Synthesis of Stable Acyclic Aminals Derived from L-(+)-Aspartic Acid and Their Application in Asymmetric Henry Reactions

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Z. Naturforsch. **2013**, *68b*, 57 – 63 / DOI: 10.5560/ZNB.2013-2228
Received August 21, 2012

A series of stable acyclic aminals derived from L-(+)-aspartic acid were synthesized in excellent yields (up to 96%) and characterized by spectroscopic methods. They were applied as enantioselective catalysts in Henry reactions of nitromethane with various aldehydes in the presence of Cu(II) ions, affording the corresponding adducts in high yields (up to 90%) and enantioselectivities (up to 92% *ee*).

Key words: Acyclic Aminals, L-(+)-Aspartic Acid, Enantioselective Henry Reaction

Introduction

The catalytic asymmetric Henry (nitroaldol) reaction is an ideal, atom-economical and powerful method for stereoselective carbon-carbon bond formation. The resulting chiral adducts, β-nitro alcohols, can be conveniently converted into β-amino alcohols, α-hydroxy carboxylic acids, aziridines, and other complex target molecules that are highly versatile building blocks for the synthesis of bioactive natural products and pharmaceutical agents [1 – 6]. Since the pioneering work initiated by Shibasaki and co-workers in 1992 [7], interest in asymmetric Henry reactions has grown, and various catalysts [8 – 19] have been developed over the last two decades. Although significant progress has been made, many of the current catalytic systems still share a number of disadvantages such as low substrate generality, high cost of catalysts, and harsh reaction conditions. Therefore, the exploitation of mild, efficient, cheap, and readily available catalysts is still desirable.

Chiral cyclic aminals are one of the ligands that are used extensively in catalytic asymmetric reactions such as α-bromination of cyclic ketones [20], the Diels-Alder reaction [21] and the addition of aldehydes to substrates such as diethyl azodicarboxylate [22] or vinyl sulfones [23]. However no attention has been focused upon catalytic application of cyclic or acyclic aminals in Henry reactions.

Results and Discussion

Recently, we prepared (*S*)-2-amino-1,1,4,4-tetraphenyl-1,4-butanediol from L-(+)-aspartic acid *via* esterification and Grignard addition reactions, and this compound was converted into the chiral tridentate ONO Schiff base ligand **L** (Fig. 1). The Lewis-acidic catalyst system obtained from **L** and Cu(II) ions was observed to catalyze the Henry reaction in high yields (up to 96%) and enantioselectivities (up to 92%) [24].

We were keen to extend this chemistry in order to exploit the high enantioselectivity offered by this type of ligand, and so we attempted to prepare additional Schiff bases from (*S*)-2-amino-1,1,4,4-tetraphenyl-1,4-butanediol using a variety of 2-hydroxybenzaldehydes. However, instead of the expected Schiff base ligands, we obtained a series of stable acyclic aminals (Scheme 1).

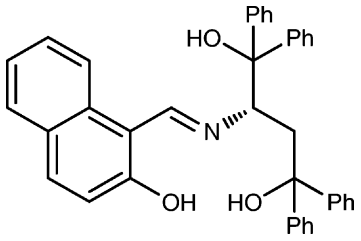
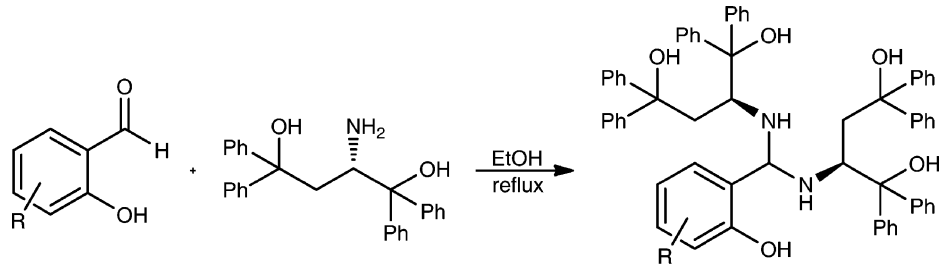


Fig. 1. The structure of the ONO Schiff base ligand **L**.



1a R = 3-OCH_3
1b R = 5-Br
1c R = H
1d R = 3-OH
1e R = 5-*t*-Bu

Scheme 1. Synthesis of the acyclic aminals.

The number of known stable acyclic aminals is quite limited, and those that are known have generally been shown to be stabilized by hydrogen bonding. In particular, a series of stable acyclic aminals obtained from pyridine carboxaldehydes and amines such as 8-aminoquinoline [25] and 2-aminopyridine [26] have been reported. Therefore, it can be expected that such an effect of multiple hydrogen bond stabilization is also present in the aminals prepared from the L-(+)-aspartic acid-derived amino alcohol (Fig. 2). At this point, it is interesting to consider that when 2-hydroxynaphtaldehyde was used as the substrate, in place of the aminal the originally expected Schiff base was obtained. In this case, it seems reasonable to assume that the naphtaldehyde ring system in some way manages to affect the hydrogen bond stabilization.

The aminal structure of the products was clearly assigned by IR and NMR spectroscopy and by elemental analysis. In particular, the presence of a characteristic singlet signal at $\delta = 5.5$ ppm for the methylene group was observed in the ^{1}H NMR spectra of all the products.

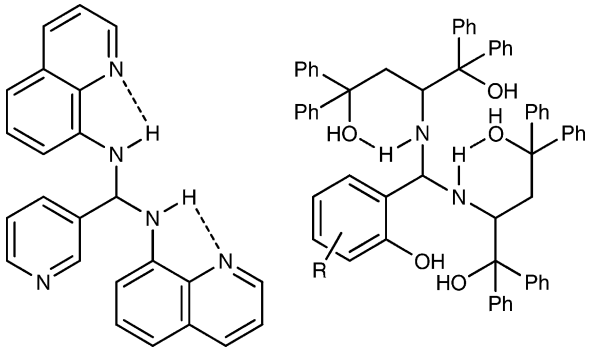
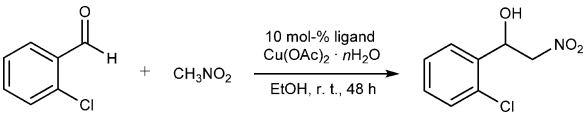


Fig. 2. Multiple hydrogen bonding in stable acyclic aminals.

Our initial experiment was performed to screen the effect of the ligand structure on the Henry reaction by using 2-chlorobenzaldehyde as a model substrate with nitromethane in the presence of a catalyst (10 mol-%) which was generated *in situ* from the aminal and $Cu(OAc)_2 \cdot nH_2O$. The results are summarized in Table 1.

It was apparent that the flexibility of the C–C bond associated with the amino and hydroxyl groups in the ligand had a strong influence on the coordination with $Cu(OAc)_2 \cdot nH_2O$, and consequently on the enantioselectivity of the reaction. Ligands **1a**, **b** were clearly superior to **1c**–**e** in terms of *ee* values, among which **1a** distinguished itself as the best ligand.

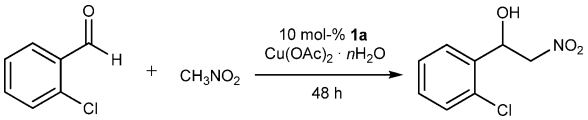
Table 1. Ligand Screening.



Entry	Ligand	R	Yield (%)[a]	*ee* (%)[b]
1	**1a**	3-OCH_3	90	92
2	**1b**	5-Br	60	90
3	**1c**	H	82	88
4	**1d**	3-OH	51	82
5	**1e**	5-*t*-Bu	61	36

[a] Isolated yields after column chromatography; [b] determined by HPLC analysis using a Chiralcel OD-H column; the absolute configuration of the major product was assigned as *S* by comparison to the literature values [27–29].

Table 2. Optimization of the reaction conditions.



Entry	Solvent	Temp. (°C)	Yield[a] (%)	*ee*[b,c] (%)
1	Ethanol	r. t.	90	92
2	Methanol	r. t.	79	78
3	2-Propanol	r. t.	90	81
4	*tert*-Butanol	r. t.	93	80
5	Tetrahydrofuran	r. t.	68	82
6	Diethyl ether	r. t.	56	66
7	Hexane	r. t.	47	54
8[d]	Ethanol	r. t.	86	80
9[e]	Ethanol	r. t.	89	74
10[f]	Ethanol	50	94	70
11[g]	Ethanol	0	22	86

[a] Isolated yields after column chromatography; [b] determined by HPLC analysis using a Chiralcel OD-H column; [c] the absolute configuration of the major product was assigned as *S* by comparison to literature values [27–29]; [d] 5 mol-% catalyst loading; [e] 20 mol-% catalyst loading; [f] the reaction was completed within 12 h; [g] the reaction was completed within 5 d.

In subsequent studies, the reaction parameters, including solvents, catalyst loadings and reaction temperatures, were optimized. From the data listed in Table 2, we noted that the reaction was highly sensitive to the nature of solvent employed; ethanol was found to be the superior solvent in terms of yield (90 %) and *ee* value (92 %) (Table 2, entry 1). Catalyst loadings (Table 2, entry 1, 8, 9) also had a significant effect on the enantioselectivities; 10 mol-% loading of catalyst gave the highest *ee* value (92 %, Table 2, entry 1).

Finally, we examined the substrate tolerance of the reaction by carrying out reactions using a variety of aromatic aldehydes (Table 3). All of the substrates used in this study, regardless of whether the aromatic ring contained electron-withdrawing or electron-donating groups at the *ortho*, *meta* or *para* positions, gave the corresponding *S*-enriched products in moderate to good yield (61 % – 90 %) of isolated products with good enantioselectivities (66 % – 92 %) in most cases.

Conclusion

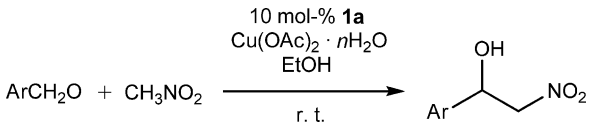
We have successfully synthesized five stable acyclic aminals containing a chiral L-(+)-aspartic acid skeleton and applied these aminals as enantioselective catalysts in asymmetric Henry reactions for the first time. The mild reaction conditions, tolerance of air and moisture, lack of additives, high efficiency and enantioselectivity makes this catalytic system useful for the synthesis of many valuable compounds.

Experimental Section

Materials and physical measurements

All chemicals were purchased from Merck, Sigma-Aldrich, Alfa Aesar, or Fluka and used without any further purification. Solvents were used as received from commercial suppliers. Silica gel F_{254} (Merck 5554) precoated plates were used for thin layer chromatography. For column chromatography silica gel 60 (Merck 7743) was used. IR spectra were recorded using a Mattson FTIR 1000 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were carried out using a 400 MHz Varian NMR spectrometer at ambient temperature. Melting points were recorded with an electrothermal

Table 3. Substrate scope.



Entry	ArCHO	Time (h)	Yield (%)[a]	*ee* (%)[b]	Config.[c]
1	2-Nitrobenzaldehyde	18	71	84	*S*
2	3-Nitrobenzaldehyde	12	66	74	*S*
3	4-Nitrobenzaldehyde	12	76	66	*S*
4	2-Chlorobenzaldehyde	48	90	92	*S*
5	4-Methoxybenzaldehyde	120	61	72	*S*
6	4-Methylbenzaldehyde	120	79	73	*S*
7	4-Ethylbenzaldehyde	120	82	90	n. d.
8	Benzaldehyde	120	69	72	*S*

[a] Isolated yields after column chromatography; [b] determined by HPLC analysis using a Chiralcel OD-H column; [c] the absolute configuration of the major product was assigned by comparison to literature values [27–29]; n. d. = not determined.

digital melting point apparatus. Optical rotations were determined using a Rudolph Research Analytical Autopol I automatic polarimeter. HPLC analyses were performed using a Chiralcel OD-H column.

Preparation of (S)-dimethyl-2-aminosuccinate

$SOCl_2$ (12 mL) was added dropwise to a suspension of L-(+)-aspartic acid (354 mg, 2.66 mmol) in 60 mL of methanol at 0 °C. The resulting colorless solution was refluxed until all L-(+)-aspartic acid had been consumed. Methanol was evaporated *in vacuo*, and water (5 mL) was added. Saturated aqueous $NaHCO_3$ was then added dropwise (pH = 8), and the mixture was extracted with ethyl acetate. The organic phase was dried with Na_2SO_4 and filtered. Ethyl acetate was evaporated to give the title compound as a yellow oil (82 % yield). – IR (NaCl): ν = 3385, 2956, 2851, 1738, 1438, 1366, 1203 cm^{-1}. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.84 (dd, J = 4.8, 7.6 Hz, 1H), 3.76 (s, 3H, CH_3), 3.71 (s, 3H, CH_3), 2.82 (dd, J = 4.8, 16.4 Hz, 1H), 2.71 (dd, J = 7.6, 16.4 Hz, 1H), 1.88 (bs, 2H, -NH_2). – ^{13}C NMR (400 MHz, $CDCl_3$): δ = 174.7, 171.8, 52.5, 52.0, 38.9. – $C_6H_{11}O_4N$ (161.2): calcd. C 44.72, H 6.88, N 8.69; found C 43.86, H 6.04, N 9.01.

Preparation of (S)-2-amino-1,1,4,4-tetraphenylbutane-1,4-diol

To a solution of L-(+)-aspartic acid dimethyl ester (1 mmol) in dry ethyl ether was added an excess of a freshly prepared 1 M PhMgBr solution in 10 mL of dry ether. The resulting solution was refluxed until all L-(+)-aspartic acid dimethyl ester had been consumed. The reaction was quenched with saturated NH_4Cl solution. The product was extracted with ether-water, and the organic phase was dried with Na_2SO_4 and filtered. Then the ether fraction was evaporated *in vacuo*. The crude product was purified with column chromatography (1 : 3 ethyl acetate-hexane) to give the title compound as colorless crystals (78 % yield); m. p. 145.9 – 149.5 °C. – IR (NaCl): ν = 3376, 1491, 1596, 1447 700 cm^{-1}. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.12 – 7.41 (m, 20H, Ar-H), 3.65 (dd, J = 10.8, 1.2 Hz, 1H), 2.60 (bs, -OH), 2.44 (dd, J = 1.2, 14.4, Hz, 1H), 2.05 (dd, J = 10.8, 14 Hz, 1H). – ^{13}C NMR (400 MHz, $CDCl_3$): δ = 128.8, 128.6, 128.2, 128.1, 127.4, 127.2, 126.9, 126.8, 126.7, 125.96, 125.91, 125.8, 81.4, 78.2, 55.2, 40.1. – $C_{28}H_{27}O_2N$(409,5): calc. C 82.12, H 6.65, N 3.42; found C 81.11, H 6.61, N 3.61.

General procedure for the synthesis of aminals

The solution of aldehyde (1 mmol) and (*S*)-2-amino-1,1,4,4-tetraphenylbutane-1,4-diol (2 mmol) in 20 mL ethanol was refluxed until all of the starting materials were consumed. Ethanol was evaporated *in vacuo*, and the products were crystallized using dichloromethane-hexane solvent systems.

*(2S,2′S)-2,2′-(((2-Hydroxy-3-methoxyphenyl)methylene)-bis(azanediyl))bis(1,1,4,4-tetraphenylbutane-1,4-diol) (**1a**)*

79 % yield; m. p. 103 – 104 °C. – IR (NaCl): ν = 3504, 3276, 3058, 2936, 2938, 1628, 1598, 1492, 1463, 1448, 1266, 1169, 1060, 1031, 736, 700 cm^{-1}. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46 – 7.09 (m, 43H, Ar-H), 5.56 (s, 1H), 4.31 (dd, J = 5.6, 3.2 Hz, 1H), 4.22 (dd, J = 11.2, 1.6 Hz, 1H), 3.84 (s, 2H), 3.82 (s, 3H), 2.87 (bs, 1H), 2.65 (bs, 1H), 2.38 (m, 2H), 2.00 (dd, J = 14.4, 12 Hz, 1H). – ^{13}C NMR (400 MHz, $CDCl_3$): δ = 167.14, 148.13, 147.98, 147.92, 147.11, 145.31, 144.88, 144.28, 144.03, 142.02, 129.02, 128.69, 128.46, 128.21, 128.16, 128.10, 128.04, 127.93, 127.49, 127.37, 127.13, 127.07, 127.02, 126.92, 126.70, 126.66, 126.56, 126.49, 126.17, 126.00, 125.88, 125.59, 125.47, 125.38, 124.89, 124.82, 123.26, 118.98, 118.35, 118.09, 117.37, 113.75, 111.81, 81.17, 81.08, 80.66, 79.09, 77.41, 72.65, 56.85, 55.91, 55.85, 53.35, 42.90, 35.24. – $C_{64}H_{60}N_2O_6$ (953.2): calc. C 80.65, H 6.34, N 2.94; found C 79.98, H 6.28, N 2.69. – $[\alpha]_D^{25}$ = +5.60 (c = 2.5, CH_2Cl_2).

*(2S,2′S)-2,2′-(((5-Bromo-2-hydroxyphenyl)methylene)-bis(azanediyl))bis(1,1,4,4-tetraphenylbutane-1,4-diol) (**1b**)*

90 % yield; m. p. 201 – 203 °C. – IR (NaCl): ν = 3460, 3271, 3059, 3027, 2926, 1632, 1493, 1476, 1448, 1374, 1274, 1173, 1061, 1031, 738, 700 cm^{-1}. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83 (dd, J = 2.4, 0.8 Hz, 1H), 7.49 – 7.13 (m, 41H, Ar-H), 6.64 (d, J = 8.8 Hz, 1H), 5.43 (s, 1H), 4.36 (dd, J = 6.8, 2 Hz, 1H), 4.17 (d, J = 11.6 Hz, 1H), 2.80 (m, 1H), 2.50 (s, 1H), 2.43 (dd, J = 14, 2 Hz, 1H), 1.99 (dd, J = 14, 11.6, 1H). – ^{13}C NMR (400 MHz, $CDCl_3$): δ = 165.91, 159.86, 154.76, 147.59, 147.11, 145.27, 144.30, 144.09, 144.00, 143.81, 141.68, 134.87, 133.68, 132.47, 129.23, 128.77, 128.74, 128.35, 128.27, 128.25, 128.08, 127.79, 127.52, 127.24, 127.23, 127.12, 127.00, 126.97, 126.88, 126.49, 126.17, 126.03, 125.95, 125.57, 125.25, 124.93, 119.76, 118.76, 118.52, 111.49, 109.62, 81.53, 81.06, 80.07, 79.44, 77.45, 72.68, 57.12, 42.52, 35.52. – $C_{63}H_{52}BrN_2O_5$ (1002.0): calc. C 75.51, H 5.73, N 2.80; found C 74.96, H 5.6, N 2.70. – $[\alpha]_D^{25}$ = +14.8 (c = 1.08, CH_2Cl_2).

*(2S,2′S)-2,2′-(((2-Hydroxyphenyl)methylene)bis-(azanediyl))bis(1,1,4,4-tetraphenylbutane-1,4-diol) (**1c**)*

87 % yield; m. p. 204 – 205 °C. – IR (NaCl): ν = 3555, 3449, 3275, 3058, 3027, 1628, 1583, 1492, 1448, 1389, 1347, 1266, 1153, 1108, 1032, 893, 755, 699 cm^{-1}. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74 (d, J = 7.6 Hz, 1H), 7.46 – 7.07 (m, 38H, Ar-H), 6.97 – 6.89 (m, 2H), 6.78 – 6.67 (m, 3H), 5.48 (s, 1H), 4.32 (dd, J = 8, 2 Hz, 1H), 4.16 (dd,

$J = 11.6$, 1.6 Hz, 1H), 2.90 – 2.78 (m, 2H), 2.65 (bs, 1H), 2.43 (dd, $J = 14.4$, 2 Hz, 1H), 1.99 (dd, $J = 14$, 11.6 Hz, 1H). – ^{13}C NMR (400 MHz, $CDCl_3$): $\delta = 160.68$, 155.60, 147.93, 147.15, 145.46, 144.42, 144.21, 144.15, 144.01, 142.02, 132.28, 131.71, 129.68, 129.11, 128.65, 128.63, 128.26, 128.17, 128.15, 128.13, 127.97, 127.61, 127.43, 127.36, 127.09, 127.06, 126.98, 126.78, 126.74, 126.63, 126.54, 126.19, 126.09, 126.06, 125.68, 125.32, 124.87, 124.09, 119.33, 118.39, 118.25, 116.69, 116.66, 81.18, 81.08, 80.71, 79.41, 77.48, 72.78, 57.11, 42.71, 35.39. – $C_{63}H_{58}N_2O_5$ (923,1): calc. C 81.97, H 6.33, N 3.03; found C 81.96, H 6.30, N 3.00. – $[\alpha]_D^{25} = +21.4$ ($c = 0.56$, CH_2Cl_2).

*(2S,2′S)-2,2′-(((2,3-Dihydroxyphenyl)methylene)-bis(azanediyl))bis(1,1,4,4-tetraphenylbutane-1,4-diol) (**1d**)*

96 % yield; m. p. 198 °C. – IR (NaCl): $\nu = 3426$, 3059, 3027, 1639, 1599, 1545, 1493, 1465, 1448, 1391, 1359, 1266, 1241, 1166, 1066, 1031, 894, 738, 699 cm^{-1}. – ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.47 – 6.77$ (m, 41H, Ar-H), 6.38 (t, $J = 8$ Hz, 1H), 6.25 (dd, $J = 8$, 1.2 Hz, 1H), 5.51 (s, 1H), 4.35 (dd, $J = 8.2$, 6.8 Hz, 1H), 4.19 (dd, $J = 11.6$, 2 Hz, 1H), 2.88 (m, 3H), 2.42 (dd, $J = 14$, 2 Hz, 1H), 2.03 (dd, $J = 14$, 11.6 Hz, 1H). – ^{13}C NMR (400 MHz, $CDCl_3$): $\delta = 166.05$, 147.92, 147.02, 146.36, 145.93, 145.06, 144.31, 144.08, 143.84, 143.49, 142.46, 141.98, 129.16, 128.71, 128.67, 128.55, 128.35, 128.32, 128.16, 128.14, 127.66, 127.41, 127.39, 127.19, 127.15, 127.03, 126.83, 126.66, 126.18, 126.14, 125.97, 125.75, 125.27, 124.91, 124.27, 122.66, 119.55, 116.92, 116.06, 115.41, 114.86, 114.78, 81.23, 81.08, 80.74, 79.56, 77.37, 68.93, 57.13, 42.07, 35.48, 31.57, 22.63, 14.09. – $C_{63}H_{58}N_2O_6$ (939.1): calc. C 80.57, H 6.22, N 2.98; found C 80.56, H 6.31, N 2.97. – $[\alpha]_D^{25} = +44.3$ ($c = 0.63$, CH_2Cl_2).

*(2S,2′S)-2,2′-(((5-(tert-Butyl)-2-hydroxyphenyl)methylene)-bis(azanediyl))bis(1,1,4,4-tetraphenylbutane-1,4-diol) (**1e**)*

91 % yield, liquid at r. t. – IR (NaCl): $\nu = 3450$, 3058, 2962, 1633, 1594, 1493, 1448, 1363, 1265, 1031, 831, 748, 700 cm^{-1}. – ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.75$ (d, $J = 2.4$ Hz, 1H), 7.48 – 7.09 (m, 40H, Ar-H), 6.91 (t, $J = 7.2$ Hz, 1H), 6.71 (m, 2H), 5.48 (s, 1H), 4.38 (dd, $J = 6.4$, 2 Hz, 1H), 4.18 (dd, $J = 11.6$, 2 Hz, 1H), 2.83 (m, 2H), 2.44 (dd, $J = 14.4$, 2 Hz, 1H), 2.00 (dd, $J = 14.4$, 11.6 Hz, 1H), 1.27 (s, 9H). – ^{13}CNMR (400 MHz, $CDCl_3$): $\delta = 167.36$, 158.87, 152.96, 148.06, 147.23, 145.57, 144.39, 144.31, 144.27, 142.15, 141.72, 140.44, 129.59, 128.93, 128.35, 128.29, 128.13, 128.01, 127.94, 127.89, 127.80, 127.39, 127.01, 126.98, 126.82, 126.76, 126.62, 126.50, 126.34, 126.20, 125.99, 125.78, 125.32, 124.59, 123.34, 122.52, 117.48, 116.34, 116.06, 80.92, 80.84, 80.76, 79.13, 77.24, 72.40, 65.54, 57.08, 42.73, 35.12, 33.99, 33.63, 31.52, 31.42, 31.23, 31.07, 22.49, 15.01, 13.99. – $C_{67}H_{66}N_2O_5$ (979.3): calc. C 82.18, H 6.90, N 2.46; found C 81.98, H 6.88, N 2.49. – $[\alpha]_D^{25} = +18.2$ ($c = 0.88$, CH_2Cl_2).

General procedure for the Henry reaction

The dark-green solution of $Cu(OAc)_2 \cdot nH_2O$ (0.1 mmol) and the aminal ligand (0.05 mmol) in 2 mL of solvent was stirred at r. t. for 2 h. Then the appropriate aldehyde (0.5 mmol) and nitromethane (2.5 mmol) were added. The reaction mixture was stirred at r. t. until most of the aldehyde had been consumed. The solvent was evaporated *in vacuo*, and the crude product was purified by column chromatography.

(S)-1-(2-Chlorophenyl)-2-nitroethanol

Colorless oil, 95 % yield. – ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.56$ (dd, $J = 2$, 7.6 Hz, 1H, Ar-H), 7.24 (m, 3H, Ar-H), 5.75 (m, 1H), 4.57 (dd, $J = 2.4$, 13.6 Hz, 1H), 4.36 (dd, $J = 9.6$, 13.6 Hz, 1H). – HPLC conditions: 93 : 7 hexane : *i*-PrOH, 0.8 mL min^{-1}, 267 nm, $t_{minor} = 14.4$ min (*R*), $t_{major} = 15.3$ min (*S*), 90 % *ee*. – $[\alpha]_D^{25} = +44.0$ ($c = 0.55$, CH_2Cl_2).

(S)-1-(2-Nitrophenyl)-2-nitroethanol

Brown crystals, 81 % yield. – ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.06$ (dd, $J = 1.2$, 8 Hz, 1H, Ar-H), 7.95 (d, $J = 8$ Hz, 1H, Ar-H), 7.75 (td, $J = 0.8$, 7.6 Hz, 1H, Ar-H), 7.55 (td, $J = 1.6$, 8.4 Hz, 1H, Ar-H), 6.03 (d, $J = 8$ Hz, 1H), 4.85 (dd, $J = 2.4$, 14 Hz, 1H), 4.56 (dd, $J = 9.2$, 13.6 Hz, 1H), 3.35 (bs, 1H, -OH). – HPLC conditions: 90 : 10 hexane : *i*-PrOH, 1 mL min^{-1}, 267 nm, $t_{minor} = 15.9$ min (*R*), $t_{major} = 18.3$ min (*S*), 88 % *ee*. – $[\alpha]_D^{25} = +23.5$ ($c = 0.89$, CH_2Cl_2).

(S)-1-(3-Nitrophenyl)-2-nitroethanol

Yellow oil, 90 % yield. – ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.30$ (m, 1H, Ar-H), 8.19 (m, 1H, Ar-H), 7.78 (m, 1H, Ar-H), 7.61 (t, $J = 7.6$ Hz, 1H, Ar-H), 5.61 (dd, $J = 4.4$, 7.6 Hz, 1H), 4.63 (m, 2H), 3.51 (bs, 1H, -OH). – HPLC conditions: 90 : 10 hexane : *i*-PrOH, 1 mL min^{-1}, 267 nm, $t_{minor} = 25.9$ min (*R*), $t_{major} = 28.6$ min (*S*), 70 % *ee*. – $[\alpha]_D^{25} = +28.8$ ($c = 1.04$, CH_2Cl_2).

(S)-1-(4-Nitrophenyl)-2-nitroethanol

Colorless crystals, 71 % yield. – ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.26$ (m, 2H, Ar-H), 7.63 (m, 2H, Ar-H), 5.61 (m, 1H), 4.60 (d, $J = 6$ Hz, 1H), 4.58 (d, $J = 2$ Hz, 1H), 3.17 (bs, 1H, -OH). – HPLC conditions: 90 : 10 hexane : *i*-PrOH, 1 mL min^{-1}, 267 nm, t_{minor}= 28.7 min (*R*), $t_{major} =$ 35.40 min (*S*), 76 % *ee*. – $[\alpha]_D^{25} = +29.3$ ($c = 0.75$, CH_2Cl_2).

(S)-1-Phenyl-2-nitroethanol

Yellow oil, 96% yield. – ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.38$ (m, 5H, Ar-H), 5.43 (dd, $J = 2.8$, 9.6 Hz, 1H), 4.59 (dd, $J = 9.6$, 13.6 Hz, 1H), 4.49 (dd, $J = 2.8$, 13.2 Hz, 1H), 3.08 (bs, 1H, -OH). – HPLC conditions: 90 : 10 hexane : *i*-PrOH, 1 mL min^{-1}, 267 nm, $t_{minor} = 13.8$ min (*R*), $t_{major} = 15.0$ min (*S*), 78% *ee*. – $[\alpha]_D^{25} = +35.3$ ($c = 1.36$, CH_2Cl_2).

(S)-1-(4-Methylphenyl)-2-nitroethanol

Yellow crystals, 88% yield. – ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.26$ (m, 4H, Ar-H), 5.42 (d, $J = 9.2$ Hz, 1H), 4.60 (dd, $J = 10.4$, 13.6 Hz, 1H), 4.48 (dd, $J = 2.8$, 13.2 Hz, 1H), 2.74 (bs, 1H, -OH), 2.36 (s, 3H, CH_3). – HPLC conditions: 85 : 15 hexane : *i*-PrOH, 0.5 mL min^{-1}, 267 nm, $t_{minor} = 19.8$ min (*R*), $t_{major} = 24.5$ min (*S*), 74% *ee*. – $[\alpha]_D^{25} = +17.3$ ($c = 0.81$, CH_2Cl_2).

(S)-1-(4-Ethylphenyl)-2-nitroethanol

Yellow oil, 60% yield. – ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.29$ (m, 2H, Ar-H), 7.22 (m, 2H, Ar-H), 5.42 (m, 1H), 4.50 (dd, $J = 9.6$, 13.2 Hz, 1H), 4.48 (dd, $J = 3.2$, 13.2 Hz, 1H), 2.86 (d, $J = 3.6$ Hz, 1H), 2.65 (q, $J = 7.6$ Hz, 2H, -CH_2), 1.23 (t, $J = 7.6$ Hz, 3H, CH_3). – HPLC conditions: 90 : 10 hexane : *i*-PrOH, 1 mL min^{-1}, 267 nm, $t_{minor} = 12.2$ min (*R*), $t_{major} = 15.7$ min (*S*), 76% *ee*. – $[\alpha]_D^{25} = +32.0$ ($c = 0.75$, CH_2Cl_2).

(S)-1-(4-Methoxyphenyl)-2-nitroethanol

Yellow oil, 68% yield. – ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.30$ (d, $J = 8.8$ Hz, 2H, Ar-H), 6.91 (d, $J = 8.8$ Hz, 2H, Ar-H), 5.39 (m, 1H), 4.59 (dd, $J = 9.6$, 13.2 Hz, 1H), 4.46 (dd, $J = 2.8$, 12.8 Hz, 1H), 3.81 (s, 3H, -OCH_3), 2.84 (bs, 1H, -OH). – HPLC conditions: 90 : 10 hexane : *i*-PrOH, 1 mL min^{-1}, 267 nm, $t_{minor} = 20.4$ min (*R*), $t_{major} = 25.5$ min (*S*), 70% *ee*. – $[\alpha]_D^{25} = +28.0$ ($c = 0.50$, CH_2Cl_2).

Acknowledgement

We are grateful to The Scientific and Technological Research Council of Turkey (TUBITAK) for their financial support (210T147). G. K. thanks TUBITAK for a postdoctoral fellowship.

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