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A Novel Method for Stereoselective Synthesis of (*1R,2R*)-Diarylethylenediamines by Reductive Intramolecular Coupling of Aromatic Diimines

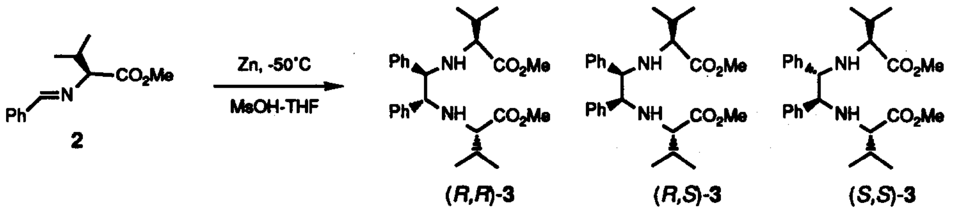
Tatsuya Shono,* Naoki Kise, Hideaki Oike, Masami Yoshimoto, and Eiichi Okazaki

Department of Synthetic Chemistry, Faculty of Engineering,
Kyoto University, Yoshida, Sakyo, Kyoto 606-01, Japan

Abstract: Reduction with zinc has been found to be an effective method for selective synthesis of (*1R,2R*)-diarylethylenediamines from the corresponding chiral aromatic diimines through their intramolecular coupling.

Although bis-sulfonamides of chiral 1,2-diphenylethylenediamine (**1**) have extensively been used as chiral catalysts for enantioselective syntheses,[1] the chiral **1** has generally been prepared by optical resolution of dl-**1**.[1a,2] On the other hand, reductive intermolecular coupling of imines has been known to be one of the useful methods for the synthesis of **1** and a variety of metal reducing agents have already been reported.[3] In these studies, however, the diastereoselectivity has been reported to be not always satisfactory[4] and, moreover, enatioselective coupling of imines has never been reported. In the present study, we have found that the synthesis of (*1R,2R*)-diarylethylenediamines was effectively achieved by diastereoselective intramolecular coupling of chiral aromatic diimines promoted by reduction with zinc powder.

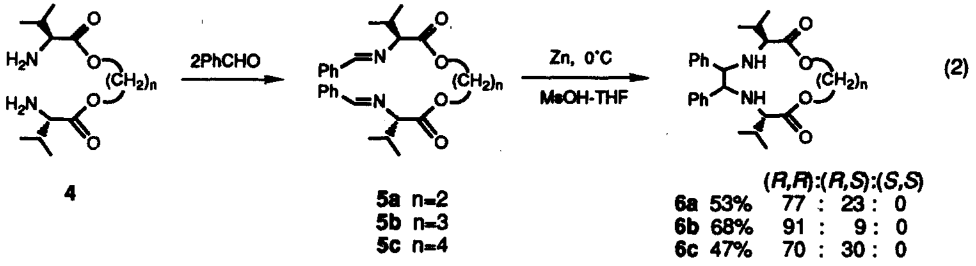
In the first place, the intermolecular coupling of chiral imine **2**, prepared from (*S*)-valine methyl ester, was investigated by using zinc as the reducing agent (eq. 1). The stereoselectivity was, however, not satisfactory, though the coupling gave the (*R,R*)-**3** as the main product.[5]



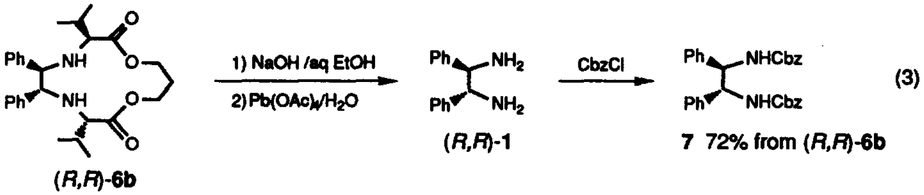
(1)

3 84% (*R,R*):(*R,S*):(*S,S*)=63:30:7

In the next place, the ester moieties of two molecules of **2** were linked by a carbon chain to transform the intermolecular coupling of imines to the intramolecular coupling of diimines **5**[6] (eq. 2).[7] As summarized in eq. 2, the stereoselectivity in the coupling of **5** was influenced by the length of carbon chain, though (*R,R*)-**6** was always the main isomer and (*S,S*)-**6** was not formed at all. The best selectivity (91%) was obtained in the case of n=3. Transformation of (*R,R*)-**6b** to (*R,R*)-**1** was achieved by its hydrolysis followed by oxidation with $Pb(OAc)_4$ (eq. 3).[8] This intramolecular coupling was also effective to synthesis of other (*1R,2R*)-diarylethylenediamines as shown in Table 1.

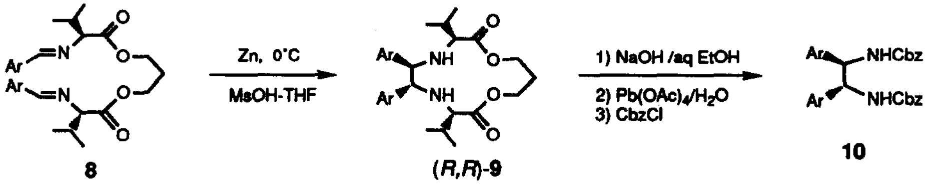


		(R,R):(R,S):(S,S)
6a	53%	77 : 23 : 0
6b	68%	91 : 9 : 0
6c	47%	70 : 30 : 0



7 72% from (*R*,*R*)-6b

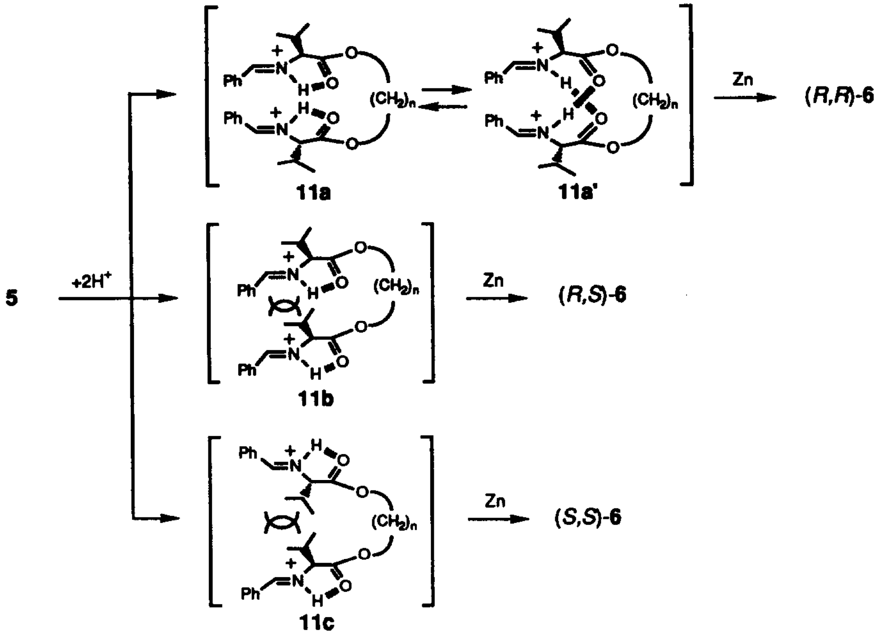
Table 1. Stereoselective Synthesis of (*1R*,*2R*)-Diarylethylenediamines



8	Ar	Yield of 9[a]	(*R*,*R*)-9:(*R*,*S*)-9[b]	Yield of 10[c]
8a	p-$MeOC_6H_4$	9a 68	97 : 3	10a 71
8b	p-ClC_6H_4	9b 63	89 : 11	10b 73
8c	p-NCC_6H_4	9c 59	72 : 28	10c 57

a. Isolated yields. b. Determined by 1H NMR spectra. See ref. 9.
c. Isolated yields. See ref. 10.

The high stereoselectivity in the coupling of **5** is explained by steric interaction of isopropyl groups in the diprotonated intermediate (**11**) (Scheme 1). Three types (**11a**, **b**, and **c**) may be depicted for the intermediates. Among them, the steric crowding seems maximum in **11c** leading to (*S*,*S*)-**6**, while minimum in **11a** which yields (*R*,*R*)-**6**. On the other hand, the steric crowding is also influenced by the chain length between two ester moieties. Thus, when n is 2, it increases even in the case of **11a**, while it decreases even in the case of **11b** when n is 4. Hence, the best selectivity was obtained when n was 3. The fact that the proton-bridged intermediate **11** is important in determination of the stereoselectivity is also supported by the effect of substituent located on the p-position of the aryl group as it is summarized in Table 1. Namely, the electron donating substituent gave the best selectivity, while the selectivity decreased when the substituents were electron withdrawing.[11]



Scheme 1

References and Notes

1. For recent reports: (a) Corey, E. J.; Imwinkelried, R.; Pikul, S.; Xiang, Y. B. *J. Am. Chem. Soc.*, **1989**, *111*, 5493. (b) Corey, E. J.; Yu, C.-M.; Lee, D.-H. *J. Am. Chem. Soc.*, **1990**, *112*, 878. (c) Corey, E. J.; Kim, S. S. *J. Am. Chem. Soc.*, **1990**, *112*, 4976. (d) Corey, E. J.; Lee, D.-H. *J. Am. Chem. Soc.*, **1991**, *113*, 4076.
2. (a) Williams, O. F.; Bailar, J. C. Jr. *J. Am. Chem. Soc.*, **1959**, *81*, 4464. (b) Saigo, K.; Kubota, N.; Takebayashi, S.; Hasegawa, M. *Bull. Chem. Soc. Jpn.*, **1986**, *99*, 931.
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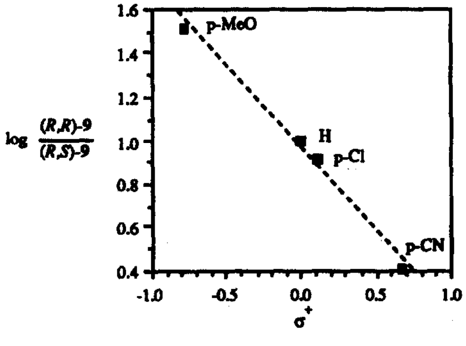
4. High *dl*-selectivity (>90%) was reported in some cases.[3a,d]
5. The diastereomeric ratio in **3** was determined by ^{1}H NMR spectra (200 MHz, $CDCl_3$). The chemical shifts (δ values) of methoxy groups (singlet) in **3** were as follows: (*R,R*)-**3** 3.65; (*R,S*)-**3** 3.43 and 3.60; (*S,S*)-**3** 3.25. (*R,R*)-**3** could be isolated by column chromatography on silica gel and its stereoconfiguration was confirmed by the same method as shown in eq. 3. (*R,R*)-**3**: mp 93-95 °C; $[\alpha]_D^{20}$ -107 (c 1.0, $CHCl_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.41 (q, 2 C), 18.53 (q, 2 C), 30.68 (d, 2 C), 50.50 (q, 2 C), 63.88 (d, 2 C), 66.86 (d, 2 C), 126.17 (d, 2 C), 126.95 (d, 4 C), 127.68 (d, 4 C), 140.36 (s, 2 C), 175.29 (s, 2 C).
6. Diamines **4** were prepared from (*S*)-*N*-methoxycarbonylvaline (2 equiv.) and 1,n-diols (1 equiv.) by esterification with DCC in THF and following *N*-deprotection with HBr/AcOH. Diimines **5** were obtained from benzaldehyde and **4** by stirring at room temperature for 6 h in CH_2Cl_2 containing $MgSO_4$.
7. General procedure is as follows: To a solution of **5** (2 mmol) in THF (20 mL) was added MsOH (0.96 g,

10 mmol) and zinc powder (0.65 g, 10 mmol) at 0 °C and the suspension was stirred for 12 h at the same temperature. After addition of 50 mL of sat. NaHCO$_3$ aq, the mixture was extracted with CH$_2$Cl$_2$. The product **6** was isolated by column chromatography on silica gel (hexane-AcOEt). The ratios of stereoisomers of **6** were determined by ^{1}H NMR spectra (200 MHz, CDCl$_3$). The chemical shifts (δ values) of methine protons (doublet) adjacent to carbonyl group in **6** were as follows: (*R,R*)-**6a** 2.86; (*R,S*)-**6a** 2.71 and 3.15; (*R,R*)-**6b** 2.95; (*R,S*)-**6b** 2.97 and 3.16; (*R,R*)-**6c** 2.80; (*R,S*)-**6c** 2.73 and 3.19. (*R,R*)-**6** were further purified by recrystalization from hexane-AcOEt. (*R,R*)-**6a**: mp 148 °C; $[\alpha]_D^{20}$ -204 (c 1.0, CHCl$_3$); ^{13}C NMR (50 MHz, CDCl$_3$) δ 18.92 (q, 2 C), 19.17 (q, 2 C), 31.07 (d, 2 C), 61.39 (t, 2 C), 67.83 (d, 2 C), 68.55 (d, 2 C), 127.01 (d, 2 C), 127.40 (d, 4 C), 128.46 (d, 4 C), 139.60 (s, 2 C), 175.62 (s, 2 C). (*R,R*)-**6b**: mp 103 °C; $[\alpha]_D^{20}$ -145 (c 1.0, CHCl$_3$); ^{13}C NMR (50 MHz, CDCl$_3$) δ 18.37 (q, 2 C), 19.06 (q, 2 C), 27.50 (t, 1 C), 31.65 (d, 2 C), 63.49 (t, 2 C), 67.80 (d, 2 C), 69.12 (d, 2 C), 126.97 (d, 2 C), 127.48 (d, 4 C), 128.61 (d, 4 C), 140.33 (s, 2 C), 174.94 (s, 2 C). (*R,R*)-**6c**: mp 142-143 °C; $[\alpha]_D^{20}$ -169 (c 1.0, CHCl$_3$); ^{13}C NMR (50 MHz, CDCl$_3$) δ 18.68 (q, 2 C), 18.98 (q, 2 C), 27.10 (t, 2 C), 31.28 (d, 2 C), 62.96 (t, 2 C), 66.95 (d, 2 C), 68.30 (d, 2 C), 127.17 (d, 2 C), 127.31 (d, 4 C), 128.89 (d, 4 C), 139.16 (s, 2 C), 174.17 (s, 2 C).

8. In order to make the purification easy, (*R,R*)-**1** was isolated as bis-benzylcarbamate **7**. Optical rotation of **7** was consistent with that of the sample prepared from authentic (*R,R*)-**1**.[2] **7**: mp 193-194 °C; $[\alpha]_D^{20}$ -13 (c 1.0, CHCl$_3$). (*R,S*)-**6** was transformed to *meso*-**1** by the same method as shown in eq. 3.
9. The ratios and stereoconfigurations of **9** were determined on the basis of their ^{1}H NMR spectra (200MHz, CDCl$_3$). The chemical shifts (δ values) of methine protons (doublet) adjacent to carbonyl group in **9** were as follows: (*R,R*)-**9a** 2.92; (*R,S*)-**9a** 2.92 and 3.14; (*R,R*)-**9b** 2.88; (*R,S*)-**9b** 2.86 and 3.13; (*R,R*)-**9c** 2.85; (*R,S*)-**9c** 2.82 and 3.13. (*R,R*)-**9** were further purified by recrystalization from hexane-AcOEt. (*R,R*)-**9a**: mp 75 °C; $[\alpha]_D^{20}$ -159 (c 1.0, CHCl$_3$); ^{13}C NMR (50 MHz, CDCl$_3$) δ 18.33 (q, 2 C), 19.10 (q, 2 C), 27.50 (t, 1 C), 31.54 (d, 2 C), 54.94 (q, 2 C), 63.57 (t, 2 C), 67.55 (d, 2 C), 68.19 (d, 2 C), 112.71 (d, 4 C), 128.66 (d, 4 C), 132.25 (s, 2 C), 158.60 (s, 2 C), 175.20 (s, 2 C). (*R,R*)-**9b**: mp 128 °C; $[\alpha]_D^{20}$ -189 (c 1.0, CHCl$_3$); ^{13}C NMR (50 MHz, CDCl$_3$) δ 18.26 (q, 2 C), 19.17 (q, 2 C), 27.57 (t, 1 C), 31.59 (d, 2 C), 63.79 (t, 2 C), 67.60 (d, 2 C), 68.11 (d, 2 C), 127.81 (d, 4 C), 129.92 (d, 4 C), 132.98 (s, 2 C), 138.22 (s, 2 C), 174.90 (s, 2 C). (*R,R*)-**9c**: mp 193-194 °C; $[\alpha]_D^{20}$ -221 (c 1.0, CHCl$_3$); ^{13}C NMR (50 MHz, CDCl$_3$) δ 18.26 (q, 2 C), 19.17 (q, 2 C), 27.55 (t. 1 C), 31.65 (d, 2 C), 63.93 (t, 2 C), 67.69 (d, 2 C), 68.40 (d, 2 C), 111.40 (s, 2 C), 118.75 (s, 2 C), 129.12 (d, 4 C), 131.63 (d, 4 C), 144.84 (s, 2 C), 174.51 (s, 2 C).
10. **10a**: mp 214 °C; $[\alpha]_D^{20}$ -18 (c 1.0, CHCl$_3$). **10b**: mp 215 °C; $[\alpha]_D^{20}$ +13 (c 1.0, CHCl$_3$). **10c**: mp 176 °C; $[\alpha]_D^{20}$ +39 (c 1.0, CHCl$_3$)
11. A plot of log (*R,R*)-**9**/(*R,S*)-**9** versus the Hammett's constants σ^+ showed a good linear correlation (slope: ~-0.8) as depicted in the following figure.



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