New Chiral Hydroxyoxazolines Based on Ketopinic Acid and Their Use in the Asymmetric Diels–Alder Reaction

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Abstract: Several chiral hydroxyoxazolines have been prepared starting from (1*S*)-(+)-ketopinic acid and enantiopure β-amino alcohols by short synthetic routes. They have been employed in the catalytic asymmetric Diels–Alder reaction, resulting in ee values of up to 90%.

Key words: asymmetric catalysis, Diels–Alder reactions, copper, alkenes, ligands

Asymmetric metal catalysis is one of the most important and rapidly growing research fields in organic chemistry.[1] In this context, it is particularly important to search for new compounds which can serve as chiral ligands, and to explore their applicability in the synthesis of optically active compounds. In the last few years, considerable success has been achieved in this field mainly with the introduction of C_2-symmetric[2] compounds and, more recently, of C_1-symmetric compounds.[3] Oxazoline-based ligands have played an important role in asymmetric metal-catalyzed reactions, especially with copper and other transition metals. By far, most successful examples involve the use of C_2-symmetric bisoxazolines (BOX).[4] Nevertheless, a number of C_1-symmetric ligands containing the oxazoline moiety have been employed in asymmetric catalysis providing products with high enantiomeric excesses.[5] Recently, Bolm et al. have described the catalytic asymmetric phenyl transfer reaction to aldehydes using a series of hydroxyoxazolines derived from β-amino alcohols and mandelic acid[6] or α-keto acid derivatives[7] (Figure 1). These examples prompted us to look for other keto acids that can be used as scaffolds for the synthesis of hydroxyoxazoline ligands (Figure 1). (1*S*)-(+)-Ketopinic acid was considered a good candidate since it bears a carboxylic acid, precursor for an oxazoline ring, and a ketone moiety on a rigid norbornyl skeleton. A number of compounds based on the norbornyl framework have been used as chiral auxiliaries and ligands.[8] In this letter we describe the preparation of several hydroxyoxazolines starting from (*S*)-(+)-ketopinic acid (Figure 1) and their use as ligands in the copper(II)-catalyzed Diels–Alder reaction. To the best of our knowledge, this is the first example of a copper(II)–hydroxyoxazoline-catalyzed reaction.

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The general route for the synthesis of the ligands is outlined in Scheme 1. Commercially available[9] (*S*)-(+)-ketopinic acid (**1**) was treated with thionyl chloride and the resulting acyl chloride was subsequently reacted with the corresponding amino alcohol **3a**–**d** in dichloromethane at 0 °C in the presence of excess of triethylamine. The corresponding hydroxyamides **4a**–**d** were obtained in good yields of 80–90% (Table 1).

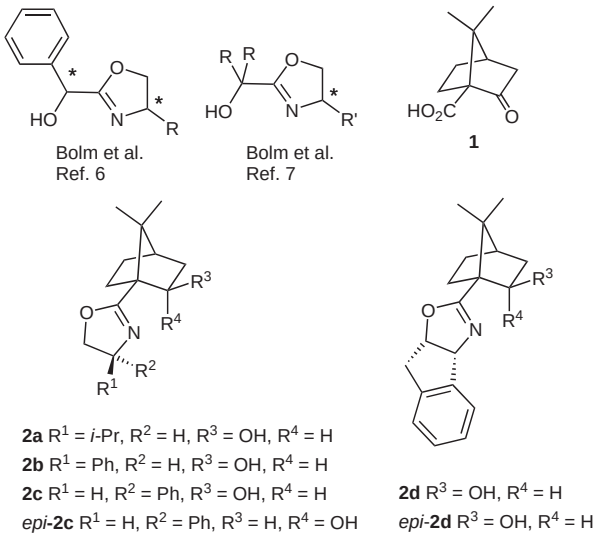
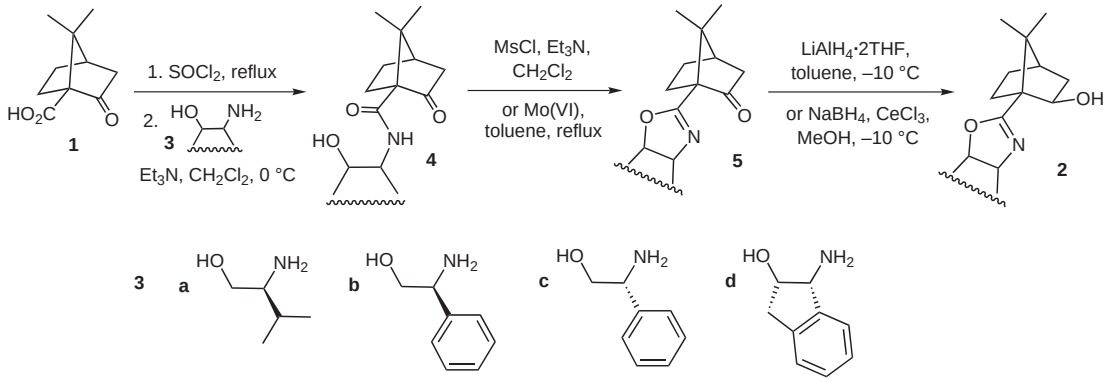


Figure 1

The next step involved cyclization of the hydroxyamide to the oxazoline ring. With hydroxyamides **4a**–**c** derived from primary alcohols this step was achieved by treatment with mesyl chloride and triethylamine, providing the expected oxazolines **5a**–**c** in good yields (81–96%). However, this method could not be used for the synthesis of oxazoline **5d** because epimerization of the carbon bearing the hydroxyl group of the aminoindanol unit was possible. Therefore, cyclization was carried out according to the procedure described by Ishihara et al,[10] using $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ as catalyst in toluene at reflux temperature. In this way, compound **5d** was obtained in 64% yield. The last step involved reduction of the C(2) ketone. This carbonyl group could not be reduced with $NaBH_4$ or $LiBH_4$. Treatment of **5a** with $LiAlH_4$ gave complex mixtures. Fortunately, reduction could be achieved by using the $LiAlH_4\cdot 2THF$ complex in toluene at –40 °C. In this way compounds **5a** and **5b** were reduced with complete stereoselectivity to give hydroxyoxazolines **2a** and **2b** in



Scheme 1 Synthesis of ligands **2** from (*S*)-(+)-ketopinic acid

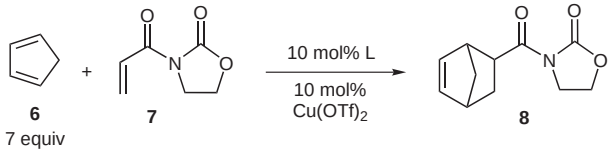
63% and 70% yields, respectively. Reduction of compound **5c** under similar conditions gave the two epimeric alcohols in 62% yield for the *exo* alcohol **2c** and 15% yield for the *endo* alcohol *epi*-**2c**. Reduction of compound **5d** took place with no stereoselectivity affording both alcohols **2d** and *epi*-**2d** in 45% and 47% yields, respectively. In this case, hydroxyoxazoline **2d** could be obtained stereoselectively (5:1) using $NaBH_4$ in the presence of $CeCl_3 \cdot 7H_2O$ in MeOH at –10 °C.

Table 1 Yields of Compounds **4**, **5**, and **2**[a]

Entry	**3**	**4**	Yield	**5**	Yield	**2**	Yield
1	**3a**	**4a**	90%	**5a**	90%[b]	**2a**	63%[d]
2	**3b**	**4b**	84%	**5b**	81%[b]	**2b**	70%[d]
3	**3c**	**4c**	90%	**5c**	96%[b]	**2c**	62%[d] (15%)[e]
4	**3d**	**4d**	80%	**5d**	64%[c]	**2d**	45%[d] (47%)[e]
5						**2d**	50%[f] (10%)[e]

[a] Isolated yield.
[b] Reaction conditions: MsCl, Et_3N, CH_2Cl_2, r.t.
[c] Reaction conditions: $(NH_4)_6Mo_7O_{24} \cdot 4H_2O$, toluene, reflux.
[d] Reaction conditions: [$LiAlH_4 \cdot 2THF$], toluene, –40 °C.
[e] Yield of the C2-epimer in brackets.
[f] Reaction conditions: $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, –10 °C.

Hydroxyoxazolines **2** were used as ligands in the asymmetric catalytic Diels–Alder reaction between cyclopentadiene (**6**) and 3-acryloyl-1,3-oxazolidin-2-one (**7**) (Scheme 2). Substrates based on the oxazolidinone template have proven to be very efficient substrates with a large number of metal-based catalysts and have become standard in tests for new catalyst development.[11]



Scheme 2 Diels–Alder reaction

The reaction was carried out using 10 mol% of ligand and copper(II) triflate with respect to dienophile and seven equivalents of diene. Evaluation of the ligands and some relevant results of the optimization process are shown in Table 2. We first evaluated the effect of the substituent on the oxazoline ring with ligands **2a** and **2b** (entries 1 and 2). The presence of a phenyl group seemed to be advantageous and therefore some modifications of the reaction conditions were tested with **2b**. Toluene and dichloromethane as solvent gave similar results, while the reaction was much slower and less selective in acetone (entry 3). However, the ee with this ligand was never higher than 47%. Fortunately, a change in the stereochemistry of the stereogenic center of the oxazoline ring (as in **2c**) brought about an increase in the stereoselectivity, giving the Diels–Alder adduct **8** with 75% ee at –65 °C (entry 6). Remarkably, the Diels–Alder product was obtained with the opposite absolute stereochemistry with respect to the

Table 2 Evaluation of Ligands and Optimization

Entry	L	Solvent	T (°C)	T (h)	*endo*:*exo*[a]	ee (*endo*)[a,b]
1	**2a**	CH_2Cl_2	–30	45	85:15	19 (*R*)
2	**2b**	CH_2Cl_2	–30	0.6	80:20	46 (*R*)
3	**2b**	acetone	–20	20	90:10	24 (*R*)
4	**2b**	toluene	–30	1	85:15	47 (*R*)
5	**2c**	CH_2Cl_2	–30	1	89:11	70 (*S*)
6	**2c**	CH_2Cl_2	–65	1	92:8	75 (*S*)
7	**2d**	CH_2Cl_2	–65	1	97:3	90 (*S*)
8	**2d**	CH_2Cl_2	–78	1	98:2	90 (*S*)
9	**2d**[c]	CH_2Cl_2	–20	24	90:10	24 (*S*)
10	*epi*-**2d**	CH_2Cl_2	–78	1	94:6	6 (*S*)

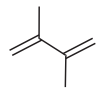
[a] Determined by chiral HPLC.
[b] Configuration of the C(2) carbon of the [2.2.1]bicyclo system in **8**.
[c] $Zn(OTf)_2$ was used instead of $Cu(OTf)_2$. The reaction did not proceed at lower temperatures.

product obtained with ligands **2a** and **2b**. Finally when rotation of the phenyl group was restricted as in the 2-aminoindanol-derived ligand **2d**, an additional increase in the enantioselectivity was observed, and the Diels–Alder product was obtained in 90% ee with high diastereoselectivity (entries 7 and 8). The use of Zn complexes gave the product with lower ee (entry 9).

The effect of the stereochemistry of the hydroxyl-bearing carbon C(2) of the isobornyl framework was also studied. Inversion of the stereochemistry of this carbon in ligand *epi*-**2d** gave the Diels–Alder adduct with good diastereoselectivity, but the product was almost racemic (entry 10).

The reaction of 3-acryloyl-1,3-oxazolidin-2-one (**7**) with other less reactive dienes was carried out using the combination **2d**–Cu(OTf)$_2$ as catalyst. The results are shown in Table 3. In general, these less reactive dienes required higher reaction temperatures and the products were obtained with good yields and fair to good enantioselectivities. Remarkably, the product of the reaction with isoprene at 0 °C (entry 3) was obtained with better stereoselectivity than that reported for the Cu(II)–BOX system (*endo*/*exo*, 97:3 and 60% ee), one of the considered 'privileged catalysts'.[12]

Table 3 Diels–Alder Reaction of 3-Acryloyl-1,3-oxazolidin-2-one and Some Dienes Catalyzed by the Complex Cu(II)–**2d**

Entry	Diene	T (°C)	T (h)	Yield (%)	*endo*/*exo*	ee (*endo*)	ee (*exo*)
1		–78	1	98	98:2	90	52
2		25	18	87	98:2	77	78
3		0	24	72	98:2	79[a]	56[b]
4		0	90	60		55	

[a] Refers to the 1,4-disubstituted regioisomer.
[b] Refers to the 1,3-disubstituted regioisomer.

In summary, we have prepared new ligands for metal-catalyzed reactions. These ligands, based on ketopinic acid, combine an oxazoline ring and a hydroxyl group as chelating groups. They are readily synthesized in a three-step sequence with good yields and structural variety is possible by modifying the starting amino alcohol. These ligands are effective in the asymmetric copper-catalyzed Diels–Alder reaction using *N*-alkenoyl-1,3-oxazolidin-2-ones as dienophiles.[13] Studies on the scope of the Diels–Alder reaction as well as toward extending the use of these ligands to other asymmetric reactions are underway.

Acknowledgment

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(13) **Experimental Procedure for the Synthesis of Compound 2d**: A solution of (*S*)-(+)-ketopinic acid (**1**, 1.0 g, 5.5 mmol) in $SOCl_2$ (4.5 mL) was refluxed for 2 h and the excess $SOCl_2$ was removed under reduced pressure. The residue dissolved in CH_2Cl_2 (3.8 mL) was added dropwise to a solution of (1*R*,2*S*)-1-amino-2,3-dihydro-1*H*-inden-2-ol (**3d**, 0.82 g, 5.5 mmol) and Et_3N (0.75 mL, 5.5 mmol) in CH_2Cl_2 (3 mL) at 0 °C under nitrogen. After 1 h, the mixture was diluted with EtOAc (150 mL), washed with 2 M HCl (2 × 30 mL), sat. aq $NaHCO_3$ (2 × 30 mL) and brine (30 mL), dried over $MgSO_4$ and concentrated. The crude product was crystallized from hexane–CH_2Cl_2 to give **4d**; yield: 2.0 g (80%); mp 163–165 °C; $[\alpha]_D^{25}$ +28.5 (*c* = 0.69, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.85 (d, *J* = 7.6 Hz, 1 H), 7.25 (m, 4 H), 5.47 (dd, *J* = 5.0, 8.1 Hz, 1 H), 4.70 (ddd, *J* = 2.1, 5.1, 5.1 Hz, 1 H), 3.19 (dd, *J* = 5.2, 16.6 Hz, 1 H), 3.00 (dd, *J* = 2.0, 16.6 Hz, 1 H), 2.63 (m, 1 H), 2.53 (m, 1 H), 2.13–2.23 (m, 3 H), 2.00 (d, *J* = 18.7 Hz, 1 H), 1.67 (m, 1 H), 1.46 (m, 1 H), 1.30 (s, 3 H), 1.10 (s, 3 H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 216.6 (s), 169.7 (s), 140.6 (s), 140.1 (s), 128.0(d), 127.0(d), 125.3 (d), 124.2 (d), 73.5 (d), 65.4 (s), 57.5 (d), 50.1 (s), 43.7 (t), 43.4 (d), 39.6 (t), 27.9 (t), 27.5 (t), 20.8 (q), 20.7 (q). MS (FAB): *m*/*z* (%) = 314 (100) [M^+ + 1], 282 (45), 154 (40). HRMS: *m*/*z* [M + H] calcd for $C_{19}H_{23}NO_3$: 313.1751; found: 314.1749.

A solution of **4d** (2.49 g, 7.9 mmol) and $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ (988 mg, 0.8 mmol) in toluene (160 mL) was refluxed with a Dean–Stark trap for 4 h. The reaction mixture was filtered through a short pad of silica gel (2 cm), concentrated and the residue was chromatographed on silica gel using hexane–EtOAc mixtures to give **5d**; yield: 1.60 g (64%); mp 118–121 °C; $[\alpha]_D^{25}$ +228.3 (*c* = 0.69, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.47 (m, 1 H), 7.21 (m, 3 H), 5.53 (d, *J* = 7.9 Hz, 1 H), 5.39 (ddd, *J* = 1.8, 6.8, 8.5 Hz, 1 H), 3.41 (dd, *J* = 6.8, 17.8 Hz, 1 H), 3.18 (dd, *J* = 1.5, 17.8 Hz, 1 H), 2.39–2.54 (m, 2 H), 2.06 (dd, *J* = 4.4, 4.4 Hz, 1 H), 1.96 (m, 1 H), 1.91 (d, *J* = 18.3 Hz, 1 H), 1.74 (ddd, *J* = 4.8, 9.3, 14.0 Hz, 1 H), 1.36 (ddd, *J* = 4.1, 9.2, 12.8 Hz, 1 H), 1.02 (s, 3 H), 0.73 (s, 3 H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 211.8 (s), 164.4 (s), 142.2 (s), 139.1 (s), 128.1 (d), 127.2 (d), 125.3 (d), 125.0 (d), 83.2 (d), 75.8 (d), 62.5 (s), 49.6 (s), 44.3 (d), 43.7 (t), 39.8 (t), 27.1 (t), 26.5 (t), 21.5 (q), 19.3 (q). MS (EI): *m*/*z* (%) = 295 (50) [M^+], 280 (10), 267 (29), 252 (39), 226 (15), 165 (16), 130 (62), 115 (100), 104 (52), 77 (39), 67 (31). HRMS: *m*/*z* [M] calcd for $C_{19}H_{21}NO_2$: 295.1572; found: 295.1551.

$NaBH_4$ (22.6 mg, 0.6 mmol) was added to a solution of **5d** (178 mg, 0.6 mmol) and $CeCl_3{\cdot}7H_2O$ (223 mg, 0.6 mmol) in MeOH (4 mL) at –10 °C. After 10 min, sat. aq NH_4Cl (5 mL) was added, the mixture was diluted with EtOAc (100 mL) and washed with brine (2 × 10 mL), dried and concentrated under reduced pressure. Column chromatography (hexane–EtOAc, 8:2) gave **2d** (88 mg, 50%) and *epi*-**2d** (18 mg). Compound **2d**: mp 98–101 °C; $[\alpha]_D^{25}$ +214.2 (*c* = 0.80, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.47 (m, 1 H), 7.27 (m, 3 H), 5.79 (br s, 1 H), 5.58 (d, *J* = 8.1 Hz, 1 H), 5.29 (ddd, *J* = 1.8, 7.2, 8.1 Hz, 1 H), 3.90 (dd, *J* = 3.5, 7.8 Hz, 1 H), 3.47 (dd, *J* = 7.0, 18.0 Hz, 1 H), 3.23 (dd, *J* = 1.6, 18.0 Hz, 1 H), 2.07 (m, 1 H), 1.91 (m, 1 H), 1.81 (m, 2 H), 1.71 (dd, *J* = 7.8, 12.9 Hz, 1 H), 1.24 (s, 3 H), 1.10 (m, 2 H), 1.07 (s, 3 H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 169.2 (s), 141.7 (s), 139.4 (s), 128.3 (d), 127.3 (d), 125.5 (d), 125.1 (d), 81.5 (d), 77.3 (d), 75.4 (d), 52.7 (s), 50.0 (s), 45.6 (d), 39.6 (t), 39.4 (t), 29.9 (t), 27.5 (t), 21.9 (q), 20.6 (q). MS (EI): *m*/*z* (%) = 297 (13) [M^+], 282 (50), 269 (69), 254 (61), 228 (17), 214 (42), 186 (13), 151 (14), 132 (20), 115 (100), 104 (23), 77 (24). HRMS: *m*/*z* [M] calcd for $C_{19}H_{23}NO_2$: 295.1729; found: 297.1723.

Experimental Procedure for the Enantioselective Diels–Alder Reaction: Copper triflate (9.0 mg, 0.025 mmol) in a Schlenk tube was dried at 90 °C under vacuum for 1 h. The tube was filled in with nitrogen and **2d** (7.5 mg, 0.025 mmol) was added followed by CH_2Cl_2 (1.5 mL). The mixture was stirred for 1 h and the dienophile **7** (35 mg, 0.25 mmol) was added. After stirring for 30 min cyclopentadiene (**6**; 115 mg, 1.75 mmol) was added at –78 °C. After 1 h, the solvent was removed under reduced pressure and the product was purified by column chromatography to give compound **8**; yield: 50.5 mg (98%); $[\alpha]_D^{25}$ –149.0 (*c* = 1.0, $CHCl_3$; for a 90% ee and 98:2 *endo*/*exo* mixture). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.23 (dd, *J* = 3.1, 5.6 Hz, 1 H), 5.86 (dd, *J* = 2.8, 5.6 Hz, 1 H), 4.40 (m, 2 H), 3.95 (m, 3 H), 3.30 (br s, 1 H), 2.93 (br s, 1 H), 1.94 (ddd, *J* = 3.7, 9.2, 12.1 Hz, 1 H), 1.50–1.38 (m, 3 H). Chiral HPLC: Chiralpak AD-H, hexane–*i*-PrOH (93:7), flow rate: 1 mL/min, exo_{minor} t_R = 16.5 min, $endo(S)_{major}$ t_R = 17.6 min, exo_{major} t_R = 21.5 min, $endo(R)_{minor}$ t_R = 22.5 min.