New Chiral Auxiliary; 4,5-Diphenyl-1-methyl-2-imidazolidinone. Its Utility in Highly Enantioselective Aldol Reaction

Wongsiri SANKHAVASI,† Makoto YAMAMOTO, Shigeo KOHMOTO, and Kazutoshi YAMADA*
Department of Materials Science, Faculty of Engineering, Chiba University,
1-33 Yayoi-cho, Chiba 260
†Graduate School of Science and Technology, Chiba University,
1-33 Yayoi-cho, Chiba 260
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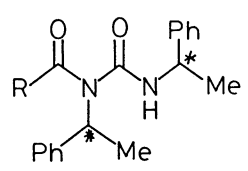
Synopsis. The aldol reaction of the boron enolate bearing the titled chiral auxiliary proceeded with high face selectivity.

In the last few years, we have investigated the utility of acyclic urea (**1**) in enantioselective Diels-Alder[1] and aldol reactions.[2] Though the stereoselectivity observed in these reactions was moderate, the urea auxiliary possessed excellent separability[1-3] so that we could obtain both of enantiomerically pure forms of the products. In order to gain absolute asymmetric induction in a modified system, we have designed the new recyclable chiral auxiliary, 4,5-diphenyl-1-methyl-2-imidazolidinone (**2**).[4] Owing to the rigidity and the planarity of five-membered ring of **2**, complete *syn* selectivity ($\geqslant$ 99% de) was resulted in this aldol addition reaction.



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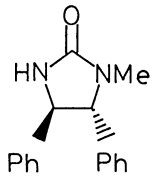
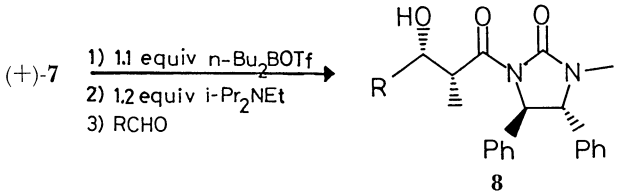


(+)-**2**

N-propionyl derivative (+)-(**7**) was prepared from (+)-(1*R*,2*R*)-1,2-diphenyl-1,2-ethanediamine (**3**) in three steps. Initially, **3** and urea (**4**) were heated with few drops of H_2O at 200 °C for 2 h to give 2-imidazolidinone (**5**) in 87% yield.[5] Monoacylated product (**6**) was obtained by treatment of **5** with 2 equiv of *n*-BuLi (−10 °C, THF) followed by stirring with 1 equiv of propionyl chloride at ambient temperature (84%).[4] The last step was carried out by deprotonation of **6** (*n*-BuLi, 1 equiv, −10 °C, THF) and methylation with excess of methyl iodide (r.t., 79%).

Our first attempt to investigate the utility and the limitations of this chiral auxiliary was made on an aldol reaction. Enolization of **7** with *n*-Bu_2BOTf (1.1 equiv)[6] and *N*,*N*-diisopropylethylamine (*i*-Pr_2NEt, 1.2 equiv) at 0 °C for 30 min, and subsequent addition of aldehydes (1—3 equiv, −73 °C then slowly warmed to room temperature) afforded only optically active syn aldol adduct (**8**). The results are summarized in Table 1. Good yields were obtained with benzaldehyde and 2-naphthaldehyde (Entries 1 and 3). In the case of benzaldehyde, triethylamine also worked well

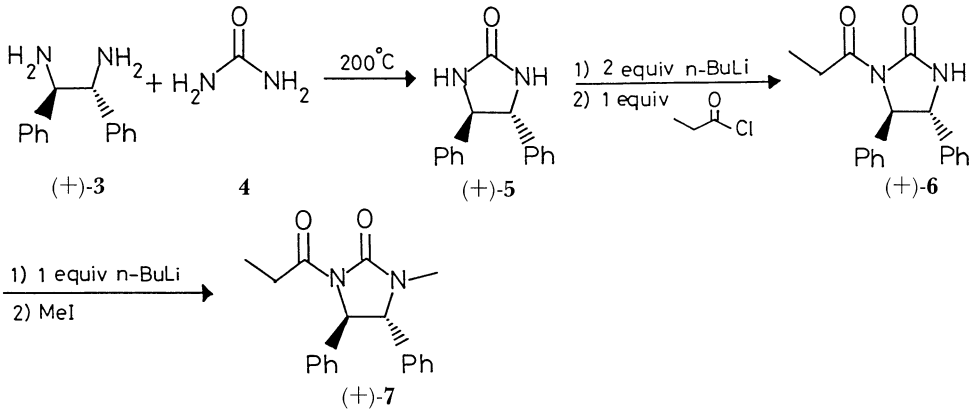


Scheme 2.

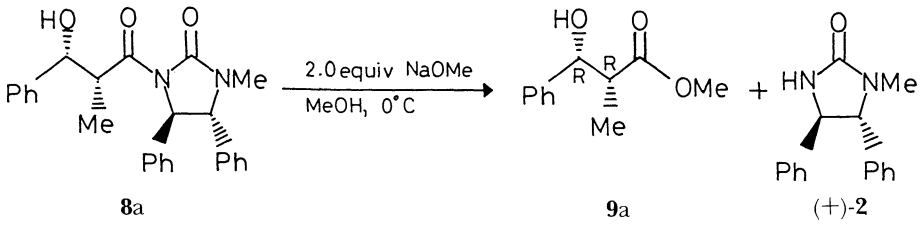
Table 1. Aldol Reaction of **7** with Aldehydes

Entry	RCHO	Yield[a]/%	de of **8**[b]/%
1	PhCHO (**8a**)	66	$\geqslant$ 99
2	PhCHO[c] (**8a**)	72	$\geqslant$ 99
3	2-NaphCHO (**8b**)	69	$\geqslant$ 99
4	MeCHO (**8c**)	48	$\geqslant$ 99
5	EtCHO (**8d**)	38	$\geqslant$ 99
6	CH_2=CHCHO (**8e**)	23	$\geqslant$ 99

a) Isolated yield after chromatography. b) Determined by 500 MHz ^{1}H NMR spectroscopy. c) The amine used was Et_3N.



Scheme 1.



8a 9a (+)-2

Scheme 3.

as a base (Entries 1 and 2). The lower yields with acetaldehyde and propionaldehyde (Entries 4 and 5) may be due to the presence of their active α hydrogens. Because of the long reaction time, acrylaldehyde might polimerize before to react with boron enolate, which resulted in only 23% yield of the aldol adduct (Entry 6). This chiral 2-imidazolidinone boron enolate did not react with hindered 2,2-dimethylpropionaldehyde.

An aldol reaction of **6** was also examined under similar conditions (2.2 equiv *n*-Bu_2BOTf, 2.3 equiv *i*-Pr_2NEt) but merely the recovery of the starting material was observed.

The absolute stereochemical assignment of aldol (**8a**) was firmly established by comparison of the optical rotation of methyl ester (**9a**) with the literature value (Scheme 2)[7,8] after methanolysis of it with sodium methoxide (2 equiv, 0 °C then r.t., 17 h, MeOH). In a similar manner all aldol adducts were attested to have syn stereochemistry.

From the results above we propose that the boron enolate formed should have *Z*-geometry as in the oxazolidinone system and the observed stereoselectivity can be rationalized by the transition state model proposed by Evans.[8]

These results demonstrate that chiral 2-imidazolidinone has the comparable efficacy in asymmetric induction as a 2-oxazolidinone,[8] oxazolidine,[9] 2-oxazolidinethione,[10] or prolinol.[9]

Experimental

Melting points were determined on a Yanaco MP-S3 apparatus and are uncorrected. Infrared spectrum were run on a JASCO A-202 infrared spectrophotometer. ^1H NMR spectra were recorded on a Hitachi R-600, JOEL JNM-GX270, JNM-FX270, GSX-400, and GSX-500 spectrometers. ^{13}C NMR spectra were recorded on a JEOL JNM-GX270 and JNM-FX270 spectrometers. Chemical shifts are reported in ppm downfield from trimethylsilane and splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Mass spectra were taken with a Hitachi RMU-7M mass spectrometer at 70 eV. Optical rotations were recorded at 21 °C on a JASCO DIP-140 Digital Polarimeter. Tetrahydrofuran (THF) was distilled from lithium aluminium hydride and stored over molecular sieves 5A 1/16. Dichloromethane was distilled from calcium hydride and stored over molecular sieves 5A 1/16. Diisopropylethylamine and triethylamine were used after simple distillation. The purity of all the aldol adducts were shown to be diastereomerically pure by HPLC and ^1H NMR spectroscopy.

Preparation of (4*R*,5*R*)-4,5-Diphenyl-2-imidazolidinone (5). (1*R*,2*R*)-1,2-Diphenyl-1,2-ethanediamine **3** (0.606 g, 2.86 mmol), urea **4** (0.172 g, 2.86 mmol), and H_2O (5 drops) were reflux at 200 °C for 2 h. Flash chromatography (ethyl acetate) of the residue gave 0.590 g (87%) of **5**; mp 196.0—197.5 °C; $[\alpha]_D^{22}$ +58.6° (*c* 1.06, $CHCl_3$); IR ($CHCl_3$) 3460, 3250 (broad), 3010, 1710, and 700 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ=4.55 (s, 2H), 5.85 (br s, 2H) 7.33 (s, 10H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ=66.0, 126.5, 128.3, 128.8, 140.2, 163.0; HRMS Found: *m/z* 238.1098. Calcd for $C_{15}H_{14}N_2O$: 238.1107. Found: C, 75.33; H, 5.93; N, 11.75%. Calcd for $C_{15}H_{14}N_2O$: C, 75.60; H, 5.92; N, 11.76%.

Preparation of (4*R*,5*R*)-4,5-Diphenyl-1-propionyl-2-imidazolidinone (6). To a solution of **5** (0.856 g, 3.60 mmol) in 20 ml of THF, butyllithium (1.55 M in hexane (1 M=1 mol dm^{-3}), 4.60 ml, 7.13 mmol) was added drpowise at −10 °C and stirred for 30 min before propionyl chloride (0.330 g, 3.57 mmol) was added. The reaction temperature was gradually raised to room temperature and stirring was continued overnight. After quenching the reaction mixture with saturated aqueous ammonium chloride, the solution was diluted with dichloromethane and the organic layer was separated. The aqueous layer was extracted with dichloromethane (20 ml×2) and the combined organic layer was dried ($MgSO_4$) and evaporated. Flash chromatography (ethyl acetate-hexane) gave white solid **6** (0.885 g, 84%); mp 120.0—121.0 °C; $[\alpha]_D^{22}$ +98.6° (*c* 0.29, $CHCl_3$); IR ($CHCl_3$) 3475, 3280, 3230, 1740, 1695, 1455, 1374, 1340, 1280, and 700 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ=1.02 (t, *J*=7.6 Hz, 3H), 2.91 (q, *J*=7.6 Hz, 2H), 4.48 (d, *J*=3.4 Hz, 1H), 5.10 (d, *J*=3.4 Hz, 1H), 6.65 (br s, 1H), 7.31 (s, 10H); ^{13}C NMR ($CDCl_3$) δ=8.4, 29.4, 61.0, 66.1, 125.5, 125.6, 128.2, 128.7, 129.1, 129.3, 140.8, 140.9, 156.4, 174.0; HRMS Found: *m/z* 294.1371. Calcd for $C_{18}H_{18}N_2O_3$: 294.1369. Found C, 73.32; H, 6.17; N, 9.55%. Calcd for $C_{18}H_{18}N_2O_3$: C, 73.45; H, 6.16; N, 9.52%.

Preparation of (4*R*,5*R*)-4,5-Diphenyl-1-methyl-3-propionyl-2-imidazolidinone (7). Butyllithium (1.58 M in hexane, 0.75 ml, 1.18 mmol) was added to a solution of **6** (0.317 g, 1.08 mmol) in THF (10 ml) at −10 °C. The mixture was stirred for 30 min and methyl iodide (0.296 g, 2.09 mmol) was added. The temperature was raised to ambient temperature and stirred overnight. Work up with saturated aqueous ammonium chloride and extraction with dichloromethane (10 ml×2) before flash chromatography (ethyl acetate-hexane) afforded **7** (0.262 g, 79%); mp 67.5—69.5 °C; $[\alpha]_D^{21}$ +119.6° (*c* 0.76, $CHCl_3$); IR ($CHCl_3$) 3040, 1733, 1670, 1430, 1390, 1195, 1150, and 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ=1.13 (t, *J*=7.3 Hz, 3H), 2.79 (s, 3H), 3.06 (q, *J*=7.3 Hz, 2H), 4.26 (d, *J*=3.6 Hz, 1H), 5.05 (d, *J*=3.6 Hz, 1H), 7.16—7.43 (m, 10H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ=8.6, 29.1, 29.4, 63.5, 67.4, 125.4, 126.2, 128.1, 129.0, 129.1, 129.4, 138.6, 141.0, 155.0, 174.0; MS *m/z* (rel intensity, %) 308 (M^+, 83), 251 (79), 175 (23), 132 (100), 120 (49), 118 (38), 91 (20), 77 (20), 57 (20), 29 (20). Found; C, 73.86; H, 6.56; N, 9.05%. Calcd for $C_{19}H_{20}N_2O_3$: C, 74.00; H, 6.54; N, 9.09%.

General Procedure for the Aldol Addition of 7. To a solution of **7** (0.2 mmol) in dichloromethane (0.2—0.5 M) at 0 °C were added dibutylboron triflate (1 M in dichloromethane, 1.1 equiv) and diisopropylethylamine (1.2 equiv).

The mixture was stirred at 0 °C for 30 min and cooled to −73 °C, and the solution of the corresponding aldehyde in dichloromethane (1—2 equiv) was added. After stirring at −73 °C for 2 h, the mixture was slowly warmed to ambient temperature and stirred overnight. The mixture was quenched with phosphate buffer (pH 7) and diluted with ether. The layers were separated, the aqueous layer was extracted with ether (4 ml×2), and the solvent was removed on a rotary evaporator. The residue was dissolved in 3 ml of methanol and cooled to 0 °C, and 1 ml of 30% H_2O_2 was added dropwise. After 60 min at 0 °C, 3 ml of water was added and the methanol was removed in vacuo. The aqueous layer was extracted with ether (3 ml×3) and the combined organic layer was washed with saturated aqueous sodium hydrogencarbonate (3 ml), and brine (3 ml), and dried ($MgSO_4$). After evaporation of the solvent, the crude product was purified by flash chromatography (ethyl acetate-hexane) to give the corresponding aldol adducts.

(4*R*,5*R*)-3-[(2*R*,3*R*)-3-Hydroxy-2-methyl-1-oxo-3-phenylpropyl]-4,5-diphenyl-1-methyl-2-imidazolidinone (8a). Yield 66%. Colorless glass; $[\alpha]_D^{22}$ +45.4° (*c* 0.32, $CHCl_3$); IR ($CHCl_3$) 3510, 3070, 3010, 2945, 1720, 1665, 1450, 1430, 1380, 1360, and 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ=1.15 (d, *J*=7.2 Hz, 3H), 2.77 (s, 3H), 3.42 (d, *J*=2.2 Hz, 1H, OH), 4.23 (d, *J*=3.8 Hz, 1H), 4.42 (dq, *J*=3.6, 7.2 Hz, 1H), 5.0 (d, *J*=3.6 Hz, 1H), 5.1 (m, 1H), 7.08—7.44 (m, 15H); ^{13}C NMR (125 MHz, $CDCl_3$) δ=11.0, 29.1, 44.4, 63.4, 67.2, 73.3, 124.9, 126.2, 127.1, 128.1, 128.3, 129.0, 138.2, 140.4, 141.6, 154.3, 177.2. HRMS Found: *m/z* 414.1954. Calcd for $C_{26}H_{26}N_2O_3$: 414.1945.

(4*R*,5*R*)-3-[(2*R*,3*R*)-3-Hydroxy-2-methyl-3-(2-naphthyl)-1-oxopropyl]-4,5-diphenyl-1-methyl-2-imidazolidinone (8b). Yield 69%. White solid; mp 171.0—172.5 °C, $[\alpha]_D^{22}$ +22.9° (*c* 0.19, $CHCl_3$); IR ($CHCl_3$) 3510, 3025, 1725, 1665, 1382, 1360, and 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ=1.19 (d, *J*=7.0 Hz, 3H), 2.75 (s, 3H), 3.57 (br s, 1H, OH), 4.20 (d, *J*=3.8 Hz, 1H), 4.57 (dq, *J*=3.7, 7.0 Hz, 1H), 5.04 (d, *J*=3.8 Hz, 1H), 5.29 (d, *J*=3.7 Hz, 1H), 7.00—7.91 (m, 17H); ^{13}C NMR (125 MHz, $CDCl_3$) δ=11.3, 29.1, 44.2, 63.4, 67.1, 73.5, 124.4, 124.9, 125.0, 125.6, 125.9, 126.1, 127.6, 127.8, 128.1, 128.2, 128.9, 129.2, 129.4, 132.8, 133.2, 138.1, 139.1, 140.3, 154.3, 177.0. HRMS Found: *m/z* 464.2089. Calcd for $C_{30}H_{28}N_2O_3$: 464.2101. Found: C, 77.39; H, 6.15; N, 5.99%. Calcd for $C_{30}H_{28}N_2O_3$: C, 77.56; H, 6.08; N, 6.03%.

(4*R*,5*R*)-3-[(2*R*,3*S*)-3-Hydroxy-2-methyl-1-oxobutyl]-4,5-diphenyl-1-methyl-2-imidazolidinone (8c). Yield 48%. Colorless oil; IR ($CHCl_3$) 3525, 3010, 2950, 2900, 1728, 1665, 1445, 1430, 1390, 1280, 1240, 930, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ=1.19 (d, *J*=6.6 Hz, 3H), 1.23 (d, *J*=7.1 Hz, 3H), 2.79 (s, 3H), 3.28 (br s, 1H), 4.03 (dq, *J*=2.6, 7.1 Hz, 1H), 4.16 (dq, *J*=2.6, 6.6 Hz, 1H), 4.26 (d, *J*=3.8 Hz, 1H), 5.08 (d, *J*=3.8 Hz, 1H), 7.18—7.44 (m, 10H); ^{13}C NMR (68 MHz, $CDCl_3$) δ=10.7, 19.3, 29.1, 43.1, 63.5, 67.2, 67.6, 124.9, 126.2, 128.2, 129.0, 129.2, 129.4, 138.2, 140.4, 154.6, 177.4. HRMS Found: *m/z* 352.1789. Calcd for $C_{21}H_{24}N_2O_3$: 352.1788.

(4*R*,5*R*)-3-[(2*R*,3*S*)-3-Hydroxy-2-methyl-1-oxopentyl]-4,5-diphenyl-1-methyl-2-imidazolidinone (8d). White solid; IR ($CHCl_3$) 3510, 3020, 2975, 1730, 1663, 1454, 1428, 1389, and 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ=0.99 (t, *J*=7.4 Hz, 3H), 1.22 (d, *J*=7.2 Hz, 3H), 1.45 (m, 1H), 1.58 (m, 1H), 2.79 (s, 3H), 3.23 (br s, 1H, OH), 3.86 (m, 1H), 4.09 (dq, *J*=2.2, 7.2 Hz, 1H), 4.25 (d, *J*=3.8 Hz, 1H), 5.08 (d, *J*=3.8 Hz, 1H), 7.18—7.45 (m, 10H); ^{13}C NMR (68 MHz, $CDCl_3$) δ=10.5, 10.6, 26.5, 29.2, 41.6, 63.5, 67.2, 72.9, 76.5, 124.9, 125.0, 126.0, 126.2, 128.2, 129.1, 129.2, 129.5, 129.6, 138.2, 140.5, 154.5, 177.9. HRMS Found: *m/z* 366.1933. Calcd for $C_{22}H_{26}N_2O_3$: 366.1945.

(4*R*,5*R*)-3-[(2*R*,3*S*)-3-Hydroxy-2-methyl-1-oxo-4-butenyl]-4,5-diphenyl-1-methyl-2-imidazolidinone (8e). Colorless oil. IR ($CHCl_3$) 3500, 3010, 1725, 1660, 1450, 1425, 1390, 923, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ=1.21 (d, *J*=7.0 Hz, 3H), 2.79 (s, 3H), 3.20, (br s, 1H), 4.17 (dq, *J*=3.1, 7.0 Hz, 1H), 4.26 (d, *J*=3.8 Hz, 1H), 4.52 (br m, 1H), 5.09 (d, *J*=3.8 Hz, 1H), 5.20 (ddd, *J*=1.6, 1.6, 10.4 Hz, 1H), 5.36 (ddd, *J*=1.6, 1.6, 17.0 Hz, 1H), 5.85 (ddd, *J*=5.2, 10.4, 17.0 Hz, 1H), 7.17—7.45 (m, *J*=10 Hz). HRMS Found: *m/z* 364.1779. Calcd for $C_{22}H_{24}N_2O_3$: 366.1788.

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6) The addition reaction of lithium and magnesium enolate with benzaldehyde was performed but the remarkable selectivity was not observed. Nevertheless, all of the diastereomers could be purified by high-performance liquid chromatography.

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