A Novel General Route for the Preparation of Enantiopure Imidazolines

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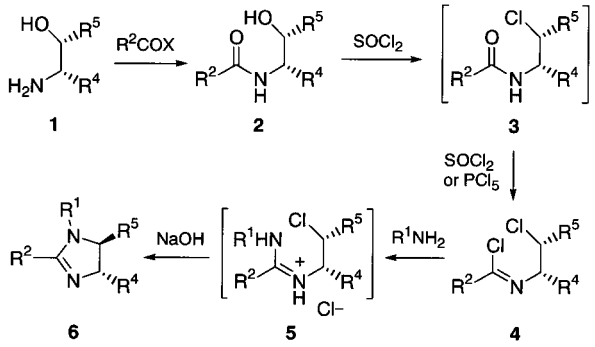
Abstract: A novel procedure for the preparation of enantiopure 1,4-disubstituted 2-imidazolines is reported. Enantiopure *β*-amino alcohols are converted into *N*-hydroxyethylamides, which are reacted with excess thionyl chloride, or with thionyl chloride followed by phosphorus pentachloride to yield *N*-chloroethylimidoyl chlorides. These intermediates are treated with amines and anilines to produce *N*-chloroethylamidines, which are converted into imidazolines upon workup with aqueous hydroxide. The method is simple and efficient and has been used to prepare a wide variety of enantiopure imidazolines, in a modular fashion, from readily available amino alcohols.

The 2-imidazoline ring system is of considerable importance because derivatives exhibit a wide variety of biological activities, including potent antihypercholesterolemic,[1] antiinflammatory,[2] antidiabetic,[3] and antihypertensive[4] activity, and the imidazoline nucleus is also found in biologically active natural products.[5] Moreover, imidazolines have found numerous other applications, e.g., as synthetic intermediates,[6] and as auxiliaries[7] and catalysts[8] for asymmetric synthesis. Our interest in imidazolines **6** stemmed from their potential as novel ligands and catalysts. They are structural analogues of the widely used oxazolines but differ in being much more basic and in having potential for tuning of their basicity, nucleophilicity, and donor strength, over a wide range, by changing the substituent on N-1.[9] Tuning the electronic properties of ligands can have dramatic effects on enantioselectivity in metal-catalyzed reactions.[10] Surprisingly, there are very few reports of the use of imidazolines as ligands in catalytic reactions[11] and in enantioselective catalysis.[12] As a prelude to a wider study of their use in asymmetric catalysis, we have developed a convenient new method for preparing enantiopure imidazolines.

Scheme 1



Enantiopure 4-substituted imidazolines **6** are generally prepared from 1,2-diamines,[7,8,12] although other precursors have occasionally been used.[6c,d,13] We now report (i) the development of a novel, simple, and general method for the preparation of enantiopure imidazolines **6** from amido alcohols **2**, which are easily prepared from amino alcohols **1**, or from alkenes by asymmetric aminohydroxylation.[14] We felt that imidazolines **6** could be obtained from the hydroxy amides **2** simply by conversion into chloroethyl imidoyl chlorides **4** and reaction with amines by two chloride displacements (Scheme 1).[15] The conversion of chloroethyl amides **3**[16] and chloroethyl imidoyl chlorides **4**[17] into imidazolines was reported some time ago, but these precursors were obtained from imidates and alkenes, respectively, and the methods have

(1) Li, H.-Y.; Drummond, S.; DeLucca, I.; Boswell, G. A. *Tetrahedron* **1996**, *52*, 11153−11162.

(2) Ueno, M.; Imaizumi, K.; Sugita, T.; Takata, I.; Takeshita, M. *Int. J. Immunopharmac.* **1995**, *17*, 597−603.

(3) Rondu, F.; Le Bihan, G.; Wang, X.; Lamouri, A.; Touboul, E.; Dive, G.; Bellahsene, T.; Pfeiffer, B.; Renard, P.; Guardiola-Lemaître, B.; Manéchez, D.; Pénicaud, L.; Ktorza, A.; Godfroid, J.-J. *J. Med. Chem.* **1997**, *40*, 3793−3863.

(4) Bousquet, P.; Feldman, J. *Drugs* **1999**, *58*, 799−812.

(5) (a) Tsujii, S.; Rinehart, K. L.; Gunasekera, S. P.; Kashman, Y.; Cross, S. S.; Lui, M. S.; Pomponi, S. A.; Diaz, M. C. *J. Org. Chem.* **1988**, *53*, 5446−5453. (b) Ohtani, I.; Moore, R. E.; Runnegar, M. T. C. *J. Am. Chem. Soc.* **1992**, *114*, 7941−7942.

(6) (a) Jones, R. C. F.; Nichols, J. R. *Tetrahedron Lett.* **1990**, *31*, 1771−1774. (b) Jones, R. C. F.; Smallridge, M. J.; Chapleo, C. B. *J. Chem. Soc., Perkin Trans. 1* **1990**, 385−391. (c) Hayashi, T.; Kishi, E.; Soloshonok, V. A.; Uozumi, Y. *Tetrahedron Lett.* **1996**, *37*, 4969−4972. (d) Lin, Y.-R.; Zhou, X.-T.; Dai, L.-X.; Sun, J. J. *Org. Chem.* **1997**, *62*, 1799−1834. (e) Hsiao, Y.; Hegedus, L. S. *J. Org. Chem.* **1997**, *62*, 3586−3591. (f) Jung, M. E.; Huang, A. *Org. Lett.* **2000**, *2*, 2659−2661.

(7) (a) Jones, R. C. F.; Turner, I.; Howard, K. J. *Tetrahedron Lett.* **1993**, *34*, 6329−6332. (b) Jones, R. C. F.; Howard, K. J.; Snaith, J. S. *Tetrahedron Lett.* **1996**, *37*, 1707−1710. (c) Langlois; Y.; Dalko, P. I. *J. Org. Chem.* **1998**, *63*, 8107−8117.

(8) (a) Corey, E. J.; Grogan, M. J. *Org. Lett.* **1999**, *1*, 157. Isobe, T.; Fukuda, K.; Araki, Y.; Ishikawa, T. *Chem. Commun.* **2001**, 243.

(9) The pK_a values of 1-substituted 2-phenylimidazolines range from 6.65 to 10.70. (a) Fernández, B. M.; Perillo, I. A.; Lamdan, S. *J. Chem. Soc., Perkin Trans. 2* **1973**, 1371−1374. (b) Elguero, J.; Gonzalez, É.; Imbach, J.-L.; Jacquier, R. *Bull. Soc. Chim. Fr.* **1969**, 4075−4077.

(10) (a) Saitoh, A.; Achiwa, K.; Tanaka, K.; Morimoto, T. *J. Org. Chem.* **2000**, *65*, 4228−4240. (b) Clyne, D. S.; Mermet-Bouvier, Y. C.; Nomura, N.; RajanBabu T. V. *J. Org. Chem.* **1999**, *64*, 7601−7611.

(11) (a) Çetinkaya, B.; Alici, B.; Özdemir, I.; Bruneau, C.; Dixneuf, P. H. *J. Organomet. Chem.* **1999**, *575*, 187−192. (b) Çetinkaya, B.; Çetinkaya, E.; Hitchcock, P. B.; Lappert, M. F.; Özdemir, I. *J. Chem. Soc., Dalton Trans.* **1997**, 1359−1362. (c) Bastero, A.; Ruiz, A.; Claver, C.; Castillón, S. *Eur. J. Inorg. Chem.* **2001**, 3009−3011.

(12) (a) Botteghi, C.; Schionato, A.; Chelucci, G.; Brunner, H.; Kürzinger, A.; Obermann, U. *J. Organomet. Chem.* **1989**, *370*, 17−31. (b) Morimoto, T.; Tachibana, K.; Achiwa, K. *Synlett* **1997**, 783−785. (c) Davinport, A. J.; Davies, D. L.; Fawcett, J.; Russell, D. R. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1500−1503. (d) Dupont, J.; Ebeling, G.; Delgado, M. R.; Consorti, C. S.; Burrow, R.; Farrar, D. H.; Lough, A. J. *Inorg. Chem. Commun.* **2001**, *4*, 471−474. (d) Busacca, C. A. US Patent 6,316,620, 2001.

(13) (a) Hunter, D. H.; Sim, S. K. *Can. J. Chem.* **1972**, *50*, 669−677. (b) Borisova, E. Y.; Kropotova, N. V.; Cherkasova, E. M. USSR Patent 466 231, 1975; *Chem. Abstr.* **1976**, *83*, 79277. (c) Oi, R.; Sharpless, K. B. *Tetrahedron Lett.* **1991**, *32*, 999−1002. (d) Legters, J.; Willems, J. G. H.; Thijs, L.; Zwanenburg, B. *Rec. Trav. Chim. Pays-Bas* **1992**, *111*, 59−68. (e) Molina, P.; Díaz, I.; Tárraga, A. *Synlett* **1995**, 1031−1032. (f) Hulme, C.; Ma, L.; Romano, J.; Morrissette, M. *Tetrahedron Lett.* **1999**, *40*, 7925−7928.

(14) Demko, Z. P.; Bartsch, M.; Sharpless, K. B. *Org. Lett.* **2000**, *2*, 2221−2223.

(15) Goure, W. F. *J. Heterocycl. Chem.* **1993**, *30*, 71−80.

(16) Partridge, M. W.; Turner, H. A. *J. Chem. Soc.* **1949**, 1308−1310.

(17) Beger, J.; Schöde, D.; Vogel, J. *J. Prakt. Chem.* **1969**, *311*, 408−419.

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Table 1. Preparation of Imidazolines 6 from Amides 2

R^1	R^2	R^4	R^5	method[a]	product	yield[b] (%)
Tol	Ph	*i*-Pr	H	A	**6a**	63
Me	Ph	*i*-Pr	H	A[c]	**6b**	72
H	Ph	*i*-Pr	H	A[d]	**6c**	79
Tol	2-FC_6H_4	*i*-Pr	H	A	**6d**	66
4-ClC_6H_4	2-FC_6H_4	*i*-Pr	H	A	**6e**	71
4-$CF_3C_6H_4$	2-FC_6H_4	*i*-Pr	H	A	**6f**	64
Me	2-FC_6H_4	*i*-Pr	H	A[c]	**6g**	63
Tol	Ph	Me	Ph	A	**6h**	60
Me	Ph	Ph	H	A	**6i**	76[e]
Tol	2-pyridyl	*i*-Pr	H	B	**6j**	74
Tol	2-pyridyl	*i*-Bu	H	B	**6k**	43[f]
Tol	$PhCH_2CH_2$	*i*-Pr	H	C	**6l**	47
i-Pr	Me	Bn	H	C	**6m**	46
Tol	H	*i*-Pr	H	C	**6n**	68

[a] Method A: $SOCl_2$, reflux; 1.1 equiv of R^1NH_2, 3 equiv of Et_3N, CH_2Cl_2, rt; NaOH(aq) wash. Method B: 1.1 equiv of $SOCl_2$, $CHCl_3$, 60 °C; 1.1 equiv of PCl_5, $CHCl_3$, 60 °C; 1.1 equiv of R^1NH_2, 3 equiv of Et_3N, MeCN, 60 °C; NaOH(aq) wash. Method C: 1.1 equiv of $SOCl_2$, $CHCl_3$, 60 °C; 1.1 equiv of PCl_5, 1.1 equiv of R^1NH_2, toluene or $CHCl_3$, reflux; NaOH(aq) wash. [b] Yield, based on hydroxyamide, after chromatography or recrystallization. [c] Using excess aqueous $MeNH_2$. [d] By addition of the imidoyl chloride to a solution of dry NH_3 in $CHCl_3$. [e] The (*R*)-amino acid was used. [f] Crude yield.

not been used subsequently. The use of amido alcohols as precursors would represent a convenient and powerful new method for imidazoline synthesis.[18]

This concept was readily implemented (Table 1). Enantiopure hydroxyethyl amides **2** were obtained from several readily available amino alcohols **1** in a straightforward manner. Chlorination with thionyl chloride gave the chloroethyl amides **3**, and a second chlorination, using either excess thionyl chloride or phosphorus pentachloride, gave the chloroethyl imidoyl chlorides **4**. The two chlorinations could be carried out separately or in a one-pot reaction. Heating to >50 °C with a slight excess of thionyl chloride was invariably successful in providing the chloro amides **3**. This reaction proceeds by ring-opening of oxazolinium chlorides, formed by cyclization of the initially formed chlorosulfites, and occurs with net retention of configuration.[19] The conditions required for the second chlorination were strongly dependent on the nature of the acyl group. Benzamides were smoothly converted into the imidoyl chlorides by heating to reflux in neat thionyl chloride, and both chlorinations were effected in one pot under these conditions (method A). More electron-poor amides required the use of phosphorus pentachloride. For example, treatment of the picolinamides with 1 equiv of thionyl chloride and then 1 equiv of phosphorus pentachloride, both in refluxing chloroform, furnished the desired chloroethyl imidoyl chlorides (method B).[20] Formation of the imidoyl chlorides could be monitored by the disappearance of the NH signal in the ^1H NMR and by the appearance of the diagnostic signal at ca. 140 ppm due to the imidoyl carbon.[21] The imidoyl chlorides were isolated by evaporation of the reaction mixtures and were used without purification. Reaction of the benzimidoyl chlorides with ammonia, anilines, and alkylamines in chlorinated solvents at room temperature, in the presence of triethylamine, gave amidine hydrochlorides **5**, and workup with aqueous hydroxide brought about cyclization and furnished the desired imidazolines **6a**−**i** (method A). The picolinimidoyl chlorides were much less reactive[22] but gave the pyridyl imidazolines **6j**,**k** on treatment with amines in refluxing acetonitrile and workup with aqueous hydroxide (method B). Formamides were converted into chloroethyl amides **3** using a small excess of thionyl chloride, and the imidoyl chlorides were formed using phosphorus pentachloride in refluxing chloroform. In these cases, the amines needed for imidazoline formation were added to the chlorination mixtures, so that the unstable formimidoyl chlorides would react in situ (method C).[16] 2-Chloroethylalkanamides were converted into 2-alkylimidazolines **6l,m** using the same procedure, but in refluxing toluene.

The imidazolines were purified by recrystallization, distillation, or chromatography on alumina. The 2-pyridylimidazolines **6j**,**k** underwent hydrolysis on alumina and were purified by careful chromatography on silica. All the imidazolines were susceptible to slow hydrolysis on exposure to the air but were stable when stored under nitrogen. The ee of the phenylglycine-derived product **6i** was found to be >98%, by HPLC comparison with the racemate. The complete retention of configuration at C-4 in the phenylglycinol case, and the formation of just one diastereomer from norephedrine, confirms that, as expected, configurational instability at C-4 is not a concern. The trans stereochemistry of the norephedrine derivative **6h** was assigned on the basis of the chemical shift of the methyl group[23] and nOe experiments.[24] Formation of the trans isomer was in accord with the expected stereochemical course of the reaction, i.e., retention at C-4 and net inversion at C-5 (chlorination with retention and substitution with inversion).

As can be seen from Table 1, a wide variety of imidazolines were prepared by this method. Various substitution patterns can be obtained, but it is noteworthy that the method provides a regiospecific route to 1,2,4-trisubstituted imidazolines in which the potentially ligating nitrogen (N-3) is immediately adjacent to the chiral center. The amino alcohols derived from phenylalanine, valine, leucine, and phenylglycine were all used successfully, and norephedrine furnished a 4,5-disubstituted imidazoline **6h**. The 2-position may be unsubstituted **6n** or may bear an alkyl, aryl, or heteroaryl substituent. Yields were uniformly good for the 2-arylimidazolines but were only moderate for the 2-pyridyl and 2-alkyl analogues. Further optimization will be required in those cases. N-1 may bear an alkyl group or an aryl group, which may be electron-rich or electron-poor. Use of ammonia provided the 1-unsubstituted analogues, which should prove useful for the preparation of *N*-acyl and other derivatives. Variation of the N-1 substituent

(18) Amino alcohols have been used as precursors for fused imidazolines, using a different route: Cookson, R. F.; Rodway, R. E. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1854−1857 and references therein. During the preparation of this manuscript, an alternative method for converting amino alcohols into imidazolines was reported: Isobe, T.; Fukuda, K.; Yamaguchi, K.; Seki, H.; Tokunaga, T.; Ishikawa, T. *J. Org. Chem.* **2000**, *65*, 7779−7785.

(19) Fry, E. M. *J. Org. Chem.* **1949**, *14*, 887−894. (b) Holerca, M. N.; Percec, V. *Eur. J. Org. Chem.* **2000**, 2257−2263. Oxazolines were not observed as byproducts in our reactions.

(20) Mørkved, E. H.; Cronyn, M. W. *Acta Chem. Scand. B* **1978**, *32*, 231−234.

(21) Böhme, H.; Drechsler, H.-J. *Tetrahedron Lett.* **1978**, 1429−1432.

(22) Ta−Shma, R.; Rappoport, Z. *J. Am. Chem. Soc.* **1976**, *98*, 8460−8467.

(23) The methyl signal is expected at much higher field for the cis isomer (ca. 0.70 ppm) than for the trans isomer (ca. 1.28 ppm): Bloom, A. J.; Fleischmann, M.; Mellor, J. M. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2357−2362. It was observed at 1.45 ppm in compound **6h**.

(24) Irradiation of the 4-methyl signal gave a strong enhancement of the benzylic hydrogen and no enhancement of the 5-phenyl signal. Conversely, irradiation of the ring hydrogen adjacent to the methyl group gave a strong enhancement of the 5-phenyl signal.

in this way will allow preparation of series of imidazolines in which the electronic properties are varied over a wide range, without changing the chiral environment around the donor nitrogen.

This new route to enantiopure imidazolines has several advantageous features. It uses readily accessible starting materials, involves simple transformations, and has very wide scope. Being modular, our route allows independent variation of the 1-, 2-, and 4-/5-substituents, so it should be amenable to combinatorial synthesis of libraries of imidazolines. Our work makes enantiopure imidazolines more readily available than before, and it will allow a more thorough exploration of their use in medicinal chemistry and in asymmetric synthesis.[25]

Experimental Section

Hydroxy amide starting materials were synthesized according to literature procedures.[26−30] Column chromatography was carried out using Merck aluminum oxide 90 (Brockmann activity II to III) (1097) or Merck silica gel 60 (230−400 mesh) (9385). Oxalates of oily imidazolines were prepared by adding solutions of oxalic acid (1 equiv) in Et_2O (1 mL) to solutions of the imidazolines (100 mg) in Et_2O (1 mL) and filtering off the precipitated salts.

(*S*)-4-Isopropyl-1-(4-methylphenyl)-2-phenyl-4,5-dihydroimidazole 6a (Method A). A solution of *N*-benzoylvalinol[26] (1 g, 4.8 mmol) in thionyl chloride (1.41 mL, 19.2 mmol) was stirred for 4 h at reflux (reaction completion was confirmed by NMR) to form the chloroalkylimidoyl chloride. Excess thionyl chloride was removed by rotary evaporation, and the crude dichloride was dissolved in dry diethyl ether (10 mL). Any insoluble impurities were removed by filtration. Dry triethylamine (2 mL, 14.4 mmol) was added, followed by *p*-toluidine (0.565 g, 5.28 mmol), and the reaction mixture was stirred for 3 h at room temperature. The solution was washed with 10% NaOH (20 mL) and the aqueous was extracted with dichloromethane (2 × 20 mL). The combined organics were washed with brine and dried over $MgSO_4$, and the solvent was removed in vacuo. The resulting crude oil was then distilled at 135 °C, 0.1 mbar, using a Kugelrohr apparatus, to yield the imidazoline as a pale yellow oil, 0.84 g (63%): $[\alpha]^{23}_D = -6.2$ (*c* 0.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 (d, 3H, J = 6.6 Hz), 1.03 (d, 3H, J = 6.6 Hz), 1.95 (m, 1H), 2.24 (s, 3H), 3.63 (m, 1H), 4.05 (m, 2H), 6.66 (d, 2H, J = 8.2 Hz), 6.94 (d, 2H, J = 8.2 Hz), 7.22−7.34 (m, 3H) 7.51 (m, 2H); ^{13}C (75 MHz, $CDCl_3$) δ 161.8, 141.1, 133.1, 131.8, 129.9, 129.5, 129.0, 128.3, 122.9, 70.3, 56.8, 33.3, 20.9, 19.1, 18.1. Anal. Calcd for $C_{19}H_{22}N_2$: C, 81.97; H, 7.97; N, 10.06. Found: C, 81.87; H, 7.85; N, 9.72.

(*S*)-4-Isopropyl-1-methyl-2-phenyl-4,5-dihydroimidazole 6b: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93 (d, 3H, J = 6.7 Hz), 1.01 (d, 3H, J = 6.7 Hz), 1.85 (m, 1H), 2.76 (s, 3H), 3.07 (t, 1H, J = 9.3 Hz), 3.52 (t, 1H, J = 9.3 Hz), 3.87 (m, 1H), 7.39 (m, 3H) 7.52 (m, 2H); ^{13}C (75 MHz, $CDCl_3$) δ 166.7, 131.2, 129.7, 128.3, 128.2, 70.2, 56.2, 36.2, 33.2, 19.1, 18.0. Anal. Calcd for $C_{13}H_{18}N_2 \cdot C_2H_2O_4$ (oxalate): C, 61.63; H, 6.90; N, 9.58. Found: C, 61.42; H, 6.73; N, 9.23.

(*S*)-4-Isopropyl-2-phenyl-4,5-dihydroimidazole 6c: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (d, 3H, J = 6.7 Hz), 0.96 (d, 3H, J = 6.7 Hz), 1.77 (m, 1H), 3.52 (dd, 1H, J = 7.5, 11.6 Hz), 3.71−3.89 (m, 2H), 4.80 (broad s, 1H), 7.35−7.46 (m, 3H), 7.79 (m, 2H); ^{13}C (75 MHz, $CDCl_3$) δ 164.0, 130.9, 130.5, 128.6, 127.4, 66.9, 54.9, 33.4, 19.1, 18.3. Anal. Calcd for $C_{12}H_{16}N_2 \cdot H_2C_2O_4$ (oxalate): C, 60.43; H, 6.47; N, 10.07. Found: C, 60.12; H, 6.47; N, 9.73.

(*S*)-2-(2-Fluorophenyl)-4-isopropyl-1-(4-methylphenyl)-4,5-dihydroimidazole 6d: from *N*-(2-fluorobenzoyl)valinol;[27] ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.99 (d, 3H, J = 6.7 Hz), 1.05 (d, 3H, J = 6.7 Hz), 1.96 (m, 1H), 2.22 (s, 3H), 3.68 (t, 1H, J = 7.0 Hz), 4.00−4.14 (m, 2H), 6.65 (d, 2H, J = 8.6 Hz), 6.90−6.96 (m, 3H), 7.13 (dt, 1H, J = 1.2, 7.6 Hz), 7.26−7.36 (m, 1H), 7.54 (dt, 1H, J = 1.8, 7.3 Hz); ^{13}C (75 MHz, $CDCl_3$) δ 161.6, 158.0, 139.6, 133.2, 131.8, 131.2, 129.6, 124.2, 121.3, 120.8, 116.2, 70.3, 55.3, 33.3, 21.0, 19.0, 18.1. Anal. Calcd for $C_{19}H_{21}N_2F \cdot H_2C_2O_4$ (oxalate): C, 65.28; H, 5.96; N, 7.25; F, 4.92. Found: C, 65.02; H, 6.13; N, 7.14; F, 4.71.

(*S*)-1-(4-Chlorophenyl)-2-(2-fluorophenyl)-4-isopropyl-4,5-dihydroimidazole 6e: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.98 (d, 3H, J = 6.7 Hz), 1.05 (d, 3H, J = 6.7 Hz), 1.94 (m, 1H), 3.69 (t, 1H, J = 7.9 Hz), 3.99−4.14 (m, 2H), 6.66 (d, 2H, J = 8.8 Hz), 6.96 (ddd, 1H, J = 1.2, 8.5, 9.9 Hz), 7.07 (d, 2H, J = 8.8 Hz), 7.16 (dt, 1H, J = 1.2, 7.6 Hz), 7.33−7.41 (m, 1H), 7.56 (dt, 1H, J = 1.7, 7.3 Hz); ^{13}C (75 MHz, $CDCl_3$) δ 161.4, 157.6, 140.5, 132.1, 131.1, 129.0, 128.4, 124.6, 121.8, 120.7, 116.4, 70.5, 54.9, 33.2, 19.0, 18.2. Anal. Calcd for $C_{18}H_{18}N_2FCl$: C, 68.25; H, 5.69; N, 8.85; Cl, 11.22; F, 6.00. Found: C, 67.80; H, 5.84; N, 8.70; Cl, 11.27; F, 5.88.

(*S*)-2-(2-Fluorophenyl)-4-isopropyl-1-(4-trifluoromethylphenyl)-4,5-dihydroimidazole 6f: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.99 (d, 3H, J = 6.7 Hz), 1.07 (d, 3H, J = 6.7 Hz), 1.96 (m, 1H), 3.78 (m, 1H), 4.05−4.16 (m, 2H), 6.73 (d, 2H, J = 8.5 Hz), 6.99 (ddd, 1H, J = 1.2, 8.5, 9.9 Hz), 7.21 (dt, 1H, J = 1.2, 7.6 Hz), 7.34−7.46 (m, 3H), 7.58 (dt, 1H, J = 1.7, 7.3 Hz); ^{13}C (75 MHz, $CDCl_3$) δ 161.5, 157.1, 144.5, 132.4, 131.0, 126.2, 124.8, 124.2, 120.5, 119.0, 116.5, 70.4, 54.3, 33.1, 19.0, 18.2. Anal. Calcd for $C_{19}H_{18}N_2F_4$.: C, 65.14; H, 5.14; N, 8.00; F, 21.72. Found: C, 65.19; H, 5.20; N, 7.79; F, 21.72.

(*S*)-2-(2-Fluorophenyl)-4-isopropyl-1-methyl-4,5-dihydroimidazole 6g: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.94 (d, 3H, J = 6.9 Hz), 1.02 (d, 3H, J = 6.9 Hz), 1.85 (m, 1H), 2.68 (s, 3H), 3.10 (t, 1H, J = 9.3 Hz), 3.52 (dd, 1H, J = 9.3, 10.4 Hz), 3.93 (ddd, 1H, J = 6.0, 9.3, 10.4 Hz), 7.06−7.20 (m, 2H), 7.35−7.43 (m, 1H), 7.48 (dt, 1H, J = 1.9, 7.2 Hz); ^{13}C (75 MHz, $CDCl_3$) δ 162.4, 161.7, 158.4, 131.6, 131.2, 124.5, 116.1, 71.2, 55.8, 34.8, 33.3, 19.2, 18.3.

(4*S*,5*S*)-4-Methyl-1-(4-methylphenyl)-2,5-diphenyl-4,5-dihydroimidazole 6h: from *N*-benzoylnorephedrine;[28] ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 (d, 3H, J = 6.7 Hz), 2.16 (s, 3H), 4.10 (m, 1H), 4.42 (d, 1H, J = 7.1 Hz), 6.60 (d, 2H, J = 8.5 Hz), 6.85 (d, 2H, J = 8.5 Hz), 7.24−7.41 (m, 8H), 7.60−7.63 (m, 2H); ^{13}C (75 MHz, $CDCl_3$) δ 162.4, 143.5, 134.4, 130.2, 129.6, 129.3, 129.1, 128.3, 127.9, 126.9, 124.3, 78.2, 70.1, 22.6, 21.0. Anal. Calcd for $C_{23}H_{22}N_2 \cdot C_2H_2O_4$ (oxalate): C, 72.12; H, 5.77; N, 6.73. Found: C, 72.03; H, 5.52; N, 6.78.

(*R*)-1-Methyl-2,4-diphenyl-4,5-dihydroimidazole 6i: from *N*-benzoylphenylglycinol;[29] ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.84 (s, 3H), 3.32 (t, 1H, J = 10.0 Hz), 3.96 (t, 1H, J = 10.0 Hz), 5.20 (t, 1H, J = 10.0 Hz), 7.25−7.44 (m, 8H), 7.63 (m, 2H); ^{13}C (75 MHz, $CDCl_3$) δ 168.1, 144.7, 131.4, 130.2, 128.74, 128.70, 128.6, 127.2, 126.9, 67.9, 62.1, 36.6. Anal. Calcd for $C_{16}H_{16}N_2 \cdot C_2H_2O_4$ (oxalate): C, 66.26; H, 5.52; N, 8.59. Found: C, 65.96; H, 5.56; N, 8.43. The ee was measured by HPLC using a Chiralcel OD H column, with 80:20 hexane/2-propanol as eluent and UV detection at 254 nm. With a flow rate of 0.7 mLmin^{-1}, $t_R(S)$ = 47 min and $t_R(R)$ = 53 min.

(*S*)-4-Isopropyl-1-(4-methylphenyl)-2-(2-pyridyl)-4,5-dihydroimidazole 6j (Method B). A solution of *N*-(picolinoyl)-valinol (5.0 g, 24 mmol) in chloroform (10 mL) and thionyl chloride (2.2 mL, 26.4 mmol) was stirred at reflux for 2 h (completion was confirmed by ^{1}H NMR) to form the chloropicolinamide. Phosphorus pentachloride (5.0 g, 24 mmol) was added, and the resulting suspension was stirred at reflux for a further 2 h (reaction completion was monitored by ^{1}H NMR). The solution was cooled to 0 °C and a solution of *p*-toluidine (2.8 g, 26.4 mmol) in triethylamine (10 mL, 72 mmol) and chloroform (25 mL) was added via cannula. The solution was stirred at 0 °C for 30 min and then at reflux for 12 h. The chloroform was removed in vacuo and 20% NaOH (100 mL) was added to the crude product. The aqueous was extracted with

(25) We have obtained high enantioselectivity in several reactions using imidazolines as ligands or catalysts.

(26) Lewanowicz, A.; Lipinski, J.; Siedlecka, R.; Skarzewski, J.; Baert, F. *Tetrahedron* **1998**, *54*, 6571−6586.

(27) Schultz, A. G.; Pinto, D. J. P.; Welch, M. *J. Org. Chem*. **1988**, *53*, 1372−1380.

(28) Colman, B.; Sousa, S. E. de; O'Brien, P.; Towers, T. D.; Watson, W. *Tetrahedron*: *Asymmetry* **1999**, *10*, 4175−4182.

(29) Lee, K.-Y.; Kim, Y.-H.; Park, M.-S.; Oh, C.-Y.; Ham, W.-H. *J. Org. Chem*. **1999**, *64*, 9450−9458.

(30) Meyers, A. I.; Dickman, D. A.; Bailey, T. R. *J. Am.Chem. Soc.* **1985**, *107*, 7974−7978.

dichloromethane (2 × 100 mL), the combined organics were dried over $MgSO_4$, and the solvent was removed in vacuo. The resulting crude oil was taken up in 20% hydrochloric acid (100 mL), and the aqueous layer was washed with dichloromethane (2 × 100 mL). The aqueous layer was basified to pH 14 using 20% NaOH, and the product was extracted with dichloromethane (3 × 150 mL). The combined extracts were dried over $MgSO_4$, and the solvent was removed in vacuo to yield the pyridylimidazoline as a brown oil, 4.6 g (74%): $[\alpha]^{23}_D = +17.86$ (c 0.7, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.98 (d, 3H, J = 6.7 Hz), 1.08 (d, 3H, J = 6.7 Hz), 1.94−2.01 (m, 1H), 2.25 (s, 3H), 3.66−3.77 (m, 1H), 4.07−4.14 (m, 2H), 6.65 (d, 2H, J = 8.3 Hz), 6.96 (d, 2H, J = 8.3 Hz), 7.24−7.29 (m, 1H), 7.68−7.70 (m, 2H), 8.53 (d, 1H, J = 4.8 Hz); ^{13}C (67.8 MHz, $CDCl_3$): δ 18.0, 19.1, 20.7, 33.0, 56.4, 70.4, 122.0, 124.2, 124.3, 129.3, 132.9, 136.5, 140.3, 149.3, 150.4, 160.7.

(*S*)-4-Isobutyl-1-(4-methylphenyl)-2-(2-pyridyl)-4,5-dihydroimidazole 6k. Acid−base workup did not improve the purity; data for the crude product (43%) are reported: ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.92−1.00 (m, 6H), 1.41−1.50 (m, 1H), 1.77−1.95 (m, 2H), 2.23 (s, 3H), 3.62 (t, 1H, J = 8.8 Hz), 4.15 (dd, 1H, J = 8.8, 10.0 Hz), 4.29−4.35 (m, 1H), 6.63 (d, 2H, J = 7.9 Hz), 6.92 (d, 2H, J = 7.9 Hz), 7.22−7.26 (m, 1H), 7.60−7.67 (m, 2H), 8.51 (d, 1H, J = 4.4 Hz); ^{13}C (75 MHz, $CDCl_3$) δ 20.7, 22.7, 22.9, 25.2, 46.1, 59.8, 62.8, 121.9, 124.3, 124.4, 129.3, 133.0, 136.4, 140.2, 149.3, 150.2, 160.4.

(*S*)-4-Isopropyl-1-(4-methylphenyl)-2-phenethyl-4,5-dihydroimidazole 6l (Method C). A mixture of *N*-(2-phenylethanoyl)valinol (0.7 g, 2.97 mmol) and thionyl chloride (0.24 mL, 3.27 mmol) in chloroform (5 mL) was heated at reflux for 4 h to form the chloroamide (**6a**), a white solid, in 73% yield after recrystallization ($MeOH/H_2O$). The chloroamide was dissolved in a hot solution of PCl_5 (0.497 g, 2.38 mmol) in toluene (10 mL), and the mixture was refluxed for 10 min. A solution of *p*-toluidine (0.22 g, 2.06 mmol) in toluene (5 mL) was added, and the reaction mixture was refluxed overnight. The solvent was removed by rotary evaporation to give a black oil, which was basified by addition of 10% NaOH. The product was extracted into dichloromethane (20 mL), washed with brine (20 mL), and dried over $MgSO_4$, and the solvent was removed in vacuo. The resulting oil was chromatographed on alumina (petroleum spirits/diethyl ether 30/70) to yield the imidazoline as an orange oil, 0.418 g (47% overall): $[\alpha]^{23}_D = -21.43$ (*c* 0.35, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (d, 3H, J = 6.7 Hz), 1.01 (d, 3H, J = 6.7 Hz), 1.84 (m, 1H), 2.33 (s, 3H), 2.55 (m, 2H), 2.88 (m, 2H) 3.48 (t, 1H, J = 8.7 Hz), 3.78 (dd, 1H, J = 8.7, 10.2 Hz), 3.84 (m, 1H), 6.93 (d, 2H, J = 8.3 Hz), 7.10−7.30 (m, 7H); ^{13}C (75 MHz, $CDCl_3$) δ 163.5, 141.5, 139.3, 135.1, 130.1, 128.6, 128.5, 126.2, 124.2, 69.4, 55.8, 33.4, 33.2, 30.6, 21.1, 19.3, 18.1.

(*S*)-4-Benzyl-1-isopropyl-2-methyl-4,5-dihydroimidazole 6m: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.00 (d, 3H, J = 6.6 Hz), 1.07 (d, 3H, J = 6.6 Hz), 1.91 (s, 3H), 2.60 (m, 1H, J = 9.0, 13.6 Hz), 2.94 (dd, 1H, J = 8.1, 8.9 Hz), 3.10 (dd, 1H, J = 4.8, 13.6 Hz), 3.22 (dd, 1H, J = 8.9, 9.9 Hz), 3.63 (septet, 1H, J = 6.6 Hz), 4.22 (m, 1H), 7.19−7.29 (m, 5H); ^{13}C (75 MHz, $CDCl_3$) δ 163.8, 138.4, 129.7, 128.6, 126.5, 62.4, 47.7, 46.2, 42.1, 20.6, 19.9, 14.0.

(*S*)-4-Isopropyl-1-(4-methylphenyl)-4,5-dihydroimidazole 6n: from *N*-formylvalinol;[30] ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.94 (d, 3H, J = 6.7 Hz), 1.02 (d, 3H, J = 6.7 Hz), 1.82 (m, 1H), 2.30 (s, 3H), 3.37 (t, 1H, J = 9.2 Hz), 3.70 (dd, 1H, J = 9.2, 10.5 Hz), 4.05 (m, 1H), 6.83 (d, 2H, J = 8.5 Hz), 7.11 (d, 2H, J = 8.5 Hz), 7.53 (d, 1H, J = 1.8 Hz); ^{13}C NMR (75 MHz $CDCl_3$) δ 18.5, 19.0, 20.7, 33.3, 49.2, 72.5, 114.3, 130.3, 130.9, 138.2, 149.1. Anal. Calcd for $C_{13}H_{18}N_2$: C, 77.22; H, 8.91; N, 13.86. Found: C, 77.01; H, 9.12; N, 14.21.

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Supporting Information Available: Spectroscopic and analytical data for the hydroxy amides **2** and copies of the ^{1}H NMR spectra of imidazolines **6g**,**j**−**l**. This material is available free of charge via the Internet at http://pubs.acs.org.

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