14 are omitted for clarity.

We can consider three conformations **I**~**III** that may result in the (*R*)-configuration, as shown in Scheme 4.¹



Scheme 4. Stereochemical models

Felkin-Anh polar model **I** where *N*-tosyl group is located perpendicular to the carbonyl group, appears to be unfavorable due to the steric reason. Another Felkin-Anh model **II** and the chelate model **III** can predict the correct stereochemistry. Model **II** is in accord with the X-ray structure of ketone **4**, which shows that the carbonyl group, situated inside the oxazine ring is nearly perpendicular to the α -C-O bond.²⁰ The chelate model **III** where the sulfonyl oxygen, not the ring oxygen as in model **IV** takes part in chelation can also explain the formation of (*R*)-alcohol.²¹

To see the effect of crown ether on the chelation, we performed the reduction in the presence of crown ethers.⁹ Little decrease in selectivity in the presence of crown ether was observed in the LiAlH₄ and L-Selectride[®] reductions (entries 3a, 3b, 4b). This fact may be explained by assuming that Felkin-Anh model **II** is operating or chelation in model **III** is rather strong as not to be disturbed by crown ether.

However, decrease in selectivity in THF which is a better solvating solvent than ether (entry 3a vs. 3b, 5a vs. 5b, 6a vs. 6b, and 7a vs. 7b) may support that the chelate model is more important. In contrast, in the case of LiEt₃BH and NaEt₃BH reduction the presence of crown ether dramatically affected the degree and/or direction of selectivity. For example, the diastereoselectivity of LiEt₃BH reduction in toluene changed from 70% de to 30% in the presence of 12-crown-4 (entry 6c). Surprisingly, the use of 15-crown-5, which is known to complex with sodium cation more efficiently than lithium cation resulted in the opposite stereochemistry (entry 6c).²² Similar trend was also observed in the NaEt₃BH reduction (entry 7). Compared with the LiEt₃BH reduction the selectivity in the NaEt₃BH reduction was better, decreasing in a larger extent in the presence of crown ether. This result is expected in that sodium chelate is less tight than lithium chelate, thus being disturbed more easily by crown ether. However, the reason for the better selectivity of less tight sodium chelate is not clear. In DIBAL-H reduction, the stereochemistry of reduction was moderate, except for the reduction in ether solvent, which gave the opposite stereochemistry to LiAlH₄ reduction. This formation of (*S*)-carbinol can be explained by invoking the dipolar model **V** where the ring oxygen atom is anti to the carbonyl group. However, the reason why ether solvent behaves differently in the DIBAL-H reduction remains to be answered.

In summary, axial phenyl ketone **4a** derived from a new camphor-based chiral auxiliary **3** was found to be reduced with chelating reducing agents in high diastereoselectivity. In the present case, the stereochemistry of this reduction could be explained by invoking a chelate model **III** where tosyl oxygen takes part in chelation. Participation of tosyl oxygen atom in chelation is in sharp contrast with the case of ketone **1** where ring oxygen atom takes part in chelation. This study shows that ketones **1** and **4a** which are similar in structures can react with reducing agents in different stereochemical sense.

EXPERIMENTAL

IR spectra were recorded with a Nicolet Magna FT-IR spectrophotometer 550. NMR spectra were recorded on Varian Gemini 400 spectrometer in CDCl₃ with tetramethylsilane (TMS) as internal standard. Melting points were determined on a Buchi and are uncorrected. Optical rotations were measured on a Jasco DIP-370 digital polarimeter. Elemental analyses were performed by Eager 200 CHNS CE Instrument. Liquid Column chromatography was performed over silica gel (Merck, silica gel 60, 70-230 mesh). Analytical TLC was performed on precoated Merck glass plates (silica gel 60 F254) and compounds were visualized under UV light or by dipping in an ethanol solution of phosphomolybdic acid, followed by heating. Dry THF was distilled over sodium benzophenone ketyl under nitrogen atmosphere.

N-Tosyl amino alcohol **3**

To a well stirred mixture of amine **2** (1.80 g, 10.6 mmol) in EtOAc (35 mL) and water (20 mL) was added

K_2CO_3 (1.47 g, 10.6 mmol) followed by *p*-TsCl (2.20 g, 11.7 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and then at rt for 10 h. Then, the organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic extracts were washed successively with brine (2 x 10 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo to give a crude yellowish product (3.30 g). Trituration in EtOAc (10 mL) gave **3** (2.00 g, 60%) as a white solid. **3**: mp 195-197 °C; $[\alpha]_D^{20}$ -4.3 (c 1.00, $CHCl_3$); IR (KBr) ν_{max} 3445 (OH), 3225, 2956, 1475, 1321, 1160; 1H -NMR (400 MHz, $CDCl_3$): δ 7.77 (2H, d, $J = 8.3$ Hz), 7.32 (2H, d, $J = 8.0$ Hz), 5.29 (1H, s, $J = 8.0$ Hz, NH), 4.04, 3.46 (2H, ABq, $J = 12$ Hz), 3.22 (1H, dd, $J = 10, 4.6$ Hz), 2.44 (s, 3H), 1.68-1.52 (5H, m), 1.35-1.20 (2H, m), 1.00 (3H, s), 0.88 (3H, s); ^{13}C -NMR (100 MHz, $CDCl_3$): δ 143.5, 136.6, 129.8, 129.2, 61.7, 59.2, 53.3, 47.0, 46.0, 39.5, 32.0, 26.4, 21.5, 21.0, 20.6; Anal. Calcd for $C_{11}H_{25}NO_3S$: C, 63.12; H, 7.81; N, 4.33; S, 9.91. Found: C, 62.51; H, 7.90; N, 4.29; S, 9.54.

Phenyl ketone 4a

A solution of **3** (970 mg, 3.00 mmol) and phenylglyoxal hydrate (790 mg, 5.89 mmol) in benzene (50 mL) was refluxed for 20 h in the presence of *p*-TsOH (75 mg). The reaction mixture was diluted with EtOAc (50 mL) and water (20 mL). The organic layer was separated and washed successively with brine (2 x 10 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo to give a crude residue, which was purified by recrystallization from EtOH to afford **4a** (660 mg, 50%). **4a**: mp 181-182 °C; $[\alpha]_D^{20}$ -65.1 (c 0.98, $CHCl_3$); IR (KBr) ν_{max} 3447 (OH), 3225, 1640 (C=O), 1329, 1160, 715; 1H -NMR (400 MHz, $CDCl_3$): δ 8.14 (2H, d, $J = 8.1$ Hz), 7.73 (2H, d, $J = 8.1$ Hz), 7.65-7.45 (3H, m), 7.31 (2H, s), 6.52 (1H, s), 4.16 (1H, dd, $J = 8.1, 4.6$ Hz), 3.78, 3.38 (2H, ABq, $J = 13$ Hz), 2.44 (s, 3H), 2.25-2.13 (1H, m), 1.78-1.62 (4H, m), 1.40-1.09 (2H, m), 0.98 (3H, s), 0.83 (3H, s); ^{13}C -NMR (100 MHz, $CDCl_3$): δ 195.2, 143.2, 139.6, 134.1, 133.8, 129.3, 129.2, 128.6, 127.3, 84.9, 63.5, 59.4, 47.2, 46.5, 45.5, 35.6, 30.9, 26.6, 21.6, 21.4, 20.2; Anal. Calcd for $C_{25}H_{29}NO_4S$: C, 68.23; H, 6.66; N, 3.19; S, 7.29. Found: C, 68.16; H, 6.68; N, 3.16; S, 6.91.

Reduction of phenyl ketone 4a

An example: A solution of **4a** (0.50 g, 1.18 mmol) in dry ether (20 mL) was treated with a solution (2.0 mL) of 1 M $LiAlH_4$ in ether under nitrogen atmosphere at -70 °C. After stirring for 1 h, the reaction mixture was quenched with NH_4Cl aq. and extracted with EtOAc (20 mL). The organic layer was separated and washed successively with brine (2 x 10 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo to give a crude residue **5** (0.45 g, 90%), whose 1H -NMR spectrum showed that the diastereoselective excess was 98%. Recrystallization from EtOH gave **5** as a single diastereomer. **5**: mp

172-173 °C; $[\alpha]_{\text{D}}^{20}$ -93.1 (c 1.02, CHCl₃); IR (KBr) ν_{max} 3487 (OH), 1160, 1057, 975; ¹H-NMR (400 MHz, CDCl₃): δ 7.71 (2H, d, J = 8.3 Hz), 7.51-7.23 (7H, m), 5.66 (1H, d, J = 3.7 Hz), 5.40 (1H, d, J = 3.7 Hz), 4.40, 3.61 (2H, ABq, J = 12 Hz), 4.15 (1H, dd, J = 8.1, 5.1 Hz), 2.40 (s, 3H), 2.08-1.98 (2H, m), 1.70-1.08 (5H, m), 0.77 (3H, s), 0.76 (3H, s); ¹³C-NMR (100 MHz, CDCl₃): δ 143.2, 140.2, 140.1, 129.4, 128.3, 127.6, 127.0, 125.9, 86.0, 79.0, 62.8, 60.3, 46.9 46.3, 45.2, 35.8, 31.7, 26.5, 21.5, 20.7, 20.3.

1-Phenyl-1,2-ethanediol (**6**)

A solution of **5** (0.40 g, 0.91 mmol, derived from L-Selectride[®] reduction (entry 4b)) in MeOH (50 mL) was treated with 5% HCl aq. (10 mL) and the whole mixture was refluxed for 3 h. After adjusting pH to 4~5 by adding Na₂CO₃, the reaction mixture was treated with NaBH₃CN (60 mg, 0.95 mmol) and refluxed for 30 min. Concentration in vacuo gave a yellow solid, which upon column chromatography (hexanes:EtOAc = 2:1) yielded **6** (0.10 g, 79%) and **3** (0.25 g, 85%). Kugelrohr distillation (145~150 °C, 0.1 mmHg) of crude **6** gave a pure known diol **6**. **6**: $[\alpha]_{\text{D}}^{20}$ -35.5 (c 1.01, EtOH) [lit.¹³ for (*R*)-isomer $[\alpha]_{\text{D}}^{20}$ -39.7 (c 4.33, EtOH)]; ¹H-NMR (400 MHz, CDCl₃): δ 7.36 (5H, s), 4.80 (1H, X part of ABX, HOCH₂CH-, J = 8.0, 3.5 Hz), 3.74, 3.65 (2H, AB part of ABX, HOCH₂CH-, J = 11.4, 8.0, 3.5 Hz), 3.11-2.20 (2H, s).

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