Asymmetric Synthesis Using Chiral Piperazine. I. Asymmetric Synthesis of 2-Substituted Alcohol and Carboxylic Acid by Diastereoselective Alkylation of Chiral Diamides Derived from Piperazines

Kenso SOAI,* Hiroshi HAYASHI, Akihiro SHINOZAKI, Hideaki UMEBAYASHI, and Yasuyuki YAMADA
Department of Applied Chemistry, Faculty of Science, Science University of Tokyo, Shinjuku, Tokyo 162
(Received February 17, 1987)

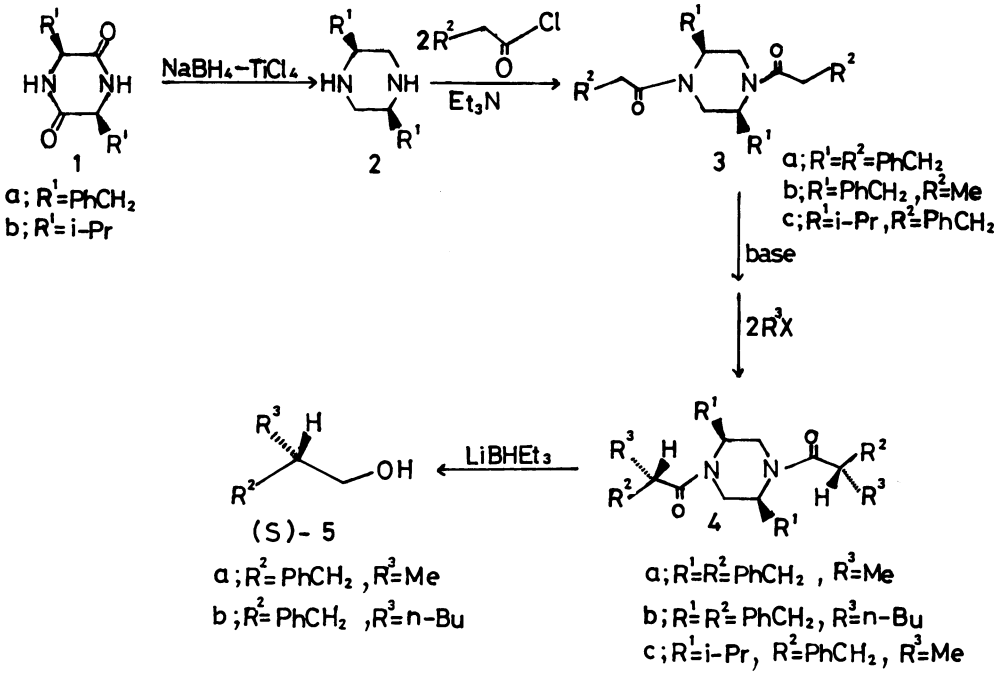
Synopsis. The diastereoselective alkylation of chiral diamides derived from chiral piperazines afforded optically active alcohols and acids in moderate enantiomeric excesses (up to 68% e.e.).

The diastereoselective alkylation of enolates derived from chiral amides is an important method for the synthesis of chiral acids.[1] However, in these reactions one mole is the maximum quantity of the product that can be obtained from one mole of the chiral auxiliary.

In this paper, we report a diastereoselective alkylation of chiral diamides derived from chiral piperazines. In the present system, one mole of chiral diamide affords (in principle) two moles of the product. Chiral 2,5-disubstituted piperazines(**2a,b**)[2] were synthesized by a reduction of the corresponding 2,5-piperazinediones(**1a,b**)[3] with sodium borohydride-titanium tetrachloride[4] (Scheme 1). Chiral diamides(**3a—c**) were obtained in good yields from **2a,b** by the *N*-acylation using the corresponding acid chloride and triethylamine.

The diamides(**3a—c**) were deprotonated and treated with various alkyl halides. The reduction of the alkylated diamides(**4a—c**) with lithium hydrotriethylborate($LiBHEt_3$) removed the chiral auxiliary to afford the corresponding optically active 2-substituted alcohols(**5a,b**). Results are shown in Table 1.

Lithium enolate was formed from **3a** by lithium diisopropylamide (LDA), and was alkylated with methyl iodide. The reductive removal of the chiral auxiliary afforded (*S*)-2-methyl-3-phenyl-1-propanol (**5a**, S:R=71:29) (Entry 1). In diastereoselective alkylation, additives to the enolates had a considerable effect on the degree of diastereoselectivity and the sense of the asymmetric induction. Diastereoselectivities increased in the presence of hexamethylphosphoric triamide(HMPA). Thus, (*S*)-**5a** (S:R=81:19) was obtained from the methylation of lithium enolate of **3a** in the presence of HMPA (LDA:HMPA=1:1) (Entry 3). Butylation under the same conditions showed better diastereoselectivity, and (*S*)-2-benzylhexanoic acid(**6**, S:R=84:16, 68% e.e., Entry 9) was obtained after the oxidation of alcohol(**5b**) (Eq. 1). Meanwhile, the benzylation of **3b** using LDA without any additive afforded (*R*)-**5a**. However, (*S*)-**5a** was obtained from the reaction in the presence of HMPA or *N,N,N′,N′*-tetramethylethylenediamine (TMEDA). This shows that the sense of the asymmetric induction in benzylation was reversed by these additives. Crown ethers as additives showed



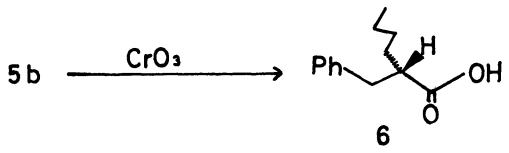
Scheme 1.

Table 1. Diastereoselective Alkylation of Diamide **3** via Metal Enolates

Entry	3	R^3X	Base	Yield of 4/%	Yield of 5/%		Ratio of 5 S:R[a]
1	**3a**	MeI	LDA	53	**5a**	33	71:29
2	**3a**	MeI	LDA:HMPA=1:2	66	**5a**	38	73:27
3	**3a**	MeI	LDA:HMPA=1:1	65	**5a**	64	81:19[b]
4	**3a**	MeI	LDA:HMPA=1:0.5	81	**5a**	59	74:26
5	**3a**	MeI	LDA:TMEDA=1:0.5	80	**5a**	66	76:24
6	**3a**	MeI	LDA:TMEDA=1:0.25	67	**5a**	27	72:28
7	**3a**	MeI	LDA:12-Crown-4=1:1	42	**5a**	59	70:30
8	**3a**	*n*-BuI	LDA	80	**5b**	38	74:26[c]
9	**3a**	*n*-BuI	LDA:HMPA=1:1	64	**5b**	32	84:16[c,d]
10	**3a**	*n*-BuI	LDA:TMEDA=1:0.5	72	**5b**	45	64:36[c]
11	**3b**	$PhCH_2Br$	LDA	81	**5a**	48	45:55
12	**3b**	$PhCH_2Br$	LDA:TMEDA=1:1	52	**5a**	45	50:50
13	**3b**	$PhCH_2Br$	LDA:TMEDA=1:0.5	41	**5a**	59	59:41
14	**3b**	$PhCH_2Br$	LDA:HMPA=1:1	58	**5a**	49	63:37
15	**3c**	MeI	LDA	72	**5a**	19	59:41
16	**3c**	MeI	LDA:HMPA=1:2	90	**5a**	14	68:32
17	**3c**	MeI	LDA:HMPA=1:1	76	**5a**	14	63:37
18	**3c**	*n*-BuI	LDA:HMPA=1:1	76	**5b**	14	82:18[c]
19	**3a**	MeI	$NaN(SiMe_3)_2$	69	**5a**	37	65:35
20	**3a**	MeI	$NaN(SiMe_3)_2$: 18-Crown-6=1:1	82	**5a**	41	70:30[e]

a) Determined by the measurement of the optical rotation. Literature value of **5a**; $[\alpha]_{578}^{22}$ −11.5° (*c* 0.5, C_6H_6). M. M. Leclercq, J. Billed, and J. Jacques, *Mol. Cryst. Liq. Cryst.*, **8**, 367 (1969). b) Observed $[\alpha]_{577}^{28}$ −7.07° (*c* 0.99, C_6H_6). c) Alcohol **5b** was oxidized to the acid **6**, and the optical rotation of **6** was measured. Lit value; $[\alpha]_D^{20}$ −22.8° (*c* 2.06, C_6H_6), M. B. Atson and G. W. Youngson, *J. Chem. Soc. C*, **1968**, 258. d) Observed $[\alpha]_D^{23}$ +15.5° (*c* 0.69, C_6H_6). e) Observed $[\alpha]_{577}^{24}$ −4.58° (*c* 1.02, C_6H_6); $[\alpha]_D^{22}$ −4.29° (*c* 0.63, C_6H_6), 39% e.e. based on lit value for 74% e.e., $[\alpha]_D^{24}$ −8.2° (*c* 4.63, C_6H_6), S. Terashima and S. Yamada, *Chem. Pharm. Bull.*, **16**, 1953 (1968).

relatively little effect. The addition of 12-crown-4 (1 molar equiv) to lithium enolate of **3a** gave **5a** (S:R=70:30, Entry 7).



6 (1)

Lithium enolate was more effective than sodium and zirconium enolates. Sodium enolate was formed using sodium disilazane, and was alkylated by methyl iodide at room temperature to give **5a** (S:R=65:35, Entry 19). The addition of 18-crown-6 (1 molar equiv) to sodium enolate gave **5a** (S:R=70:30, Entry 20). The desired product was not obtained in an attempted methylation of zirconium enolate, which had been prepared from lithium enolate using dicyclopentadienylzirconium dichloride.[1a]

Experimental

(2*S*,5*S*)-2,5-Dibenzylpiperazine (2a) was synthesized by the reduction of *cyclo*-L-Phe-L-Phe (**1a**) with sodium borohydride–titanium tetrachloride ($NaBH_4$–$TiCl_4$) according to a previously reported procedure.[2]

(2*S*,5*S*)-2,5-Diisopropylpiperazine (2b): Compound **2b** was synthesized from *cyclo*-L-Val-L-Val (**1b**) by the same procedure as above (64% yield); mp as dihydrochloride, 265.5—267.0 °C (decomp), $[\alpha]_D^{25}$ −21.1° (*c* 1, H_2O). ^1H NMR (CCl_4) δ=0.90 (dd, 12H), 1.30 (s, 2H), 2.09 (m, 4H), 2.65 (s, H, NH), 2.72 (m, 2H); IR (neat) 3000, 1540, 920 cm^{-1}; Found: *m/z* 170.1779. Calcd for $C_{10}H_{22}N_2$: M, 170.1785.

(2*S*,5*S*)-2,5-Dibenzyl-1,4-bis(3-phenylpropanoyl)piperazine (3a): To a solution of **2a** (1.697g, 5mmol) in 20ml of CH_2Cl_2 in ice-cooling bath, triethylamine (Et_3N, 1.012g, 10mmol) was added. Then, 3-phenylpropanoyl chloride (2.023g, 12mmol) in 10ml of CH_2Cl_2 and Et_3N (1.214g 12mmol) were added successively. The mixture was stirred for 1h. The cooling bath was removed and the mixture was stirred for 12h. The mixture was filtered, and the filtrate was evaporated under reduced pressure. The residue was dissolved in ethyl acetate and was washed successively with 1 M† HCl, H_2O, satd. aq $NaHCO_3$. Purification by silica-gel column chromatography (eluent EtOAc–hexane=1:2) gave **3a** as an oil in 82% yield; ^1H NMR (CCl_4) δ=2.3—2.7 (m, 14H), 4.1 (broad, 4H), 7.0 (m, 20H); IR (neat) 3050, 1640, 1420, 740 cm^{-1}; Found: *m/z* 530.2906. Calcd for $C_{36}H_{38}N_2O_2$: M, 530.2935; $[\alpha]_D^{22}$ +55.0° (*c* 1.073, EtOH).

(2*S*,5*S*)-2,5-Dibenzyl-1,4-dipropanoylpiperazine (3b): Compound **3b** was prepared by the same procedure as described above in 62% yield as an oil; ^1H NMR (CCl_4) δ=1.0 (t, 6H), 1.95 (m, 4H), 2.7 (m, 6H), 4.2 (m, 4H), 7.05 (s, 10H);

† 1 M=1 mol dm^{-3}.

IR (neat) 3000, 1640, 1430 cm^{-1}; Found: *m/z* 378.2278. Calcd for $C_{24}H_{30}N_2O_2$: M, 378.2309; $[\alpha]_D^{27}$ +64.0° (*c*1.00, EtOH).

(2*S*,5*S*)-2,5-Diisopropyl-1,4-bis(3-phenylpropanoyl)piperazine (3c): Compound **3c** was prepared by the same procedure as described for **3a** in 95% yield; ^1H NMR (CCl_4) δ=0.90 (dd, 12H), 1.68 (m, 2H), 2.45—2.83 (m, 10H), 4.05 (m, 4H), 7.05 (s, 10H); IR (neat) 2950, 1640, 1420 cm^{-1}; MS (70 eV) *m/z* 434(M^+), 391, 259, 127, 91; $[\alpha]_D^{22}$ +100.3° (*c* 1.00, EtOH).

Diastereoselective Alkylation of the Lithium Enolate Derived from 3a in the Presence of HMPA. Typical Procedure: A THF solution of lithium diisopropylamide-(LDA)[5] (0.50 M, 2.3 mmol) was added slowly to diamide (**3a**, 0.512 g, 0.96 mmol) dissolved in THF (6 ml) at −78 °C under an argon atmosphere; the mixture was stirred for 30 min at −30 °C and HMPA (0.412 g, 2.3 mmol) was added. Then, the mixture was cooled again to −78 °C. Methyl iodide (0.545 g, 3.84 mmol) was added and the mixture was stirred for 3 h, quenched with phosphoric acid buffer (pH 7), and 1 M HCl was added. The mixture was extracted with $CHCl_3$, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The purification by silica-gel TLC (developing solvent EtOAc–hexane=1 : 2) gave dialkylated diamide **4a** in 65% yield as an oil; ^1H NMR (CCl_4) δ=1.00 (s, 6H), 2.40—2.67 (m, 12H), 4.02(broad, 4H), 7.05 (s, 20H); IR (neat) 3000, 1640, 1420 cm^{-1}.

Diastereoselective Methylation of Sodium Enolate of 3a in the Presence of 18-Crown-6 (Table 1, Entry 20): A solution of sodium disilazane (1.0 M, 2.0 mmol) was slowly added to the mixture of diamide **3a** (0.264 g, 0.5 mmol) and 18-crown-6(0.529 g 2.0 mmol) dissolved in THF (3.0 ml) at room temperature under an argon atmosphere; the mixture was stirred for 30 min at room temperature. Methyl iodide (0.426 g, 3.0 mmol) was added and the mixture was then stirred over night at room temperature and worked up in the same manner as described above. Compound **4a** was obtained in 82% yield.

Preparation of Optically Active Alcohols 5a, b by the Reductive Cleavage of the Alkylated Diamide 4a—c with Lithium Hydrotriethylborate: $LiBHEt_3$ (1.0 M solution in THF, 5 ml) was added to **4** and stirred for 24 h at 35 °C; it and was then quenched with a careful addition of H_2O. The mixture was made acid with 1 M HCl. The mixture was extracted with $CHCl_3$, evaporated under reduced pressure. The residue was purified on silica gel TLC (developing solvent $CHCl_3$) followed by bulb-to-bulb distillation to afford 2-methyl-3-phenyl-1-propanol (**5a**) or 2-benzyl-1-hexanol (**5b**), respectively. The enantiomeric excess of **5a** was determined by the optical rotation of the sample. The enantiomeric excess of **5b** was determined by optical rotation after **5b** was oxidized to **6**.

(*S*)-2-Benzylhexanoic Acid (6): Chromium(VI) oxide[6] (2.32 g) in sulfuric acid (4M, 5 ml) was added to an acetone solution (2.0 ml) of **5b** in an ice cooled bath. After the mixture was stirred for 1 h, sodium sulfite (4.0 ml of 10% aq solution) was added; extraction was performed using ether. The extract was dried over anhydrous sodium sulfate, evaporated under reduced pressure. The residue was purified on silica-gel TLC (developing solvent EtOAc–hexane=1 : 1). (*S*)-**6** was obtained in 64% yield.

References

1) a) D. A. Evans, "Asymmetric Synthesis," ed by J. D. Morrison, Academic Press, New York (1984), Vol. 3, p. 11; b) W. Oppolzer, P. Dudfield, T. Stevenson, and T. Godel, *Helv. Chim. Acta*, **68**, 212 (1985).

2) K. Soai, H. Hayashi, and H. Hasegawa, *Heterocycles*, **24**, 1287 (1986).

3) T. Ueda, M. Saito, T. Kato, and N. Izumiya, *Bull. Chem. Soc. Jpn.*, **56**, 568 (1983).

4) S. Kano, Y. Tanaka, E. Sugino, and S. Hibino, *Synthesis*, **1980**, 695.

5) E. Vedejs, D. A. Engler, and J. E. Telschow, *J. Org. Chem.*, **43**, 188 (1978).

6) K. Bowden, I. M. Heilbron, and E. R. H. Jones, *J. Chem. Soc.* **1946**, 39.