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EFFICIENT PREPARATION OF 2-IMIDAZOLINES FROM ALDEHYDES AND ETHYLENEDIAMINES WITH 1,3-DIIODO-5,5-DIMETHYLHYDANTOIN

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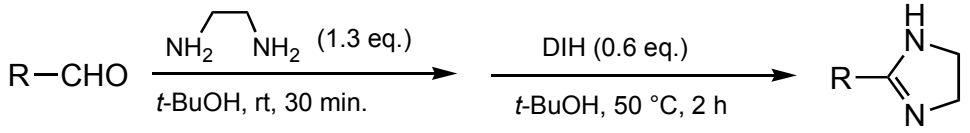
Abstract - Various 2-imidazolines were prepared in high yields by reacting aldehydes and ethylenediamines with 1,3-diiodo-5,5-dimethylhydantoin. Moreover, chiral 1,3-bis(imidazolin-2'-yl)benzene and 2,6-bis(imidazolin-2'-yl)-pyridines, which function as a chiral ligand, could be directly obtained from corresponding dialdehydes in high yields.

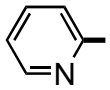
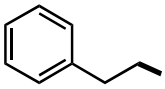
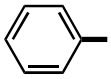
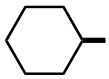
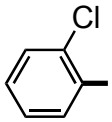
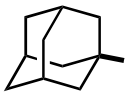
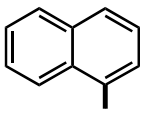
Dedicated to Professor Ryoji Noyori on the occasion of his 70th birthday.

The imidazoline ring is a very important unit due to its potent pharmacological activity[1] *i.e.,* tolazoline,[1d] xylometazoline,[1f] and synthetic utility as a chiral ligand.[2] There are many synthetic methods for the preparation of 2-imidazolines starting from nitriles and esters.[3] However, methods for the preparation of 2-imidazolines from aldehydes and ethylenediamine are limited. Recently, the direct preparation of 2-imidazolines from aldehydes and ethylenediamine using NBS[4] and pyridinium hydrobromide perbromide[5] was reported. We also reported the preparation of 2-imidazolines from aldehydes and ethylenediamine with molecular iodine[6] or *t*-butyl hypochlorite.[7] The yield of 2-alkylimidazolines was low when aliphatic aldehydes were reacted with molecular iodine. In contrast, the yield of 2-arylimidazolines was high when aromatic aldehydes were reacted with molecular iodine. On the other hand, *t*-butyl hypochlorite could be used for the efficient preparation of both 2-arylimidazolines and 2-alkylimidazolines when aldehydes and ethylenediamine were used as starting materials. Here, as part of our basic study of the utility of molecular iodine and related iodine reagents for organic synthesis,[8] we would like to report another efficient and practical method for the oxidative conversion of aldehydes into 2-arylimidazolines and 2-alkylimidazolines by reacting aldehydes and ethylenediamine with 1,3-diiodo-5,5-dimethylhydantoin (DIH). DIH has low toxicity, however, to the best of our knowledge, the synthetic use of DIH for organic synthesis is extremely limited, *i.e.*, iodination of aromatics[9] and oxidative conversion of alcohols into nitriles.[10] DIH is a pale yellow solid and does not sublimate like

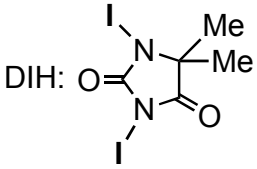
molecular iodine; thus it is more convenient to use than molecular iodine or *t*-butyl hypochlorite. The addition of DIH (0.6 eq.) to a mixture of 4-nitrobenzaldehyde (1.0 eq.) and ethylenediamine (1.3 eq.) in *t*-BuOH provided corresponding 2-(4-nitrophenyl)imidazoline quantitatively, as shown in Table 1 (entry 1). Based on these conditions, various aromatic and aliphatic aldehydes were treated with ethylenediamine and DIH in *t*-BuOH under the same conditions to provide corresponding 2-arylimidazolines and 2-alkylimidazolines in quite good yields (entries 3~20). When *N*-iodosuccinimide (NIS, 1.1 eq.) was used instead of DIH, corresponding 2-imidazoline was obtained in good yield like NBS (entry 2). However, DIH is more effective and practical than NIS, because DIH works efficiently with a half amount.

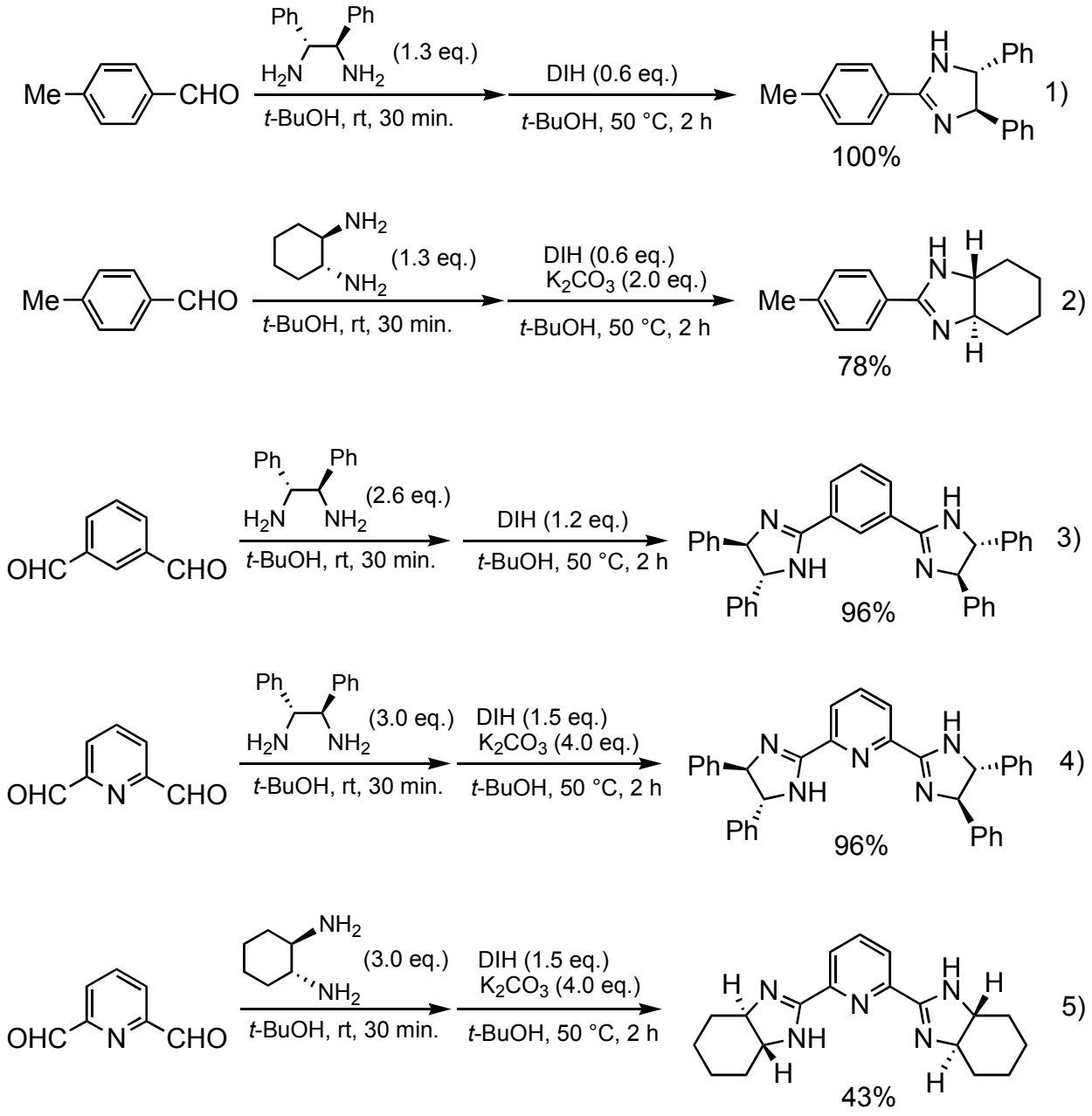
Table 1. Preparation of 2-Imidazolines from Aldehydes with DIH



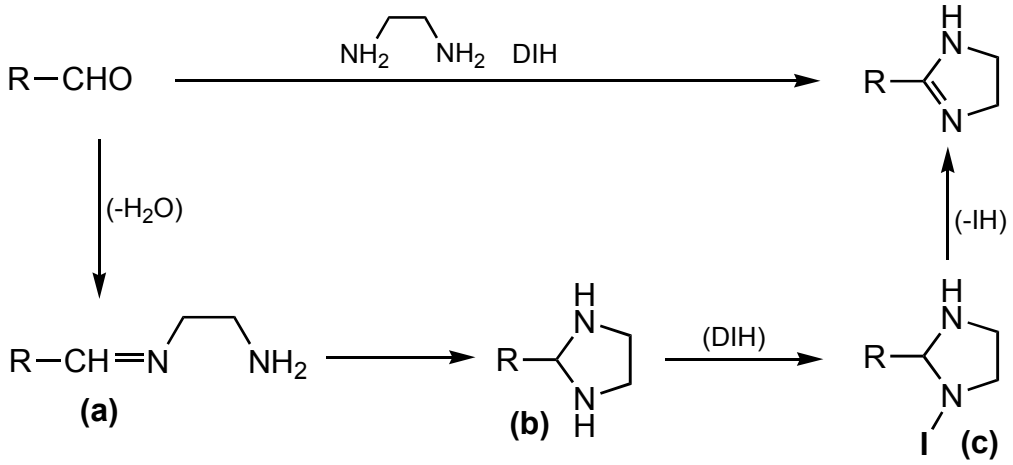
Entry	R—	Yield (%)	Entry	R—	Yield (%)
1	O_2N—	93	11		86
2[a]		95	12[a]		94
3	NC—	90	13		90
4	Br—	94	14		28
			15[b]		78
5		96	16	$Me(CH_2)_6$—	86
6	Me—	97	17	Me_3C—	36
			18[b]		81
7	MeO—	95	19[b]		77
8		86			
9[b]		94	20		90
10		96			

[a] NIS (1.1 eq.) was used, instead of DIH.
[b] K_2CO_3 (2.0 eq.) was added at 2nd step.





The same treatment of 4-tolualdehyde with (*R,R*)-(+)-diphenylethylenediamine and (*R,R*)-(-)-1,2-cyclohexanediamine provided corresponding (*4R,5R*)-2-(4'-methylphenyl)-4,5- diphenylimidazoline and (*4R,5R*)-2-(4'-mehthylphenyl)-4,5-tetramethyleneimidazoline, respectively, in good yields (eqs. 1, 2). Then, 1,3-benzenedialdehyde and 2,6-pyridinedialdehyde were treated with (*R,R*)-(+)-diphenylethylene diamine and (*R,R*)-(-)-1,2-cyclohexanediamine using DIH under the same conditions to provide corresponding 1,3-bis(imidazolin-2'-yl)benzene and 2,6-bis(imidazolin-2' -yl)pyridines, respectively, in good yields, which are known as a chiral ligand (eqs. 3~5). Recently, 2,6-bis(imidazolin-2'-yl)pyridine was prepared from 2,6-dicyanopyridine in two steps.[2e] However, the present method gave a high yield in a single step using commercially available 2,6-pyridinedialdehyde. The possible reaction mechanism is shown in Scheme 1. N-iodination of cyclic amine **(b)** with DIH occurs, followed by β-elimination of **(c)** to form corresponding 2-imidazoline.



Scheme 1. Possible Reaction Mechanism

In summary, various 2-aryl- and 2-alkylimidazolines could be easily obtained in good yields by reacting aldehydes and ethylenediamine with DIH. Moreover, 1,3-bis(imidazolin-2'-yl)benzene and 2,6-bis(imidazolin-2'-yl)pyridines, which function as a chiral ligand, could be directly prepared from corresponding dialdehydes in high yields. DIH is a pale yellow solid and it is convenient to use in the reaction. Thus, the present method using DIH may become another simple and useful means for the preparation of 2-imidazolines from aldehydes.

EXPERIMENTAL

Typical Procedure for Preparation of 2-Imidazolines from Aldehydes with DIH

To a solution of *p*-tolualdehyde (120.2 mg, 1 mmol) in *t*-butyl alcohol (10 mL) was added ethylenediamine (78.1 mg, 1.1 mmol). The obtained mixture was stirred at rt under argon atmosphere for 30 min, and then 1,3-diiodo-5,5-dimethylhydantoin (DIH) (228.0 mg, 0.6 mmol) was added and the mixture was stirred at 50 °C. After 2 h, the reaction mixture was quenched with sat. aq. Na_2SO_3 until iodine color disappeared, and was extracted with $CHCl_3$. The organic layer was washed with sat. aq. K_2CO_3 and brine, and dried over Na_2SO_4. After filtration, the mixture was evaporated to provide 155.4 mg of 2-(4'-methylphenyl)imidazoline in 97% yield in an almost pure state. If necessary, the product was purified by flash column chromatography on neutral silica gel (eluent: $CHCl_3/Et_3N$ = 10/1) to give pure 2-(4'-methylphenyl)imidazoline.

2-(Phenyl)imidazoline. mp 101.5-102 °C (*lit.*[11]: mp 100-101 °C); IR (KBr): 3200, 2930, 1600, 1510, 1270, 985, 695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 3.90 (s, 4H), 7.46 (t, *J* = 7.2 Hz, 2H), 7.57 (t, *J* = 7.2 Hz, 1H), 7.95 (d, *J* = 7.2 Hz, 2H).

2-(4'-Methylphenyl)imidazoline, mp 181-182 °C (*lit.*[11]: mp 181 °C): IR (KBr): 3140, 2925, 1600, 1495, 985, 830 cm^{-1}. ^1H NMR (400MHz, $CDCl_3$): δ = 2.38 (s, 3H), 3.77 (s, 4H), 7.21 (d, *J* = 8.3 Hz, 2H), 7.67 (d, *J* = 8.3 Hz, 2H).

2-(4'-Methoxyphenyl)imidazoline. mp 136-138 °C (*lit.*[12]: mp 137-139 °C); IR (KBr): 3120, 2830,

1605, 1490, 1255, 1035, 845 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 3.77 (s, 4H), 3.84 (s, 3H), 6.91 (d, *J* = 8.9 Hz, 2H), 7.73 (d, *J* = 8.9 Hz, 2H).

2-(4'-Bromophenyl)imidazoline. mp 177-177.5 °C ; IR (KBr): 3150, 2930, 1610, 1470, 1270, 1010, 835 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 3.79 (s, 4H), 7.54 (d, *J* = 8.7 Hz, 2H), 7.65 (d, *J* = 8.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) d = 125.0, 128.5, 129.4, 131.6, 163.8; HRMS (FAB); Obsd M+H = 225.0021. Calcd for $C_9H_{10}N_2Br$ M+H = 225.0027.

2-(4'-Nitrophenyl)imidazoline. mp 235-237 °C (*lit.*[13]: mp 231 °C); IR (KBr): 3180, 2935, 1580, 1520, 1335, 1105, 855 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ =3.85 (s, 4H), 7.95 (d, *J* = 8.9 Hz, 2H), 8.27 (d, *J* = 8.9 Hz, 2H).

2-(4'-Cyanophenyl)imidazoline. mp 195-196 °C ; IR (KBr): 3160, 2230, 1595, 1490, 1275, 985, 850 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 3.83 (s, 4H), 7.70 (d, *J* = 8.5 Hz, 2H), 7.88 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 114.2, 118.4, 127.7, 132.4, 134.7, 163.2; HRMS (FAB) Obsd M+H = 172.0883. Calcd for $C_{10}H_{10}N_3$ M+H = 172.0875.

2-(2'-Chlorophenyl)imidazoline. mp 83 °C (*lit.*[14]: mp 69-70 °C); IR (KBr): 3100, 2920, 1610, 1505, 1260, 985, 765 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 3.80 (s, 4H), 7.28-7.41 (m, 3H), 7.78 (dd, *J* = 7.5 and 1.9 Hz Hz, 1H).

2-(2'-Pyridyl)imidazoline. mp 95-96 °C; IR (KBr): 3270, 1595, 1505, 1280, 975, 805, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 3.85 (s, 4H), 7.36 (dd, *J* = 4.8 and 1.2 Hz, 1H), 7.77 (td, *J* = 7.8 and 0.7 Hz, 1H), 8.14 (d, *J* = 7.8 Hz, 1H), 8.57 (dt, *J* = 4.8 and 0.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 50.4, 122.2, 125.0, 136.5, 148.5, 148.6, 164.2; HRMS (FAB); Obsd M+H = 148.0876. Calcd for $C_8H_{10}N_3$ M+H = 148.0875.

2-(1'-Naphthyl)imidazoline. mp 131-133 °C (*lit.*[15]: mp 134 °C); IR (KBr): 3140, 2860, 1570, 1515, 1270, 980, 775 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 3.89 (s, 4H), 7.45-7.57 (m, 3H), 7.75 (dd, *J* = 7.1 and 1.2 Hz, 1H), 7.85-7.91 (m, 2H), 8.68 (d, *J* = 8.5 Hz, 1H).

2-(1'-Adamantyl)imidazoline. mp 162.5-163.5 °C; IR (KBr): 3230, 3000, 1590, 1495, 1250, 1085, 980 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.69-1.77 (m, 6H), 1.86-1.87 (m, 6H), 2.03 (m, 3H), 3.56 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 28.1, 35.1, 36.5, 40.3, 49.4, 174.5; HRMS (FAB); Obsd M+H = 205.1703. Calcd for $C_{13}H_{21}N_2$ M+H = 205.1705.

2-Cyclohexylimidazoline. mp 130.5-131 °C (lit.[11]: mp 134 °C); IR (paraffin): 3085, 1600, 1510, 1275, 1060, 980 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.16-1.43 (m, 5H), 1.67-1.92 (m, 5H), 2.22 (tt, *J* = 11.5 and 3.4 Hz, 1H), 3.56 (s, 4H).

2-(2'-Phenylethyl)imidazoline. mp 101-103 °C; IR (KBr): 3160, 2925, 1605, 1500, 1285, 960, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 2.54 (t, *J* = 8.0 Hz, 2H), 2.96 (t, *J* = 8.0 Hz, 2H), 3.55 (br s, 4H), 7.21-7.36 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 31.3, 32.9, 126.3, 128.3, 128.6, 141.1, 167.2; HRMS (FAB); Obsd M+H = 175.1237. Calcd for $C_{11}H_{15}N_2$ M+H = 175.1235.

2-Heptylimidazoline. mp 62 °C; IR (paraffin): 3182, 1612, 1493, 1291, 973, 723 cm^{-1}; ^1H NMR (400MHz, $CDCl_3$): δ = 0.87 (t, 3H), 1.27-1.32 (m, 8H), 1.61 (m, 2H), 2.22 (t, 2H), 3.57 (s, 4H); HRMS (FAB); Obsd M+H = 169.1705. Calcd for $C_{10}H_{21}N_2$ M+H = 169.1705.

2-^{t}Butylimidazoline. mp 122-124 °C; IR (paraffin): 3175, 1600, 1498, 1294, 1274, 1180, 977 cm^{-1}; ^1H NMR (400MHz, $CDCl_3$): δ = 1.22 (s, 9H), 3.58 (s, 4H); HRMS (FAB); Obsd M+H = 127.1235. Calcd for $C_7H_{15}N_2$ M+H = 127.1231.

(*4R,5R*)-2-(4'-Methylphenyl)-4,5-diphenylimidazoline. mp 146.5 °C; IR (paraffin): 3150, 1600, 1130, 1020, 830, 765, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 2.43 (s, 3H), 4.75 (br, 1H), 5.07 (br, 1H), 5.33 (br, 1H), 7.26-7.37 (m, 12H), 7.84 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 21.4, 126.7, 127.3, 127.4, 128.6, 129.2, 143.6, 163.0; HRMS (FAB); Obsd M+H = 313.1676. Calcd for $C_{22}H_{21}N_2$ M+H = 313.1705.

(*4R,4R*)-2-(4'-methylphenyl)-4,5-tetramethyleneimidazoline. mp 170-172 °C; IR (paraffin): 3111, 1557, 1511, 1256, 1223, 828, 731 cm^{-1}; ^1H NMR (400MHz, $CDCl_3$): δ = 1.34-1.42 (m, 2H), 1.51-1.61 (m, 2H), 1.84 (m, 2H), 2.30 (d, 2H), 2.38 (s, 3H), 3.07-3.16 (m, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 7.68 (d, *J* = 8.0 Hz, 2H); HRMS (FAB); Obsd M+H = 215.1548. Calcd for $C_{14}H_{18}N_2$ M+H = 215.1539.

1,3-Bis[(*4'R,5'R*)-4',5'-diphenyl-2'-imidazolin-2'-yl]benzene. mp 136.5-138 °C; IR (neat): 3062, 1570, 1493, 1452, 1270, 754, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ =4.93 (br s, 4H), 7.28-7.37 (m, 20H), 7.57 (t, *J* = 7.8 Hz, 1H), 8.11 (d, *J* = 7.8 Hz, 2H), 8.50 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ =126.1, 126.6, 127.6, 128.7, 128.9, 129.0, 130.4, 143.1, 162.4; HRMS (FAB); Obsd M+H =519.2513. Calcd for $C_{36}H_{31}N_4$ M+H =519.2549.

2,6-Bis[(*4'R,5'R*)-4',5'-diphenyl-2'-imidazolin-2'-yl]pyridine. mp 124-125 °C (*lit.*[2e]: 123-126 °C); IR (neat): 3028, 1606, 1564, 1452, 999, 752, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 4.79 (d, *J* = 8.7 Hz, 2H), 5.20 (d, *J* = 8.7 Hz, 2H), 6.42 (br s, 2H), 7.25-7.35 (m, 20 H), 7.98 (t, *J* = 7.8 Hz, 1H), 8.48 (d, *J* = 7.8 Hz, 2H).

2,6-Bis[(*4'R,5'R*)-4',5'-tetramethyleneimidazolin-2'-yl]pyridine. mp 302 °C; IR (paraffin): 3336, 1586, 1560, 1223, 722, 653, 622 cm^{-1}; ^1H NMR (400MHz, $CDCl_3$): δ = 1.27-1.68 (m, 8H), 1.87 (t, 4H), 2.23 (d, 2H), 2.43 (d, 2H), 3.10 (t,, 2H), 3.28 (t, 2H), 6.18 (bs, 2H), 7.84 (t, *J* = 7.8 Hz, 1H), 8.24 (d, *J* = 7.8 Hz, 2H); HRMS (FAB); Obsd M+H = 324.2188. Calcd for $C_{19}H_{26}N_5$ M+H = 324.2180.

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