Asymmetric Addition Reaction of Phenyllithium to 1,2-Ethylenediimine with the Aid of A Chiral Ligand

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The reaction of *N,N'*-bis(4-methoxyphenyl)ethylenediimine with phenyllithium, with the mediation of a chiral ligand, provided the addition products, (1*R*,2*R*)-*N,N'*-bis(4-methoxyphenyl)-1,2-diphenylethanediamine of 67% ee and the *meso*-product, in a ratio of 41 : 59. The net reaction involves sequential double additions of phenyllithium. In the first addition a new chiral center is created, but with rather poor selectivity, and in the second addition kinetic discrimination takes place, giving the chiral double addition product.

Key words double alkylation; asymmetric reaction; kinetic discrimination; amine; imine; ligand

We have reported the external chiral ligand-mediated asymmetric reaction of organolithiums with imines to provide the corresponding optically active amines.[1] Arylimines and furylimine are appropriate substrates, giving the corresponding product amines with high enantioselectivity. It is natural to extend the reaction to an asymmetric reaction of a diimine, giving a chiral diamine.[2] We show herein that double phenylation of 1,2-diimine provided the corresponding addition product in 67% ee.[3]

It is reasonable to assume that the first addition to *N,N'*-bis(4-methoxyphenyl)ethylenediimine (**1**) gives a chiral lithium amide (**2**) as has been shown previously,[1] and the second addition to the chelate (**2**) selectively leads to chiral **3**, not *meso*-**4**, avoiding steric repulsion of the initially introduced phenyl group in **2**.[4]

The reaction of 4 eq of phenyllithium with **1**[5] at −78 °C for 0.5 h in tetrahydrofuran (THF) gave a mixture of racemic **3** and *meso*-**4** in a ratio of 96 : 4 in 94% yield. The same reaction in toluene at −78 °C for 2 h gave a mixture of **3** and **4** in a ratio of 84 : 16 in 52% yield. The preferential formation of racemic **3** indicates the involvement of the intermediate (**2**), followed by stereoselective reaction through 1,2-asymmetric induction.

The reaction in the presence of the chiral ligand (**5**) in toluene changed the situation. A solution of 4 eq of phenyllithium was added dropwise to a mixture of **1** and 5.2 eq of the ligand (**5**) in toluene at −78 °C over a period of 10 min. Stirring for 2 h gave a mixture of **3** and **4** in a decreased ratio of 49 : 51 in 87% yield. The enantiomer excess (ee) of **3** was determined to be 63% by a chiral HPLC (Daicel Chiralcel AS and AD).[6]

The use of 1.1 eq of ligand (**5**) and 4 eq of phenyllithium gave **3** with 67% ee and the ratio of **3** and **4** was 41 : 59. The ratio of **3** and **4** was improved to 74 : 26 when the amount of the ligand was reduced to 0.3 eq. However, the product **3** was obtained with only 26% ee.

We assumed that the enantio- and diastereo-selectivities would be improved if the ligand-mediated addition of phenyllithium were to proceed enantioselectively at the first addition step, with chelated substrate-controlled addition through the chiral **2** at the second step.

To test the above hypothesis, the reaction was carried out in the presence of 1.1 eq of the ligand (**5**) using 2 eq of phenyllithium and then, after near-completion of the first addition (monitored by TLC), a large excess of THF was added in order to avoid the effects of the ligand. Then, 2 eq of phenyllithium was added to bring the reaction to completion. As we expected, the ratio of **3** : **4** was improved to 76 : 24. However, the enantioselectivity of **3** dropped to 18%.

These experimental results indicate that the first phenyllithium addition took place unselectively to give **2** of poor ee, and the second addition discriminated (*R*)- and (*S*)-**2**; (*R*)-**2** was preferentially converted to (*R,R*)-**3**, and (*S*)-**2** to (*S,R*)-*meso*-**4**.

The situation described above is shown in Fig. 3. Generally, the ligand-mediated reaction of an imine proceeds through coordination of the imine nitrogen atom to the lithium cation of the organolithium-ligand complex (**6**), giving the addition product (**8**) with high ee. However, the diimine (**1**) has two coordinating nitrogen atoms which can form a five-membered chelate, so to maintain the tetravalency of the lithium, **6** is largely converted to **7**. The complex (**7**) is sterically disordered and results in the production of **8** and **9**, with poor stereoselectivity in the first addition step.

The complexes (**8** and **9**) formed by the first addition reaction are chiral complexes in which the tetravalency of the lithium cation is satisfied through coordination by the

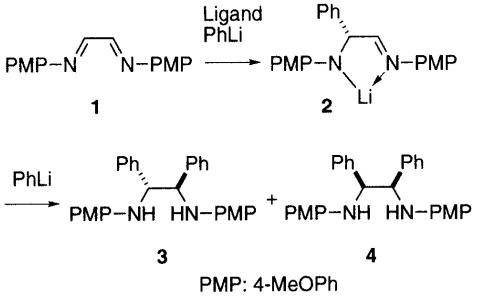

Fig. 1

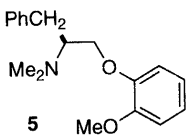

Fig. 2

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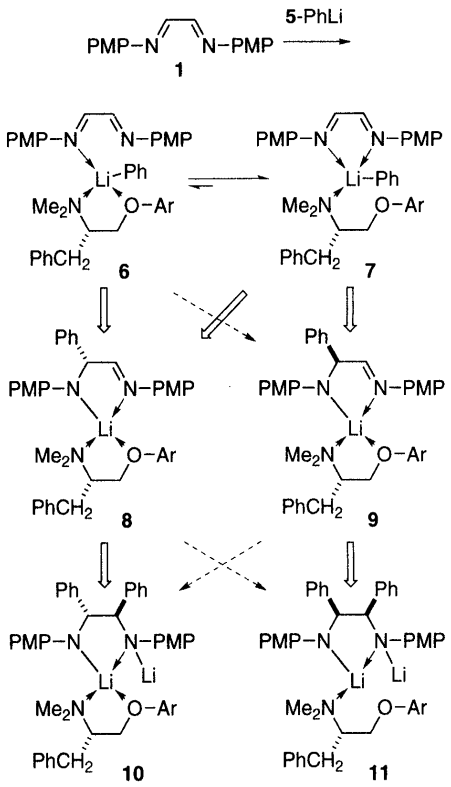

Fig. 3

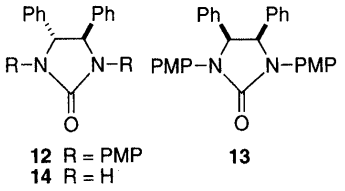

Fig. 4

imine and ligand nitrogen and oxygen atoms.

The second addition reaction takes place from **8** and **9**. The reaction from **8** takes place selectively by the combination of two control modes of 1,2-asymmetric induction and chelated ligand control to give the final product (**10**). On the other hand, directing effects by the initially created chiral center and chelated ligand in **9** are competitive, giving *meso*-**4**-ligand complex (**11**) from the reaction of **9**.

The absolute configuration of **3** was determined as follows: A 49 : 51 mixture of 38% ee-3 and *meso*-**4** was converted to the corresponding chromatographically separable cyclic ureas, (+)-**12** and *meso*-**13**, in 32 and 10% yields, respectively. Then, **12** was treated with ceric ammonium nitrate (CAN) in aqueous CH_3CN to give (+)-(*R*,*R*)-**14** of 39% ee with the established absolute configuration.[7]

In conclusion, the chiral ligand-mediated double phenylation of 1,2-ethylenediimine (**1**) provided the corresponding (*R*,*R*)-diamine **3** in 67% ee. The reaction proceeds through unselective first addition and stereoselective second addition by discrimination of diastereomeric complexes. It remains highly desirable to find a methodology for efficient asymmetric reaction of organolithiums with imines bearing several coordinating heteroatoms.

Experimental[8]

(±)-*N*,*N*′-Bis(4-methoxyphenyl)-1,2-diphenylethanediamine (3) A solution of PhLi (1.49 M, 27 ml, 40 mmol) in cyclohexane–diethyl ether was added dropwise to a suspension of diimine (**1**)[5] (2.68 g, 10.0 mmol) in THF (370 ml) at −78 °C over a period of 45 min. The whole was stirred for 5 h at the same temperature. The resulting solution was quenched with 10% aqueous HCl (100 ml) and extracted with benzene. The combined organic layer was successively washed with 10% aqueous HCl, saturated aqueous $NaHCO_3$, water, and saturated aqueous NaCl, and then dried over K_2CO_3. Concentration gave a brown oil (5.86 g, **3** : **4** = 94 : 6 by ^{1}H-NMR). Purification through silica gel column chromatography (EtOAc–benzene) gave a yellow oil. Crystallization from hexane gave racemic **3** (1.70 g, 40%) as colorless needles of mp 105.5—107.5 °C. IR (Nujol) cm^{-1}: 3350. ^{1}H-NMR δ: 3.68 (6H, s), 4.4 (2H, br s), 4.47 (2H, s), 6.58 (8H, m), 7.19 (10H, s). ^{13}C-NMR δ: 55.7, 64.9, 114.7, 115.4, 127.3, 127.3, 128.3, 140.3, 141.2, 152.4. MS *m*/*z*: 424 (M^+). *Anal.* Calcd for $C_{28}H_{28}N_2O_2$: C, 79.22; H, 6.65; N, 6.60. Found: C, 79.22; H, 6.66; N, 6.48.

(1*R*,2*R*)-*N*,*N*′-Bis(4-methoxyphenyl)-1,2-diphenylethanediamine (3) and *meso*-*N*,*N*′-Bis(4-methoxyphenyl)-1,2-diphenylethanediamine (4) A solution of PhLi (0.9 M, 1.4 ml, 1.2 mmol) in cyclohexane-diethyl ether was added dropwise to a suspension of **1** (81 mg, 0.30 mmol) and the amino ether (**5**) (94 mg, 0.33 mmol) in toluene (12 ml) at −78 °C over a period of 15 min. The whole was stirred for 2 h at the same temperature. The resulting solution was quenched with saturated aqueous NH_4Cl (10 ml) and extracted with benzene (3 × 10 ml). The combined organic layer was successively washed with saturated aqueous $NaHCO_3$, and saturated aqueous NaCl, and then dried over K_2CO_3. Concentration gave a red oil (282 mg). Purification through silica gel column chromatography (EtOAc–benzene) gave a mixture of **3** and **4** as a yellow oil (101 mg, 79%), and **5** (quant.). The ratio of **3** and **4** was determined to be 42 : 58 by ^{1}H-NMR δ: 3.68 (6H, s), 4.4 (2H, br s), 4.47 (0.42 × 2H, s), 4.87 (0.58 × 2H, s), 6.58 (8H, m), 7.19 (10H, s). The ratio of the minor enantiomer of **3**, *meso*-**4**, and the major enantiomer of **3** was determined to be 6.9 : 58.8 : 34.3 by HPLC (Daicel Chiralcel AS + AD, iso-PrOH/hexane = 1/15, 0.6 ml/min, 254 nm, 54.3 min for the minor enantiomer of **3**, 60.2 min for **4**, 66.5 min for the major enantiomer of **3**).

(+)-(4*R*,5*R*)-*N*,*N*′-Bis(4-methoxyphenyl)-4,5-diphenylimidazolidin-2-one (12) and *cis*-*N*,*N*′-Bis(4-methoxyphenyl)-4,5-diphenylimidazolidin-2-one (13) A hexane solution of BuLi (1.60 M, 2.3 ml, 3.7 mmol) was added dropwise to a 49 : 51 mixture of **3** (39% ee) and **4** (667 mg, 1.57 mmol) in THF (15 ml) at −42 °C. The whole was stirred at −42 °C for 0.5 h. Then, $NCCO_2Et$ (0.23 ml, 2.3 mmol) was added to the above mixture at −42 °C over a period of 2 min, and the whole was stirred at −42 °C for 2.5 h. The resulting solution was quenched with water (20 ml), and then extracted with CH_2Cl_2 (3 × 20 ml). The combined organic layer was successively washed with 10% aqueous HCl, saturated aqueous $NaHCO_3$ × 2, and saturated aqueous NaCl, and then dried over K_2CO_3. Concentration gave a brown oil (770 mg). Purification through silica gel column chromatography (acetone-hexane) gave (+)-**12** (227 mg, 65%) as a white solid and **13** (72 mg, 14%) as a white solid.

12: mp 179—180 °C; $[\alpha]_D^{25}$ +20.9° (*c* = 1.00, $CHCl_3$). IR ($CHCl_3$) cm^{-1}: 1690. ^{1}H-NMR δ: 3.72 (6H, s), 4.93 (2H, s), 6.77 (4H, m), 7.26 (10H, s), 7.30 (4H, m). ^{13}C-NMR δ: 55.3, 67.6, 114.0, 122.8, 126.5, 128.4, 129.1, 131.9, 139.4, 156.1, 156.5. FAB-MS *m*/*z*: 451 ($M^+ + 1$). *Anal.* Calcd for $C_{29}H_{26}N_2O_3$: C, 77.31; H, 5.82; N, 6.22. Found: C, 77.56; H, 5.85; N 6.02. The ratio of enantiomers was determined to be 69.6 : 30.4 by HPLC (Tosoh, enantioP1, iso-PrOH/hexane = 1/200, 1.2 ml/min, 254 nm, 17.9 min for the major enantiomer and 20.7 min for the minor enantiomer).

13: mp 166—166.5 °C. IR (nujol) cm^{-1}: 1685. ^{1}H-NMR δ: 3.72 (6H, s), 5.57 (2H, s), 6.77 (4H, m), 6.86 (4H, m), 7.00 (6H, m), 7.34 (4H, m). ^{13}C-NMR δ: 55.3, 63.8, 113.9, 122.6, 127.6, 127.7, 127.9, 132.0, 135.2, 155.9, 157.5. EI-MS *m*/*z*: 450 (M^+). HRMS *m*/*z*: Calcd for $C_{29}H_{26}N_2O_3$: 450.1945. Found: 450.1947.

(+)-(4*R*,5*R*)-4,5-Diphenylimidazolidin-2-one (14) A solution of CAN (1.40 g, 2.6 mmol) in water (10 ml) was added dropwise to a solution of (+)-**12** obtained above (191 mg, 0.42 mmol) in acetonitrile (43 ml) at 0 °C over a period of 30 min. The whole was stirred at the same temperature for 40 min. After addition of water (50 ml), the mixture was extracted with EtOAc (3 × 50 ml). The combined EtOAc extracts were successively washed with saturated aqueous $Na_2S_2O_3$ × 3, saturated aqueous $NaHCO_3$ × 2, water, and saturated aqueous NaCl, and then dried over $MgSO_4$. Concentration gave a brown solid (164 mg). Purification through

silica gel column chromatography (acetone–benzene) gave (+)-**14** (51 mg, 50%) as a white solid of mp 184—190 °C. IR ($CHCl_3$) cm^{-1}: 3450, 3225 (br), 3010, 1710, 700. ^{1}H-NMR δ: 4.60 (2H, s), 4.78 (2H, br s), 7.26 (6H, m), 7.35 (4H, m). ^{13}C-NMR δ: 66.0, 126.5, 128.5, 128.9, 139.8, 163.1. The IR, ^{1}H-, and ^{13}C-NMR data were in good agreement with those reported for enantiomerically pure **14**.

The absolute configuration of the major enantiomer was determined to be 4*R*,5*R* from the specific optical rotation $[\alpha]_D^{21}$ +21.3° (c=0.16, $CHCl_3$), 36% optical purity, +58.6° (c=1.06, $CHCl_3$) for optically pure (+)-(4*R*,5*R*)-**14**).[7]

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8) Melting points were measured using a Yamato MP-21 melting point apparatus and are not corrected. Optical rotations were taken with a Jasco DIP-370 polarimeter. IR spectra were taken with a Hitachi infrared spectrometer model 260-10. ^{1}H-NMR spectra were taken with a JEOL GX-270 spectrometer at 270 MHz, or a Hitachi R-90H spectrometer at 90 MHz, in $CDCl_3$ unless otherwise noted. ^{13}C-NMR spectra were taken with a JEOL GX-270 spectrometer at 67 MHz in $CDCl_3$ unless otherwise noted. Chemical shift values are expressed in ppm relative to internal tetramethylsilane. Abbreviations are as follows: s, singlet; d, doublet; t, triplet; m, multiplet. MS were taken with a JEOL-01, SG-2 mass spectrometer or a JEOL DX-300 mass spectrometer.