Asymmetric protonation of lithium enolate using 5-substituted pyrrolidin-2-one as a chiral proton source

Hidetaka Fujihara and Kiyoshi Tomioka *

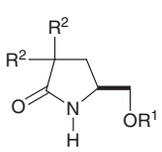
Graduate School of Pharmaceutical Sciences, Kyoto University, Yoshida, Sakyo-ku, Kyoto 606-8501, Japan

Received (in Cambridge) 26th February 1999, Accepted 4th June 1999

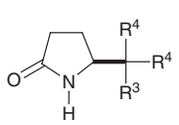
Asymmetric protonation of the lithium enolate moiety of a 2-substituted α-tetralone (3,4-dihydronaphthalen-1(2*H*)-one) was examined using 5-substituted pyrrolidin-2-ones as chiral proton sources. Among the three types of pyrrolidin-2-ones bearing either a hydroxymethyl group or steric bulk or a chelation site at the 5-position, the pyrrolidin-2-ones bearing steric bulk gave the enantiomerically enriched α-tetralone derivative in up to 72% ee.

Introduction

Enantioselective protonation of prochiral enolates represents a most useful advance in recent synthetic chemistry.[1–3] Generally, these asymmetric protonation reactions rely on the use of chiral proton sources such as an imide, phenol, alcohol, amino alcohol or amine. We have been involved in asymmetric reactions which utilize a chiral 5-substituted pyrrolidin-2-one as an auxiliary for conjugate addition of nucleophiles[4,5] or as an external ligand for organocopper.[6] The characteristic structural features of these chiral pyrrolidin-2-ones enable the conformation of the transition state to be fixed by coordination of the lactam carbonyl oxygen to a metal and also by the steric hindrance exhibited by the 5-substituent. We describe herein that 5-substituted pyrrolidin-2-ones can be utilized as chiral proton sources for enantioselective protonation of lithium enolates which give fairly good enantioselectivity.[7]



	R^1	R^2
1:	H	H
2:	Tr	H
3:	H	Me
4:	Tr	Me
5:	H	Bn
6:	Tr	Bn

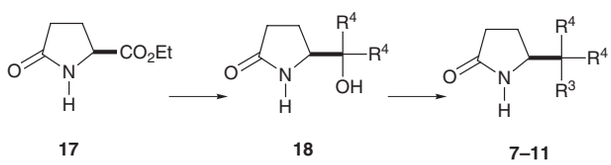


	R^3	R^4
7:	H	Ph
8:	H	3,5-Xylyl
9:	H	4-*t*-BuPh
10:	OH	Ph
11:	OTBDMS	Ph
12:	$O(CH_2)_2OMe$	H
13:	$O(CH_2)_2NBn_2$	H

Results and discussion

Synthesis of chiral 5-substituted pyrrolidin-2-ones

Three types of pyrrolidin-2-ones have been studied: (i) **1**, **3**, **5**, and **10** have a hydroxymethyl group at the 5-position; (ii) **2**, **4**, **6**–**9**, and **11** have steric bulk at the 5-position; (iii) **12** and **13** have a chelation site at the 5-position. These three types of chiral pyrrolidin-2-ones were prepared from L-glutamic acid. Lactams **1**–**6** were prepared as described previously.[4–6] The lactams **7**–**9** were prepared by Grignard reaction of ester **17**[4] followed by triethylsilane reduction of **18** without significant racemization (Scheme 1). Lactam **11** was prepared by treating **10** (**18**: R^4 = Ph) with TBDMSCl. Lactams **12** and **13** were prepared by treating the tosylate of **1** with the corresponding sodium alkoxide.

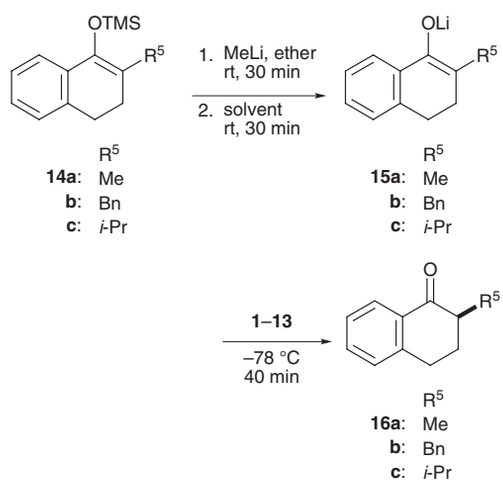


17 **18** **7–11**

Scheme 1

Asymmetric protonation of lithium enolate 15 with 1–13

The lithium enolate of α-tetralone **15** was generated from TMS enol ether **14** treated with methyllithium in ether at room temperature (rt) for 0.5 h. At this point, a solvent was added. The mixture was stirred at rt for another 0.5 h and then cooled to −78 °C. The protonation reagents **1**–**13** were added and the reaction mixture was stirred for 40 min to complete the protonation (Scheme 2). The product ketone was isolated



	R^5
14a:	Me
b:	Bn
c:	*i*-Pr

	R^5
15a:	Me
b:	Bn
c:	*i*-Pr

	R^5
16a:	Me
b:	Bn
c:	*i*-Pr

Scheme 2

through silica gel column chromatography. The ee was determined by chiral stationary phase HPLC. The absolute configuration was determined by the specific rotation. The chiral lactam was recovered for reuse in high yield without any loss of optical purity. Some of the results are summarized in Table 1.

The chiral lactam-alcohols **1**, **3**, **5**, and **10** gave **16a** (R^5 = Me) in marginal ees (Table 1, entries 1, 7, 10, 21). To our delight, the corresponding trityl ethers, **2**, **4**, **6** gave (*S*)-**16a** in 20–55% ees (entries 2, 8, 11). The solvent effect was significant (entries 2–4): toluene was superior to ether and THF, giving **16a** in 55% ee (entry 2).

The bulky dimethyl and dibenzyl substituents of **4** and **6**, introduced into **2** at the α-position of the lactam carbonyl

Table 1 Asymmetric protonation of **15** with **1**–**13** giving **16**

Entry	1–13	15	R^5	Solvent	Yield(%)	Ee(%)	*R*/*S*	Entry	1–13	15	R^5	Solvent	Yield(%)	Ee(%)	*R*/*S*
1	**1**	**a**	Me	Toluene	84	4	*S*	13	**7**	**c**	Me	Toluene	85	62	*S*
2	**2**	**a**	Me	Toluene	83	55	*S*	14	**7**	**b**	Bn	Toluene	79	54	*R*
3	**2**	**a**	Me	Ether	76	50	*S*	15	**7**	**c**	*i*-Pr	Ether	92	18	*R*
4	**2**	**a**	Me	THF	81	19	*S*	16	**8**	**a**	Me	Toluene	78	33	*S*
5	**2**	**b**	Bn	Toluene	76	55	*R*	17	**8**	**b**	Bn	Toluene	74	45	*R*
6	**2**	**c**	*i*-Pr	Ether	93	28	*R*	18	**9**	**a**	Me	Toluene	82	63	*S*
7	**3**	**a**	Me	Toluene	88	3	*S*	19	**9**	**b**	Bn	Toluene	78	64	*R*
8	**4**	**a**	Me	Toluene	87	26	*S*	20	**9**	**c**	*i*-Pr	Ether	84	38	*R*
9	**4**	**c**	*i*-Pr	Ether	85	2	*R*	21	**10**	**a**	Me	Toluene	88	6	*S*
10	**5**	**a**	Me	Toluene	81	11	*R*	22	**11**	**a**	Me	Toluene	77	45	*S*
11	**6**	**a**	Me	Toluene	88	20	*S*	23	**12**	**a**	Me	Toluene	81	39	*S*
12	**6**	**c**	*i*-Pr	Ether	99	22	*R*	24	**13**	**a**	Me	Toluene	76	39	*S*

group, were designed to direct coordination of lithium *syn* to the N–H bond. However, the steric bulk was also placed above and below the plane of the lactam ring, resulting in the loss of selectivity (entries 8–9, 11–12).

Lactams **7**–**9** were designed with the more effective steric bulk closer to the N–H bond. The most simple phenyl-lactam **7** gave 62% ee (entry 13). However, 3,5-xylyl-lactam **8** and TBDMS ether **11** gave decreased ees of 33 and 45% respectively (entries 16, 22). The best enantioselective protonation was observed using 4-*tert*-butylphenyl-lactam **9** to afford (*S*)-**16a** in 63% ee (entry 18).

We designed lactams **12** and **13** of which methoxyethoxy and dibenzylaminoethoxy moieties form a chelate with the lithium cation prior to the protonation. However, the selectivity was not high affording (*S*)-**16a** in 39% ee (entries 23, 24).

The asymmetric protonation of **15b**,**c** was also examined using the lactams. The ketone, (*R*)-**16b** (R^5 = Bn), was obtained in 45–64% ee (entries 5, 14, 17, 19). The lactam **9** again gave the best result with a 64% ee. The ketone, (*R*)-**16c** (R^5 = *i*-Pr), was obtained using lactams **2**, **4**, **6**, **7**, **9** in 18–38% ee when ether was used as the solvent (entries 6, 9, 12, 15, 20). Lactam **9** gave again the best result with 38% ee.

Protonation of **15a** with **2**, **4**, **6**–**9**, **11**–**13** led to (*S*)-**16a**: that the same absolute stereochemistry at the 5-position is obtained suggests a similar stereochemical transition state for all cases. Furthermore, protonation of **15b**,**c** gave products such that the same transition state was implied as for the reactions with **15a**.

Additive effect and importance of prior coordination

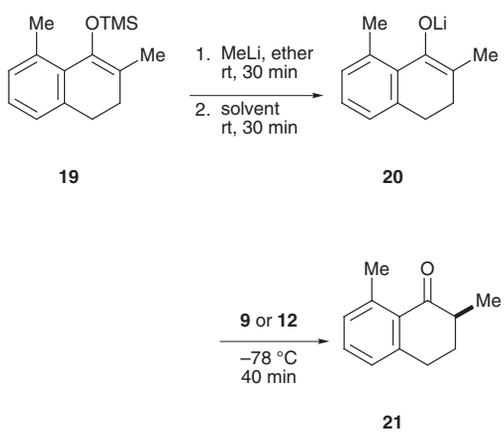
The effect of some additives was examined in the protonation of **15c** (R^5 = *i*-Pr) with **2** as summarized in Table 2. Addition of lithium bromide caused the ee to decrease (entry 2). Using a Lewis acid was also not beneficial and gave decreased selectivity, except for aluminium triisopropoxide which gave a slightly better 32% ee (entries 3–5). The effect of the lithium trapping agents, HMPA and TMEDA in toluene, also caused a significant decrease of ee (entries 7, 8). These results imply that prior coordination of the lactam carbonyl oxygen to lithium is an important step in the protonation of the lithium enolate with the lactam.

Fixation of lithium enolate conformation

It is probable that the protonation site of the enolate and the protonating N–H of the lactam come closer when the O–Li bond is placed *syn* to the 2-substituent of the enolate and the lithium is coordinated to the carbonyl oxygen of the lactam. Since it is possible to fix the orientation of the O–Li bond *syn* to the 2-substituent of the enolate by the introduction of the C8–methyl group, asymmetric protonation of **20** was examined in toluene using **9** and **12** (Scheme 3). Protonation with lactam **9** afforded **21** in 72% ee, and with **12** afforded **21** in 49% ee. Comparison of the improved 72% ee of **21** with the 63% ee obtained by the protonation of **15a** indicated that the orientation of the O–Li bond affects the selectivity.

Table 2 Additive effects on the protonation of **15c** with **2**

Entry	Solvent	Additive	Equiv.	Yield(%)	Ee(%)
1	Ether	None		93	28
2	Ether	LiBr	1.1	93	12
3	Ether	BF_3OEt_2	1.1	22	0
4	Ether	$Al(Oi\text{-}Pr)_3$	1.1	70	32
5	Ether	$Ti(Oi\text{-}Pr)_4$	1.1	74	10
6	Toluene	None		99	18
7	Toluene	HMPA	2.2	99	7
8	Toluene	TMEDA	1.1	86	6



Scheme 3

Stereochemical model for protonation with chiral pyrrolidin-2-ones

The lactams bearing an alcohol functionality behave differently from the other lactams used. Without prior coordination of lithium by the carbonyl oxygen, protonation by the alcohols **1**, **3**, **5**, and **10** proceeds using the hydroxy group as a protonating functionality to give **16a** without selectivity.

Since the coupling constants *J* are 10–11 Hz, alignment of the methine C–H of the 5-substituent with the 5-H of lactam **7**–**9** is anti-periplanar as shown in Fig. 1, which is the MM2 energy-minimized conformation of **9**. Coordination of the carbonyl oxygen to lithium would be the first step in the protonation. Subsequently, the enolate plane is placed nearly perpendicular to the lactam N–H, and the bulky part of the enolate is directed away from the 5-substituent of the lactam avoiding the steric repulsion exhibited between these moieties, as shown in **22**, to afford **21** which has stereochemistry identical with that observed. On the other hand, the model **23** leading to the antipode, suffers from steric repulsion (Scheme 4). Protonation with **2**, **4** and **6** proceeds with the same stereochemical

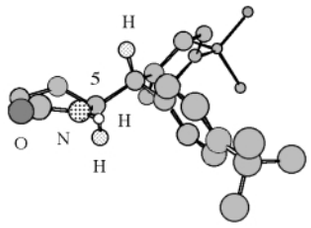
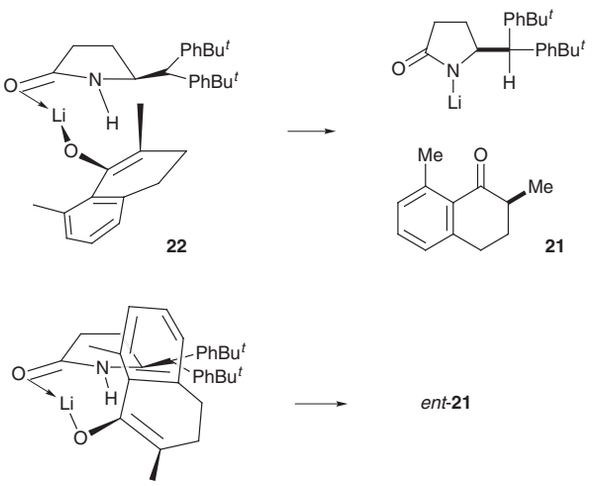


Fig. 1 Conformation of **9**.



Scheme 4

requirement. It is not clear whether the chelating moiety of lactams, **12** and **13**, is operative or not, since the same stereochemical outcome was observed with the second type of lactams bearing a bulky group.

Conclusion

Asymmetric protonation of prochiral α-tetralone lithium enolates was examined using three types of chiral 5-substituted pyrrolidin-2-ones bearing either an alcohol moiety, steric bulk or a chelation site at the 5-position. The best selectivity was obtained with lactam **9** bearing simply steric bulk at the 5-position. Further adjustment of the lactam structure may lead to a more efficient asymmetric protonation reagent, and this is currently being investigated.

Experimental

Column chromatography was carried out using silica gel. Melting points were determined using a Yamato MODEL MP-21 melting point apparatus and are not corrected. ^{1}H- (500 MHz) and ^{13}C-NMR (125 MHz) spectra were taken with a JEOL JNM LA-500 spectrometer in $CDCl_3$ unless otherwise noted. Chemical shift values are expressed in ppm (δ) relative to internal tetramethylsilane. *J* values are given in Hz. Abbreviations are as follows: s, singlet; d, doublet; t, triplet; m, multiplet. IR spectra were taken with a Shimadzu IR-435 infrared spectrometer. Mass spectra were taken with a Shimadzu GCMS-QP5000 mass spectrometer. Optical rotations were taken with a JASCO DIP-370 polarimeter.

(−)-(*S*)-5-(Hydroxydiphenylmethyl)pyrrolidin-2-one (10)

A solution of bromobenzene (15.8 cm^3, 150 mmol) in ether (20 cm^3) was added to a suspension of magnesium (3.6 g, 148 mmol) in ether (25 cm^3) at 0 °C over a period of 20 min. The resulting suspension was stirred at rt for 50 min. A solution of **17**[8] (6.0 g, 38.2 mmol) in THF (20 cm^3) was added dropwise to the mixture at 0 °C over 0.5 h, and the reaction mixture was stirred under reflux for 2 h. The mixture was quenched successively with water (100 cm^3) and acetic acid (15 cm^3) at 0 °C and was extracted with ether. The combined organic layer was washed with water and then dried over Na_2SO_4. Concentration and chromatography ($CHCl_3$–AcOEt, 2:1) gave a pale yellow solid (6.2 g, 61%). Recrystallization from EtOH gave **10** as colorless needles of mp 195–196 °C and $[\alpha]_D^{20}$ −87.3 (*c* 0.43 in $CHCl_3$).[9] IR (Nujol): 3300, 1680 cm^{-1}. ^{1}H-NMR: 1.8–2.5 (4H, m, CH_2CH_2), 3.61 (1H, s, OH), 4.71 (1H, dd, *J* 5.0, 7.9, CH), 5.42 (1H, br s, NH), 7.1–7.7 (10H, m). MS *m*/*z*: 267 (M$^+$).

(+)-(*S*)-5-(Diphenylmethyl)pyrrolidin-2-one (7)

Trifluoroborane etherate (8.3 cm^3, 67.0 mmol) was added to a solution of Et_3SiH (17.9 cm^3, 112 mmol) and **10** (6.0 g, 22.3 mmol) in CH_2Cl_2 (240 cm^3) at −20 °C over 5 min. The mixture was stirred at rt for 66 h. During this time, additional Et_3SiH (28.5 cm^3, 178 mmol) and $BF_3{\cdot}OEt_2$ (22.0 cm^3, 178 mmol) were added to complete the reaction. The reaction mixture was washed with saturated aqueous $NaHCO_3$ solution, brine, and then dried over Na_2SO_4. Concentration and chromatography ($CHCl_3$–AcOEt, 2:1) gave **7** as a white solid (4.37 g, 78%). Recrystallization from isopropanol (propan-2-ol) gave **7** as colorless plates of mp 117.5–118.5 °C and $[\alpha]_D^{20}$ +37.6 (*c* 1.88 in $CHCl_3$). IR (Nujol): 1690 cm^{-1}. ^{1}H-NMR: 1.7–2.4 (4H, m, CH_2CH_2), 3.77 (1H, d, *J* 10, $CHPh_2$), 4.41 (1H, ddd, *J* 7, 7, 10, CH), 5.56 (1H, br s, NH), 7.1–7.5 (10H, m). ^{13}C-NMR: 26.5, 30.2, 57.6, 58.5, 127.0, 127.2, 127.86, 127.93, 128.8, 129.1, 140.7, 141.6, 177.3. MS *m*/*z*: 251 (M$^+$). Found: C, 81.26; H, 6.75; N, 5.52. Calc. for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57%.

(+)-(*S*)-5-[Bis(3,5-dimethylphenyl)methyl]pyrrolidin-2-one (8)

Compound **8** was synthesized according to the same procedure for **7** in 66% yield from **17** as colorless plates of mp 165.5–166.5 °C and $[\alpha]_D^{20}$ +36.5 (*c* 2.17 in $CHCl_3$). IR (Nujol): 3200, 1690, 1600 cm^{-1}. ^{1}H-NMR: 1.7–1.85 (1H, m, CH), 2.1–2.2 (1H, m, CH_2), 2.275 (6H, s, 2 Me), 2.282 (6H, s, 2 Me), 2.3–2.4 (2H, m, CH_2), 3.59 (1H, d, *J* 11, $CHPh_2$), 4.38 (1H, ddd, *J* 7, 7, 11, CH), 5.41 (1H, br s, NH), 6.8–6.9 (6H, m). ^{13}C-NMR: 21.3, 21.4, 26.7, 30.4, 57.6, 58.4, 125.5, 125.7, 128.6, 128.8, 138.2, 138.5, 140.8, 141.8, 177.3. MS *m*/*z*: 307 (M$^+$). Found: C, 82.01; H, 8.22; N, 4.42. Calc. for $C_{21}H_{25}NO$: C, 82.04; H, 8.20; N, 4.56%.

(+)-(*S*)-5-[Bis(4-*tert*-butylphenyl)methyl]pyrrolidin-2-one (9)

Compound **9** was synthesized according to the same procedure for **7** in 67% yield from **17** as colorless plates of mp 168.5–169.5 °C and $[\alpha]_D^{20}$ +40.9 (*c* 2.02 in $CHCl_3$). IR (nujol): 3200, 1690, 1510 cm^{-1}. ^{1}H-NMR: 1.28 (18H, s, 2 *t*-Bu), 1.75–1.85 (1H, m, CH_2), 2.15–2.25 (1H, m, CH_2), 2.3–2.4 (2H, m, CH_2), 3.70 (1H, d, *J* 11, $CHPh_2$), 4.38 (1H, ddd, *J* 7, 7, 11, CH), 5.40 (1H, br s, NH), 7.15–7.35 (8H, m). ^{13}C-NMR: 26.6, 30.3, 31.3, 34.4, 57.6, 57.9, 125.6, 125.9, 127.5, 137.8, 138.8, 149.7, 150.0, 177.4. MS *m*/*z*: 363 (M$^+$). Found: C, 82.43; H, 9.26; N, 3.68. Calc. for $C_{25}H_{33}NO$: C, 82.60; H, 9.15; N, 3.85%.

(−)-(*S*)-[Diphenyl(*tert*-butyldimethylsilyloxy)methyl]pyrrolidin-2-one (11)

A solution of BuLi (6.58 cm^3, 10 mmol) in hexane was added to a solution of **10** (1.34 g, 5 mmol) in THF (40 cm^3) at −20 °C over 4 min. The solution was allowed to warm up to 10 °C for 1 h. To the mixture was added at −20 °C a solution of TBDMSCl (4.52 g, 30 mmol) in THF (5 cm^3) and the mixture was stirred at 0 °C for 30 min and at rt for 39 h. The reaction was quenched with saturated aqueous NH_4Cl solution, and was extracted with AcOEt. The combined organic layer was washed with saturated aqueous $NaHCO_3$ solution, brine and then dried over Na_2SO_4. Concentration and chromatography (benzene–AcOEt, 5:1)

gave a white solid (1.84 g, 96%). Recrystallization from isopropanol gave **11** as colorless needles of mp 163–164 °C and $[\alpha]_D^{20}$ −63.8 (*c* 1.77 in $CHCl_3$). IR (Nujol): 3200, 1690 cm^{-1}. ^{1}H-NMR: −0.39 and −0.34 (each 3H, s, Me), 0.94 (9H, s, *t*-Bu), 0.95–1.10 (1H, m, CH_2), 1.86 (1H, ddd, *J* 5, 11, 17, CH_2), 2.05–2.25 (2H, m, CH_2), 4.64 (1H, dd, *J* 3, 9, CH), 5.81 (1H, br s, NH), 7.3–7.4 (10H, m). ^{13}C-NMR: −3.29, −3.21, 18.8, 22.3, 26.1, 28.8, 59.9, 82.4, 127.7, 127.8, 128.1, 128.6, 128.8, 142.3, 142.9, 178.6. MS *m*/*z*: 324 (M^+ − *t*-Bu). Found: C, 72.10; H, 8.19; N, 3.73. Calc. for $C_{23}H_{31}NO_2Si$: C, 72.39; H, 8.19; N, 3.67%.

(+)-(*S*)-5-[(2-Methoxyethoxy)methyl]pyrrolidin-2-one (12)

2-Methoxyethanol (0.6 cm^3, 6 mmol) was added to a suspension of NaH (240 mg, 6 mmol) in THF (3 cm^3) at 0 °C over 1 min. The resulting suspension was warmed to rt and stirred for 30 min. Tosylate of **1** [8] (539 mg, 2 mmol) in THF (9 cm^3) was added to the mixture at 0 °C over 10 min. The mixture was stirred for 6 h at rt. The reaction was quenched with saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4. Concentration and chromatography (AcOEt–MeOH, 5 : 1) gave **12** (50 mg, 14%) as a pale yellow oil of $[\alpha]_D^{25}$ +65.7 (*c* 1.41 in $CHCl_3$). IR (neat): 3400, 3250, 1680 cm^{-1}. ^{1}H-NMR: 1.65–1.8 (1H, m, CH_2), 2.15–2.3 (1H, m, CH_2), 2.32 and 2.36 (each 1H, ddd, *J* 8, 8, 16, CH_2), 3.30 (1H, dd, *J* 9, 9, CH_2), 3.39 (3H, s, Me), 3.45–3.7 (5H, m, CH_2), 3.85–3.95 (1H, m, CH), 5.94 (1H, br s, NH). ^{13}C-NMR: 22.9, 29.6, 53.7, 58.9, 70.6, 71.8, 75.0, 177.8. MS *m*/*z*: 97 (M^+ − $MeOCH_2CH_2O$) Found: C, 55.54; H, 9.03; N, 8.10. Calc. for $C_8H_{15}NO_3$: C, 55.47; H, 8.73; N, 8.09%.

(+)-(*S*)-5-[(2-Dibenzylaminoethoxy)methyl]pyrrolidin-2-one (13)

Compound **13** was synthesized according to the same procedure for **12** in 10% yield as a pale yellow oil of $[\alpha]_D^{25}$ +31.9 (*c* 0.32 in $CHCl_3$). IR (neat): 3200, 1690, 1600, 1490 cm^{-1}. ^{1}H-NMR: 1.65–1.75 (1H, m, CH_2), 2.1–2.25 (1H, m, CH_2), 2.30 and 2.34 (each 1H, ddd, *J* 8, 8, 17, CH_2), 2.66 (2H, dd, *J* 6, 6, CH_2), 3.17 (1H, dd, *J* 9, 9, CH_2), 3.36 (1H, dd, *J* 4, 9, CH_2), 3.45–3.6 (2H, m, CH_2), 3.63 (4H, s, CH_2Ph), 3.7–3.85 (1H, m, CH), 5.74 (1H, br s, NH), 7.2–7.5 (10H, m). ^{13}C-NMR: 23.0, 29.6, 52.7, 53.7, 59.0, 70.0, 74.7, 126.9, 128.2, 128.7, 139.6, 177.6. MS *m*/*z*: 247 (M^+ − Bn). Found: C, 74.79; H, 7.74; N, 8.23. Calc. for $C_{21}H_{26}N_2O_2$: C, 74.52; H, 7.74; N, 8.28%.

2,8-Dimethyl-1-trimethylsilyloxy-3,4-dihydronaphthalene (19)

A solution of BuLi (3.5 cm^3, 5.5 mmol) in hexane was added to a solution of diisopropylamine (0.72 cm^3, 5.5 mmol) in THF (3 cm^3) at −78 °C over 3 min. The solution was stirred at this temperature for 30 min. A solution of **21** (0.8 g, 4.6 mmol) in THF (3 cm^3) was added at −78 °C over 5 min. After stirring at −78 °C for 1 h, TMSCl (1.17 cm^3, 9.2 mmol) was added. The mixture was stirred for 1 h at rt, and then diluted with hexane (100 cm^3) and washed successively with saturated aqueous $NaHCO_3$ solution, water, 10% citric acid, water, saturated aqueous $NaHCO_3$ solution, brine and then dried over Na_2SO_4. Concentration and chromatography (hexane) gave **19** (1.13 g, quantitative) as a colorless oil. IR (neat): 2900, 1640, 1460, 1440 cm^{-1}. ^{1}H-NMR: 0.11 (9H, s, 3 Me), 1.84 (3H, s, Me), 2.11 (2H, t, *J* 7, CH_2), 2.46 (3H, s, Me), 2.61 (2H, t, *J* 7, CH_2), 6.9–7.0 (3H, m). ^{13}C-NMR: 0.1, 17.4, 22.3, 29.3, 30.0, 119.4, 124.3, 125.7, 130.1, 132.9, 133.7, 137.9, 144.0. MS *m*/*z*: 246 (M^+). Found: C, 72.83; H, 9.14. Calc. for $C_{15}H_{22}OSi$: C, 73.11; H, 9.00%.

General procedure for protonation in toluene

A solution of MeLi (0.30 cm^3, 0.39 mmol) in ether was added to **19** (87 mg, 0.35 mmol) at 0 °C over 30 s. After stirring for 30 min at rt, toluene (3.5 cm^3) was added and the mixture was stirred at rt for another 30 min. A solution of **9** (193 mg, 0.53 mmol) in toluene (4 cm^3) was added at −78 °C over 10 min. After stirring at −78 °C for 40 min, the reaction was quenched with saturated aqueous NH_4Cl solution, and extracted with AcOEt. The combined organic layer was washed with saturated aqueous $NaHCO_3$ solution, brine, and then dried over Na_2SO_4. Concentration and chromatography (hexane–ether, 30 : 1) gave (−)-**21** (37 mg, 61%) as a colorless oil of $[\alpha]_D^{25}$ −11.0 (*c* 1.13 in dioxane). The ee was determined to be 72% by chiral stationary phase HPLC (Daicel Chiralcel OD-H, hexane, 0.4 cm^3 min^{-1}, 254 nm: minor isomer 44.1 min, major isomer 49.3 min). The absolute configuration of (−)-**21** was determined to be *R* by circular dichroism ($[\theta]_{352}$ −950 (*c* 0.033 in EtOH)).[10] IR (neat): 2900, 1675, 1590, 1460 cm^{-1}. ^{1}H-NMR: 1.24 (3H, d, *J* 7, Me), 1.75–1.9 (1H, m, CH_2), 2.1–2.2 (1H, m, CH_2), 2.5–2.65 (1H, m, CH_2), 2.63 (3H, s, Me), 2.9–3.1 (2H, m, CH_2), 7.07 (2H, d, *J* 8), 7.28 (1H, t, *J* 8). ^{13}C-NMR: 15.8, 23.2, 29.8, 31.1, 43.9, 126.7, 130.3, 131.1, 131.8, 141.2, 145.2, 202.9. MS *m*/*z*: 174 (M^+). Found: C, 82.44; H, 8.20. Calc. for $C_{12}H_{14}O$: C, 82.72; H, 8.10%.

(−)-(*S*)-16a. (Table 1, entry 22). Colorless oil (74 mg, 77%) of $[\alpha]_D^{22}$ −23.1 (*c* 2.63 in dioxane).[11] The ee was determined to be 45% by chiral stationary phase HPLC (Daicel Chiralcel OD-H, hexane–*i*-PrOH = 400 : 1, 0.4 cm^3 min^{-1}, 254 nm; minor isomer 30.6 min, major isomer 34.5 min). IR (neat): 2900, 1680, 1600 cm^{-1}. ^{1}H-NMR: 1.28 (3H, d, *J* 7, Me), 1.88 (1H, dddd, *J* 5, 10, 12, 14, CH_2), 2.20 (1H, ddd, *J* 5, 9, 14, CH_2), 2.55–2.65 (1H, m, CH), 2.85–3.15 (2H, m, CH_2), 7.0–8.1 (4H, m). ^{13}C-NMR: 15.1, 28.5, 31.1, 42.3, 126.2, 127.0, 128.4, 132.7, 132.3, 143.9, 200.3. MS *m*/*z*: 160 (M^+).

(+)-(*R*)-16b. (Table 1, entry 19). Colorless oil (92 mg, 78%) of $[\alpha]_D^{25}$ +11.8 (*c* 1.76 in MeOH).[12] The ee was determined to be 64% by chiral stationary phase HPLC (Daicel Chiralpak AS, hexane, 0.8 cm^3 min^{-1}, 254 nm; major isomer 48.4 min, minor isomer 57.6 min). IR (neat): 2900, 1680, 1600, 1500 cm^{-1}. ^{1}H-NMR: 1.79 (1H, dddd, *J* 7, 10, 12, 15, CH_2), 2.12 (1H, ddd, *J* 5, 8, 15, CH_2), 2.5–3.1 (4H, m, CH × 1, CH_2), 3.50 (1H, dd, *J* 4, 13, CH_2), 7.1–8.2 (9H, m). ^{13}C-NMR: 27.5, 28.4, 35.5, 49.2, 125.9, 126.4, 127.3, 128.2, 128.5, 129.1, 132.3, 133.0, 139.8, 143.8, 199.0. MS *m*/*z*: 236 (M^+).

(−)-(*R*)-16c. (Table 1, entry 6). Colorless oil (105 mg, 93%) of $[\alpha]_D^{25}$ −4.7 (*c* 3.8 in dioxane).[13] The ee was determined to be 28% by chiral stationary phase HPLC (Daicel Chiralpak AS, hexane, 0.5 cm^3 min^{-1}, 254 nm; major isomer 30.8 min, minor isomer 38.7 min). IR (neat): 1680 cm^{-1}. ^{1}H-NMR: 0.91 and 0.98 (each 3H, d, *J* 7 Hz, 2 Me), 1.9–2.0 (1H, m, CH_2), 2.1–2.2 (1H, m, CH_2), 2.3–2.4 and 2.5–2.6 (each 1H, m, CH), 2.9–3.1 (2H, m, CH_2), 7.2–8.1 (4H, m). ^{13}C-NMR: 18.4, 20.6, 23.4, 26.1, 28.4, 53.6, 126.4, 127.3, 128.5, 132.9, 143.8, 199.8. MS *m*/*z*: 188 (M^+).

Acknowledgements

We gratefully acknowledge financial support from the Ministry of Education, Science, Sports and Culture, JSPS (RFTF-96P00302), and the Science and Technology Agency, Japan.

References

1 For recent publications on stoichiometric protonation reactions, see: (*a*) Y. Nakamura, S. Takeuchi, Y. Ohgo, M. Yamaoka, A. Yoshida and K. Mikami, *Tetrahedron Lett.*, 1997, **38**, 2709; (*b*) H. Kosugi, K. Hoshino and H. Uda, *Tetrahedron Lett.*, 1997, **38**, 6861; (*c*) J. Martin, M.-C. Lasne, J.-C. Plaquevent and L. Duhamel, *Tetrahedron Lett.*, 1997, **38**, 7181; (*d*) H. Kosugi, M. Abe, R. Hatsuda, H. Uda and M. Kato, *Chem. Commun.*, 1997, 1857; (*e*) T. Takahashi, N. Nakao and T. Koizumi, *Tetrahedron: Asymmetry*, 1997, **8**, 3293; (*f*) G. Asensio, P. A. Aleman, L. R. Domingo and M. Medio-Simon, *Tetrahedron Lett.*, 1998, **39**, 3277.

2 For catalytic reactions, see: (*a*) A. Yanagisawa, T. Kikuchi, T. Watanabe, T. Kuribayashi and H. Yamamoto, *Synlett*, 1995, 372; (*b*) K. Ishihara, S. Nakamura, M. Kaneeda and H. Yamamoto, *J. Am. Chem. Soc.*, 1996, **118**, 12854; (*c*) Y. Nakamura, S. Takeuchi, A. Ohira and Y. Ohgo, *Tetrahedron Lett.*, 1996, **37**, 2805; (*d*) J. Muzart, F. Henin and S. J. Aboulhoda, *Tetrahedron: Asymmetry*, 1997, **8**, 381; (*e*) P. Riviere and K. Koga, *Tetrahedron Lett.*, 1997, **38**, 7589; (*f*) E. Vedejs and A. W. Kruger, *J. Org. Chem.*, 1998, **63**, 2792. For enantioselective protonation by catalytic antibodies, see: (*g*) I. Fujii, R. A. Lerner and K. D. Janda, *J. Am. Chem. Soc.*, 1991, **113**, 8528; (*h*) J.-L. Reymond, J.-L. Reber and R. A. Lerner, *Angew. Chem.*, *Int. Ed. Engl.*, 1994, **33**, 475.

3 For the use of transient enolates or enols in catalytic asymmetric protonation, see: (*a*) H. Pracejus, F.-W. Wilcke and K. Hanemann, *J. Prakt. Chem.*, 1977, **319**, 219; (*b*) N. Kobayashi, *Polym. J.*, 1981, **16**, 205; (*c*) A. Kumar, R. V. Salunkhe, R. A. Rane and S. Y. Dike, *J. Chem. Soc.*, *Chem. Commun.*, 1991, 485; (*d*) F. Toda, K. Tanaka and J. Sato, *Tetrahedron: Asymmetry*, 1993, **4**, 1771; (*e*) C. Fehr, I. Stempf and J. Galindo, *Angew. Chem.*, *Int. Ed. Engl.*, 1993, **32**, 1044; (*f*) E. Emori, T. Arai, H. Sasai and M. Shibasaki, *J. Am. Chem. Soc.*, 1998, **120**, 4043.

4 (*a*) K. Tomioka, A. Muraoka and M. Kanai, *J. Org. Chem.*, 1995, **60**, 6188; (*b*) M. Kanai,: A. Muraoka, T. Tanaka, M. Sawada, N. Ikota and K. Tomioka, *Tetrahedron Lett.*, 1995, **36**, 9349.

5 S. G. Davies, G. J.-M. Doisneau, J. C. Prodger and H. J. Sanganee, *Tetrahedron Lett.*, 1994, **35**, 2369.

6 Y. Nakagawa, M. Kanai, Y. Nagaoka and K. Tomioka, *Tetrahedron*, 1998, **54**, 10295.

7 For reviews of enantioselective protonation, see: (*a*) J. Seyden-Penne, *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*, 1995, John Wiley and Sons, Inc., New York; (*b*) C. Fehr, *Angew. Chem.*, *Int. Ed. Engl.*, 1996, **35**, 2566; (*c*) A. Yanagisawa, K. Ishihara and H. Yamamoto, *Synlett*, 1997, 411; (*d*) N. Krause, S. Ebert and A. Haubrich, *Liebigs Ann. Recl.*, 1997, 2409.

8 R. B. Silverman and M. A. Levy, *J. Org. Chem.*, 1980, **45**, 815.

9 Mp and specific rotation were identical with those reported, S. Kanao and S. Inagawa, *Yakugaku Zasshi*, 1928, **48**, 238.

10 G. Snatzke and F. Snatzke, in *Fundamental Aspects and Recent Developments in Optical Rotatory Dispersion and Circular Dichroism*, eds. F. Ciardelli and P. Salvadori, London, 1973, ch. 3.2.

11 G. Jaouen and A. Meyer, *J. Am. Chem. Soc.*, 1975, **97**, 4667; A. I. Meyers, D. R. Williams, G. W. Erickson, S. White and M. Druelinger, *J. Am. Chem. Soc.*, 1981, **103**, 3081.

12 M. Murakata, M. Nakajima and K. Koga, *J. Chem. Soc.*, *Chem. Commun.*, 1990 1657.

13 T. Yasukata and K. Koga, *Tetrahedron: Asymmetry*, 1993, **4**, 35.

Paper 9/01581G