Pergamon

Tetrahedron: Asymmetry, Vol. 8, No. 18, pp. 3079–3087, 1997

Printed in Great Britain

PII: S0957-4166(97)00323-6

0957-4166/97 $17.00 + 0.00

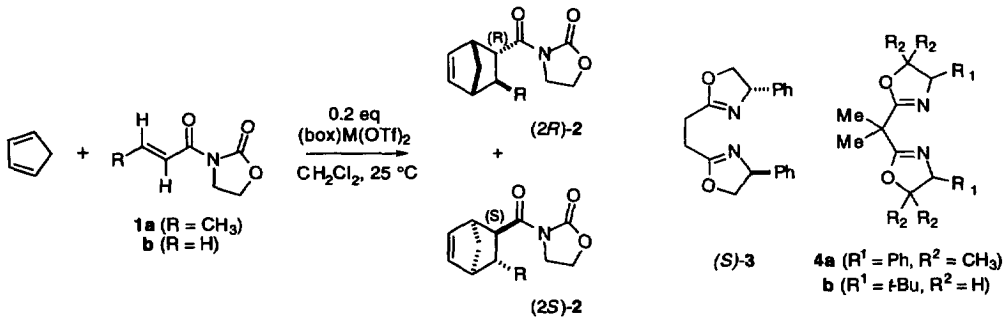
Enantioselective Diels–Alder reactions: novel constrained bis(oxazoline) ligand–metal triflate catalysts

James M. Takacs,* David A. Quincy, William Shay, Brian E. Jones and Charles R. Ross, II †

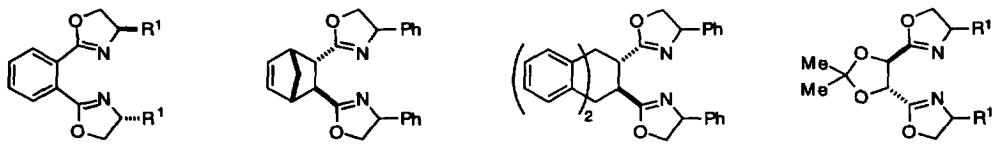
Department of Chemistry, University of Nebraska-Lincoln, Lincoln, NE 68588-0304, USA

Abstract: Five chiral 1,4-bis(oxazoline) ligands, each bearing a bicyclic backbone, were prepared and examined in $Mg(OTf)_2$-, $Zn(OTf)_2$-, and $Cu(OTf)_2$-catalyzed Diels–Alder reactions. The cycloadditions were carried out at room temperature and afforded enantiomeric excess up to 88%. Surprisingly, a non-C_2-symmetric bis(oxazoline) bearing a meso backbone was among the more efficient ligands examined. © 1997 Elsevier Science Ltd

As discussed in the preceding paper, we have been interested in room temperature $[(box)M(OTf)_2]$-catalyzed reactions, and screened a number of such complexes in the Diels–Alder reaction of N-crotonyloxazolidinone (**1a**) with cyclopentadiene.[1] Under these conditions, the combination of 1,4-box ligand (*S*)-**3** and $Zn(OTf)_2$ gave cycloadduct (2*S*)-**2** in 78% ee, and for $Zn(OTf)_2$, the 1,4-box ligand **3** was substantially more selective than any of the chiral 1,2- or 1,3-box ligands screened. In contrast, for $Mg(OTf)_2$ and $Cu(OTf)_2$, the 1,3-box ligands **4a**[2] and **4b**[3] showed substantially higher enantioselectivity than either metal triflate in combination with the 1,4-box ligands screened.



Having obtained encouraging levels of stereoinduction with the simple 1,4-box ligand **3**, we thought that a more highly constrained derivative might afford an even better $[(1,4\text{-box})Zn(OTf)_2]$-catalyst. Our initial attempt, $Zn(OTf)_2$ and **5** (R^1=Ph), failed to give appreciable enantiomeric excess; a result that is perhaps not surprising in light of Bolm's published crystal structure for the $[(\mathbf{5}, R^1=i\text{-Pr})ZnCl_2]$ complex.[4]



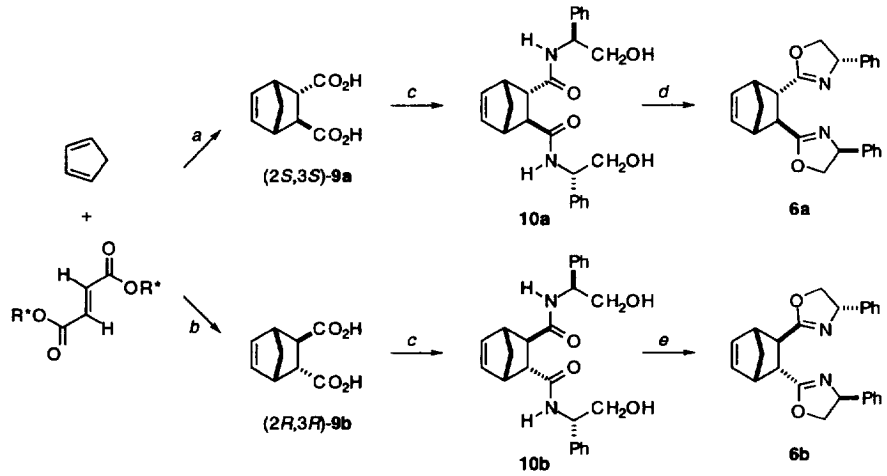
5 **6** **7** **8**

* Corresponding author. Email: jtakacs@unlinfo.unl.edu

† The author to whom questions regarding the crystal structure determination should be directed.

A number of other conformationally constrained 1,4-box ligands were considered. On the basis of molecular modeling, it was anticipated that ligands built around bicyclo[2.2.1] and bicyclo[2.2.2]-backbones would each have a substantially different bite angle and nitrogen–nitrogen distance than **3**, as a consequence of the relatively large dihedral angle between the two oxazoline moieties.[5] We therefore set out to prepare ligands related to structures **6** and **7**. During the course of our studies, a group at Merck compared 1,3-box ligands of differing bite angle,[6] and several groups reported the synthesis and use of a conceptually related tartrate-derived 1,4-box ligand **8**.[7–9]

The syntheses of **6a** and **b** are illustrated in Scheme 1. The bicyclic backbone is chiral, and hence, must be prepared in enantiomerically pure form. This is accomplished via the known Lewis acid catalyzed Diels–Alder reaction between cyclopentadiene and the (L) menthol-derived dimenthyl fumarate.[10] The cycloaddition proceeds with high diastereoselectivity, and after hydrolysis, affords the bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid **9a** possessing the (2*S*,3*S*) absolute configuration.[11] Coupling (2*S*,3*S*)-**9** with (*S*)-phenylglycinol via the mixed anhydride affords bis(hydroxyamide) **10a**.[12] Conversion of bis(hydroxyamide) **10a** to the corresponding bis(oxazoline) can be carried out in two steps with isolation of an intermediate dichloride.[13] We also find that **10a** can be converted to **6a** in one pot by treatment with PPh_3 and CCl_4 (acetonitrile, Et_3N, RT, 9h, 88%)[14] or by treatment with 2.2 equivalents of $SOCl_2$ followed after 1 hour by the addition of 4.4 equivalents of Et_3N (CH_2Cl_2, 0°C, 8 h). All of the stereocenters in **6a** are of the *S* absolute configuration. Coupling (2*R*,3*R*)-**9b** with (*S*)-phenylglycinol leads ultimately to the diastereomeric ligand, **6b**.



Conditions: a. (1) (L) dimenthyl fumarate, 1.05 equiv. Et_2AlCl, 1.3 equiv. C_5H_6, toluene, -78 °C, (4 h) -> RT (12 h), 96 % (2) 5 equiv. NaOH, 3:1 MeOH:H_2O, reflux, 24 h, 46 %; b. (1) (D) dimenthyl fumarate, 1.1 equiv. Et_2AlCl, 1.4 equiv. C_5H_6, toluene, -78 °C, (4 h) -> 25 °C (12 h), 76 % (2) 5 equiv. NaOH, 5:2 EtOH:H_2O, reflux, 24 h, 66 %; c. (1) 2.05 equiv. N-methylmorpholine, 2.05 equiv. *i*-BuOC(O)Cl, THF, -78 °C, 1 h (2) filter (3) 2.05 equiv. 2-phenylglycinol, THF, -78 °C, (3 h) -> RT (12 h), 64 % **10a**, 36 % **10b**; d. 2.3 equiv. PPh_3, 5 equiv. CCl_4, 2.3 equiv. Et_3N, acetonitrile, RT, 9 h, 88 %; e. (1) 2.2 equiv. $SOCl_2$, CH_2Cl_2, 0 °C, 1 h (2) 4.4 equiv. Et_3N, CH_2Cl_2, 0 °C, 8 h, 33 %.

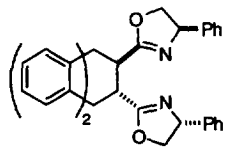
Scheme 1. Preparation of the diastereomeric bicyclo[2.2.1]-1,4-box ligands **6a** and **6b**.

The corresponding diastereomeric bicyclo[2.2.2]-1,4-box ligands **7a** and **7b** were prepared in a similar fashion.[5] However in forming the diamide intermediate some epimerization occurs, and consequently, in addition to **7a** and **7b**, we isolate small amounts of **7c**; a diastereomer chiral by virtue of the oxazoline moieties but possessing a *meso* bicyclo[2.2.2]backbone.

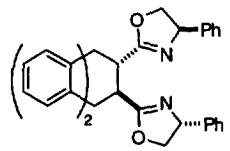
Table 1. Room temperature [(1,4-box)M(OTf)$_2$]-catalyzed cycloadditions of **1a** and **1b** with cyclopentadiene.[a]

	$Mg(OTf)_2$		$Zn(OTf)_2$				$Cu(OTf)_2$			
	2a		**2a**		**2b**		**2a**		**2b**	
ligand[b]	endo:exo	% ee[c]	endo:exo	% ee[c]	endo:exo	% ee[c]	endo:exo	% ee[c]	endo:exo	% ee[c]
3 (S)	7.4[d]	17 (S)	8.0	78 (S)	10.0	74 (S)	2.6	51 (S)		
6a (S)	2.1	10 (S)	**6.7**	**78 (S)**	**7.3**	**76 (S)**	4.9	34 (S)		
6b (S)	1.6[d]	22 (S)	**7.3**	**76 (S)**	3.4	54 (S)	**7.3**	**88 (S)**		
7a (R)	1.9[d,e]	15 (S)	6.7	58 (R)	9.0	43 (R)	2.2	24 (S)	4.0	39 (S)
7b (R)			6.1	48 (R)			1.9	28 (S)		
7c (R)	5.0[e]	12 (S)	**5.7**	**74 (R)**	9.0	46 (R)	**8.1**	**72 (R)**	**10.1**	**75 (R)**

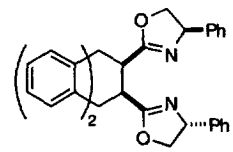
a) A mixture of **1** (0.50 mmol), M(OTf)$_2$ (0.10 mmol), and box (0.11 mmol) in dichloromethane (ca. 0.1 M in **1**, 25 °C) was allowed to equilibrate for ca. 30 min followed by the addition of cyclopentadiene (6 mmol). Reactions were run until **1** was completely consumed up to a limit of 24 h. b) The absolute configuration of the oxazoline is indicated in parenthesis. c) The absolute configuration of the 2-position in product **2** is indicated in parentheses. d) The reaction did not go to completion under these reaction conditions. e) This reaction was run in 1,2-dichloroethane.



7a



7b



7c
(meso backbone)

The results of room temperature [(1,4-box)M(OTf)$_2$]-catalyzed Diels–Alder reactions between N-acyloxazolidinones **1a** or **1b** and cyclopentadiene are tabulated (Table 1). None of the [(1,4-box)Mg(OTf)$_2$]-catalysts afford a significant level of enantioselectivity, and in most cases, the reactions do not proceed to completion within 24 hours.

The (*S*)-[(**3**)Zn(OTf)$_2$]-catalyzed reaction affords predominantly (*S*)-**2** (78% ee), and as discussed in the preceding paper, the product can be rationalized by invoking a reactive octahedral [(**3**)Zn(OTf)$_2$(**1**)]-complex. For the bicyclo[2.2.1]-derivatives **6**, the results largely mirror those obtained with (*S*)-**3**. The chirality of the backbone has little or no influence on the sense or degree of asymmetric induction. Both diastereomers of **6**, each constructed with the *S* absolute configuration within the oxazoline ring, afford (*S*)-**2a** from **1a** in 76–78% ee. In the corresponding reaction of N-acyloxazolidinone **1b**, ligand **6a** is somewhat more selective ((*S*)-**2b**, 76% ee) than **6b** ((*S*)-**2b**, 54% ee). The corresponding bicyclo[2.2.2]-box ligands **7a** and **7b** give similar results with Zn(OTf)$_2$, although the level of enantioselectivity is lower (43–58% ee).

The idea of exploiting C_2-symmetry in the design of chiral ligands remains almost irresistibly appealing, in spite of the many successful asymmetric catalysts using non-C_2-symmetric ligands and the growing recognition that C_2-symmetric ligands do not guarantee a C_2-symmetric metal complex. From the standpoint of catalysis **6a** and **b** can be considered pseudo-C_2-symmetric ligands; the asymmetric element resides far from the metal center in the complex. However, it is hard to make the same case for the bicyclo[2.2.2]-derivative bearing the meso backbone, **7c**. Nonetheless, the [(**7c**)Zn(OTf)$_2$]-catalyst is more selective (**2a** 74% ee) than the diastereomeric complexes derived from either **7a** or **7b**. The same can be said of [(**7c**)Cu(OTf)$_2$] (72% ee).

The Cu(OTf)$_2$ catalysts are unusual in other regards. In contrast to Zn(OTf)$_2$ catalysts, the bicyclo[2.2.1]-backbone chirality strongly influences the level of asymmetric induction. The [(**6b**)Cu(OTf)$_2$]-complex affords (*S*)-**2a** in 88% ee, while **6a** affords only 34% ee. Furthermore,

while Evans' square planar Cu(II) model[3] correctly predicts the major stereoisomer formed by the $Cu(OTf)_2$-complexes derived from **3**, **6a**, **6b**, and **7c**, those derived from **7a** and **7b** give the opposite sense of asymmetric induction; that is, substituted oxazolines of the *R* absolute configuration give rise to predominantly (*S*)-**2a** and **b** (24–39% ee). The reason for the change in the sense of stereoinduction is not clear, however, a rather subtle conformational change proposed by Jørgensen for a related catalyst complex could be relevant.[15,16]

In summary, five new 1,4-box ligands based on bicyclic backbones were prepared and used in combination with metal(II)triflates to catalyze asymmetric Diels–Alder reactions. The catalyzed cycloadditions were carried out at room temperature and gave products in up to 88% ee. Among the more surprising results, we found that one of the least likely candidates, ligand **7c**, is among the more efficient ligands examined.

Experimental section

For a discussion of the general procedures employed, including a detailed procedure for carrying out and analyzing the [(box)M(OTf)2]-catalyzed Diels–Alder cycloadditions, see the preceding paper.[1] (D) and (L) dimenthyl furamate were prepared via the method of Scharf and coworkers.[17]

*Preparation of di-(D)-menthyl (2R,3R)-[2.2.1]bicyclohept-5-ene-2,3-dicarboxylate [(**11b**), CAS reg #125226-88-2]*[10]

To a cooled solution (−78°C) of (D) dimenthyl fumarate (35.08 g, 89.5 mmol) in toluene (200 mL) was added diethylaluminum chloride (55.0 mL, 98.4 mmol). After stirring the resulting bright orange–red solution for 20 min (−78°C), cyclopentadiene (10.4 mL, 125 mmol) was added. The solution gradually changed to a light yellow. The reaction was maintained at −78° for 4 h, and then allowed to slowly warm to RT overnight. The reaction mixture was recooled to 0°C and quenched by the slow addition of water (10 mL). The yellow color dissipated and a white precipitate formed. After stirring for 2 h, the mixture was filtered and the filtrate washed sequentially with 1 N aq HCl (400 mL), 1 N aq $NaHCO_3$ (400 mL) and brine (250 mL). The toluene solution was dried ($MgSO_4$), filtered and concentrated to give a clear oil which crystallized on standing. The crude product was dissolved in hot methanol, filtered and crystallized to afford the desired diester (31.30 g, 76%): mp 89–90°C; $[\alpha]_D$=+0.12; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.27 (dd, J=2.8, 5.4 Hz, 1 H), 6.01 (dd, J=2.8, 5.6 Hz, 1 H), 4.68 (dt, J=10.9, 4.1 Hz, 1 H), 4.56 (dt, J=10.9 Hz, 4.5, 1 H), 3.33 (dd, J=4.0, 4.2 Hz, 1 H), 3.24 (s, 1 H), 3.09 (s, 1 H), 2.65 (dd, J=1.6, 4.4 Hz, 1 H), 2.00–1.85 (m, 4 H), 1.72–1.63 (m, 4 H), 1.60 (d, J=4.8 Hz, 1 H), 1.53–1.33 (m, 5 H), 1.10–0.93 (m, 4 H), 0.93–0.85 (m, 14 H), 0.77–0.70 (overlapping d's, J=6.8 Hz, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.9 (s), 172.7 (s), 137.6 (d), 134.8 (d), 74.6 (d), 74.5 (d), 48.1 (d), 47.6 (d), 47.3 (overlapping resonances, d and t), 47.04 (d), 46.99 (d), 45.8 (d), 40.9 (t), 40.8 (t), 34.3 (t), 31.4 (d), 31.3 (d), 26.3 (d), 26.1 (d), 23.3 (t), 23.2 (t), 21.9 (q), 20.8 (q), 16.09 (q), 16.06 (q).

Di-(L)-menthyl (2*S*,3*S*)-[2.2.1]bicyclohept-5-ene-2,3-dicarboxylate (**11a**) was similarly prepared: mp 85–87°C; $[\alpha]_D$=−0.16.

*Preparation of (2R,3R) [2.2.1]bicyclohept-5-ene-2,3-dicarboxylic acid [(**9b**), CAS reg # 32216-02-7]*

A solution of dimenthyl ester **11b** (45.0 g, 98.4 mmol) and NaOH (37.7 g, 0.94 mol) in a mixture of EtOH (1 l) and water (400 mL) was refluxed for 12 h, then cooled (RT) and the ethanol removed via rotovap. The aqueous residue was washed with hexane (5×250 mL), cooled to 0°C, and acidified to pH 2 with 12 N HCl. The resulting solution was extracted with ether (2×250 mL) and with $CHCl_3$ (250 mL). The latter organic extracts were combined, dried ($MgSO_4$) and concentrated to afford an off-white solid. Recrystallization from methanol gave the desired diacid **9b** (11.70 g, 66%): mp 167–173°C; $[\alpha]_D$=−135 (c 3.09, acetone); ^{1}H NMR (500 MHz, acetone-d_6) δ 6.28 (dd, J=2.7, 5.5 Hz, 1 H), 6.08 (dd, J=2.7, 5.5 Hz), 3.35 (m, 1 H), 3.23 (m, 1 H), 3.11 (m, 1 H), 2.61 (m, 1 H), 1.59

(d, J=8.6 Hz, 1 H), 1.39 (dd, J=1.7, 8.6 Hz, 1 H); ^{13}C NMR (125 MHz, acetone-d_6) δ 175.8 (s), 174.6 (s), 138.0 (d), 135.7 (d), 48.14 (d), 48.10 (d), 47.72 (t), 47.42 (d), 46.0 (d).

(2*S*,3*S*) [2.2.1]bicyclohept-5-ene-2,3-dicarboxylic acid (**9a**), CAS reg. # 70190-87-3) was prepared similarly: mp 173–176°C.

*Preparation of bis(hydroxyamide) **10a***

A cold (−78°C) solution of dicarboxylic acid **9a** (1.60 g, 8.8 mmol) and N-methyl morpholine (2.00 mL, 18.1 mmol) in THF (20 mL) was added to a cold (−78°C) solution of isobutyl chloroformate (2.35 mL, 2.48 g, 18.1 mmol) in THF (100 mL). After 1h (−78°C), the solution was filtered and the filtrate quickly passed through a plug of silica, keeping the filtrate as cold as possible during these manipulations. (It should be noted that epimerization of the stereogenic center adjacent to the carbonyl can be problematic, and therefore, it is important to keep the solution cold (i.e., less than ca. −10°C).) The intermediate mixed anhydride was then recooled (−78°C) and added via canula to a cold solution (−78°C) of (*S*)-phenylglycinol (2.50 g, 18.1 mmol) in THF (100 mL). The reaction mixture was slowly warmed to RT overnight, and then concentrated via rotovap. The residue was dissolved in $CHCl_3$ (500 mL) and washed sequentially with 100 mL portions of 10% aq K_2CO_3, 0.5 N aq HCl, and brine. The organic layer was dried ($MgSO_4$) and concentrated, and the residue crystallized from EtOAc–$CHCl_3$ to afford bis(hydroxyamide) **10a** as white needles (2.59 g, 64%): mp 115–118°C; $[\alpha]_D$=+180 (c 1.43, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.44 (d, J=8.1 Hz, 1 H), 8.21 (d, J=7.9 Hz, 1 H), 7.42–7.15 (m, 10 H), 6.13 (dd, J=3.1, 5.5 Hz, 1 H), 5.67 (dd, J=2.4, 5.4 Hz, 1 H), 5.40–5.30 (m, 2 H), 3.57–3.52 (m, 4 H), 3.35–3.30 (m, 1 H), 3.27 (s, 1 H), 3.15 (d, J=6.4, 0.74 H, impurity), 2.76 (s, 1 H), 2.66 (d, J=3.8 Hz, 1 H), 1.60 (d, J=7.15, 1 H), 1.20–1.10 (m, 1 H), 0.80 (d, J=10 Hz, 2.45 H, impurity); ^{13}C (75 MHz, $CDCl_3$) δ 175.6 (s), 174.5 (s), 139.2 (d), 139.0 (d), 136.5 (s) 135.3 (s), 128.5 (d), 128.4 (d), 127.4 (d), 126.8 (d), 126.5 (d), 65.8 (t), 65.6 (t), 56.0 (d), 55.9 (d), 49.98 (d), 49.59 (d), 48.37 (d), 48.22 (d), 46.67 (d); IR (thin film, NaCl) 3342 (OH), 1642 (C=O). A potion was recrystallized again: Combustion analysis ($C_{25}H_{28}N_2O_4$=71.41% C, 6.71% H) found 71.26% C, 6.70% H.

*Preparation of bis(hydroxyamide) **10b***

Using the procedure described for the preparation of bis(hydroxyamide) **10a**, dicarboxylic acid **9b** (2.28 g, 12.5 mmol), Et_3N (3.60 mL, 25.7 mmol), isobutyl chloroformate (3.30 mL, 25.7 mmol), and (*S*)-phenylglycinol (3.50 g, 25.7 mmol) afforded, after crystallization from EtOAc–hexanes, the desired bis(hydroxyamide) **10b** as a white solid (1.90 g, 36%): ^{1}H NMR (300 MHz, CD_3OD) δ 7.33–7.18 (m, 12 H), 6.28 (dd, J=3.2, 5.5 Hz, 1 H), 6.08 (dd, J=2.8, 5.6 Hz, 1 H), 5.05–4.85 (m, 2 H), 4.83 (s, CD_3OH), 3.75–3.52 (m, 4 H), 3.28 (m, CD_3OD), 3.24 (s, 1 H), 3.17 (partially resolved dd, J=3.8, 4.8 Hz, 1 H), 3.01 (s, 1 H), 2.58 (dd, J=1.4, 5.0 Hz, 1 H), 1.84 (d, J=8.3 Hz, 1 H), 1.39 (dd, J=1.3, 8.3 Hz, 1 H); Combustion analysis ($C_{25}H_{28}N_2O_4$=71.41% C, 6.71% H) found 71.66% C, 6.96% H.

*Preparation of box ligand **6a***

(a) Via the method of Vorbruggen[14]

To a suspension of bis(hydroxyamide) **10a** (1.00 g, 2.4 mmol), PPh_3 (1.40 g, 5.5 mmol), and CCl_4 (1.20 mL, 12 mmol) in acetonitrile (30 mL, RT) was added Et_3N (0.80 mL, 5.6 mmol). Within 10 min, the bis(hydroxyamide) dissolved and the solution began to turn yellow. Stirring was continued for a total of 9 h, after which the mixture passed through a plug of silica and the filtrate concentrated to dryness. The residue was triturated with ether (30 mL), and the ether soluble fraction concentrated. Chromatography on silica ($CHCl_3$–hexanes followed by 5% EtOH in $CHCl_3$ afforded box ligand **6a** (822 mg, 88%) as a waxy solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.16 (m, 10 H), 6.40 (dd, J=3, 5 Hz, 1 H), 6.20 (dd, J=3, 5 Hz, 1 H), 5.21 (t, J=8 Hz, 1 H), 5.14 (apparent t, J=9 Hz, 1 H), 4.65 (dd, J=8, 10 Hz, 1 H), 4.58 (dd, J=8, 10 Hz, 1 H), 4.13 (t, J=9 Hz, 1 H), 4.03 (t, J=8 Hz, 1 H), 3.63 (m, 1 H), 3.36 (s, 1 H), 3.27 (d, J=0.8 Hz, 1 H), 2.96 (d, J=4.8 Hz, 1 H), 1.81 (d, J=9 Hz, 1 H), 1.60 (dd, J=1, 8 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4 (s), 169.6 (s), 142.7 (s), 142.6 (s), 137.4 (d), 135.1 (d), 128.82 (d), 128.77 (d), 128.67 (d), 128.57 (d), 127.47 (d), 127.36 (d), 126.67 (d), 126.63

(d), 126.55 (d), 126.51 (d), 75.13 (t), 75.10 (t), 69.53 (d), 69.45 (d), 47.43 (d), 47.26 (d), 45.67 (d), 42.80 (d), 42.63 (d); HRMS analysis ($C_{25}H_{24}N_2O_2$=384.1838) found *m/z* 384.18491.

(b) Via the isolated bisamide dichloride

To a stirred slurry of bis(hydroxyamide) **10a** (500 mg, 1.19 mmol) in benzene (10 mL) was added $SOCl_2$ (0.70 mL, 9.5 mmol). The resulting mixture was heated to reflux under a slow N_2 purge. After 45 min, the reaction mixture was allowed to cool to RT, 1 N aq $NaHCO_3$ (10 mL) added and the mixture stirred for 1 h. The organic layer was separated, washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated. Chromatography on silica (EtOAc–hexanes) afforded the dichloride (818 mg, 75%) as a white solid: mp 161–162°C; $[\alpha]_D$=+119 (c 2.00, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.32–7.20 (m, 10 H), 7.15 (d, J=8 Hz, 1 H), 6.63 (d, J=8 Hz, 1 H), 6.30 (dd, J=3, 5 Hz, 1 H), 6.18 (dd, J=3, 5 Hz, 1 H), 5.4–5.3 (m, 2 H), 3.95–3.75 (m, 4 H), 3.25 (s, 1 H), 3.20 (s, 1 H), 3.10 (s, 1 H), 2.55 (d, J=5 Hz, 1 H), 1.78 (d, J=8 Hz, 1 H), 1.58 (dd, J=1.6, 8 Hz, 1 H); ^{13}C (75 MHz, $CDCl_3$) δ 174.1 (s), 173.1 (s), 138.6 (s), 138.4 (s), 138.0 (d), 134.4 (d), 128.8 (d), 128.1 (d), 128.0 (d), 126.6 (d), 126.5 (d), 53.8 (d), 53.7 (d), 51.1 (d), 49.1 (d), 48.6 (t), 47.8 (t), 45.4 (d), 44.5 (d); IR (thin film, NaCl) 1642 (C=O); Combustion analysis ($C_{25}H_{26}N_2O_2Cl_2$=65.65% C, 5.73% H) found 65.76% C, 5.70% H.

A solution of bisamide dichloride (379 mg, 0.83 mmol) and sodium hydroxide (133 mg, 3.32 mmol) in MeOH–water (10 mL, 4:1) was stirred at RT for 60 h. The methanol was removed in vacuo, and the residue diluted with brine and extracted with two 20 mL portions of $CHCl_3$. The combined organic extracts were dried ($MgSO_4$) and concentrated. Chromatography on silica ($CHCl_3$–hexanes) afforded **6a** (135.5 mg, 42%).

(c) One pot preparation of ent-***6a***

To a cooled (0°C) suspension of the bis(hydroxyamide) *ent*-**10a** (0.507 g, 1.2 mmol) in CH_2Cl_2 (20 mL) was added $SOCl_2$ (0.20 mL, 2.7 mmol). The bis(hydroxyamide) slowly dissolved, and after 15 min, Et_3N (0.74 mL, 5.3 mmol) was added dropwise. The reaction mixture was stirred at 0°C for 8 h, and then partitioned with 1 N aq $NaHCO_3$ (30 mL). The organic layer was dried ($MgSO_4$), filtered through a small plug of silica, and concentrated. Chromatography on basic alumina (10 g, EtOAc–hexanes) afforded some pure *ent*-**6a** (192.4 mg, 42%) and additional partially contaminated ligand (300 mg) from which additional product could be obtained upon rechromatography. Characterization data: TLC analysis (silica, 5% EtOH in $CHCl_3$) R_f=0.30; mp 84–86°C; $[\alpha]_D$=−99 (c 3.48, $CHCl_3$); HRMS analysis ($C_{25}H_{24}N_2O_2$=384.1838) found *m/z* 384.18311; Combustion analysis ($C_{25}H_{24}N_2O_2$=78.10% C, 6.29% H, 7.29% N) found 78.20% C, 6.41% H, 7.35% N.

Preparation of box ligand ***6b***

(a) Via the isolated dichloride

To a suspension of bis(hydroxyamide) **10b** (550 mg, 1.3 mmol) in benzene (10 mL) was added $SOCl_2$ (0.76 mL, 1.25 g, 10.5 mmol). The resulting mixture was refluxed for 1 h (eventually forming a homogeneous solution), and then cooled to RT and quenched by pouring onto an ice–1 N aq $NaHCO_3$ mixture. The layers were separated and the aqueous layer extracted with EtOAc (2×25 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to afford crude bisamide dichloride which was used without further purification. Spectral data (obtained on the (2*S*,3*S*) enantiomer): $[\alpha]_D$=+1.2 (c 2.4, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.38–7.22 (m, 10 H), 7.12 (d, J=8.1 Hz, 1 H), 6.60 (d, J=7.9 Hz, 1 H), 6.35 (dd, J=3.2, 5.5 Hz, 1 H), 6.23 (dd, J=2.6, 5.4 Hz, 1 H), 5.31 (m, 2 H), 3.90–3.70 (m, 4 H), 3.17 (s, 1 H), 3.14 (dd, J=0.5, 1.0 Hz, 1 H), 3.10 (dd, J=3.3, 5.2 Hz, 1 H), 2.58 (dd, J=1.9, 5.2 Hz, 1 H), 1.76 (d, J=8.0 Hz, 1 H), 1.58 (dd, J=1.6, 8.6 Hz, 1 H); ^{13}C (125 MHz, CD_3OD) δ 174.0 (s), 173.0 (s), 138.6 (s), 138.3 (s), 138.2 (d), 134.3 (d), 128.78 (d), 128.70 (d), 128.08 (d), 127.91 (d), 127.2 (d), 127.1 (d), 53.83 (d), 53.68 (d), 50.57 (d), 48.6 (d), 48.4 (t), 47.8 (t), 47.6 (t), 46.0 (d), 44.8 (d); IR (thin film, NaCl) 1643 (C=O).

A solution of the bisamide dichloride (3.10 g, 6.8 mmol) in 0.5 N NaOH in 50% aq MeOH (135 mL) was refluxed for 1 h. The resulting mixture was cooled to RT and the MeOH removed via rotovap. The aqueous residue was extracted with ether (2×100 mL), and the combined ether extracts dried ($MgSO_4$) and concentrated. Chromatography on silica (3% EtOH in $CHCl_3$) gave box ligand **6b** (800 mg, 31%): $[\alpha]_D$=+92.4 (c 2.61, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.36–7.16 (m, 10 H), 6.38 (dd, J=3, 5 Hz, 1 H), 6.20 (dd, J=3, 5 Hz, 1 H), 5.21 (t, J=8 Hz, 1 H), 5.13 (apparent t, J=9 Hz, 1 H), 4.65 (dd, J=8, 10 Hz, 1 H), 4.58 (dd, J=8, 10 Hz, 1 H), 4.13 (t, J=9 Hz, 1 H), 4.03 (t, J=8 Hz, 1 H), 3.63 (m, 1 H), 3.36 (s, 1 H), 3.27 (s, 1 H), 2.89 (d, J=4.8 Hz, 1 H), 1.81 (d, J=9 Hz, 1 H), 1.60 (dd, J=1.6, 8.9 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4 (s), 169.5 (s), 142.66 (s), 142.62 (s), 137.3 (d), 135.2 (d), 128.66 (d), 128.57 (d), 127.45 (d), 127.36 (d), 126.5 (d), 75.1 (t), 74.9 (t), 69.45 (d), 69.36 (d), 47.6 (d), 47.3 (d), 45.8 (d), 43.1 (d), 42.6 (d); HRMS analysis ($C_{25}H_{24}N_2O_2$=384.1838) found *m/z* 384.18322.

(b) One pot conversion via the dichloride

To a cooled (0°C) suspension of bis(hydroxyamide) **10b** (0.300 g, 0.7 mmol) in CH_2Cl_2 (20 mL) was added $SOCl_2$ (0.11 mL, 1.57 mmol). The bis(hydroxyamide) slowly dissolved, and after 15 min, Et_3N (0.44 mL, 3.14 mmol) was added dropwise. The resulting mixture was stirred at 0°C for 8 h, after which, the reaction mixture was partitioned with 1 N aq $NaHCO_3$ (30 mL). The organic layer was dried ($MgSO_4$), filtered through a small plug of silica, and concentrated. Chromatography on basic alumina (10 g, EtOAc–hexanes) afforded **6b** (90 mg, 33%).

Preparation of (11R,12R)-9,10-ethane-11,12-dimenthyl carboxylate-9,10-dihydro anthracene[10]

To a cooled (0°C) mixture of $AlCl_3$ (10.64 g, 80.0 mmol) and anthracene (7.30 g, 40.8 mmol) in toluene (350 mL) was added (D) dimenthyl fumarate (16.00 g, 40.8 mmol). The resulting mixture was warmed to RT and stirred for 4.5 hours. Afterwards, the reaction was quenched by the addition of water (100 mL). Ethyl acetate (200 mL) was added and the mixture stirred for several hours. The organic layer was separated and washed sequentially with satd aq NaCl (2×100 mL), 10% aq NaOH (100 mL), and satd aq NaCl (100 mL), then dried (Na_2SO_4) and concentrated. The resulting white solid was recrystallized from ethanol to give the title compound (18.00 g, 77% yield) as a white solid: mp 166–167°C; $[\alpha]_D$=+29.4 (c 4.99, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.37 (m, 2 H), 7.23 (m, 2 H), 7.12 (m, 4 H), 4.72 (s, 2 H), 4.60 (ddd, J=4.4, 4.4, 10.9 Hz, 2 H), 3.40 (s, 2 H), 2.00 (m, 2 H), 1.84 (m, 2 H), 1.70 (m, 4 H), 1.43 (m, 4 H), 0.98 (m, 18 H), 0.76 (d, J=7.2 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6 (s), 143.2 (s), 140.8 (s), 127.0 (d), 126.7 (d), 125.5 (d), 124.2 (d), 75.7 (d), 48.9 (d), 47.7 (d), 47.6 (d), 41.4 (t), 34.9 (t), 32.0 (d), 26.7 (d), 23.8 (t), 22.6 (q), 21.7 (q), 16.8 (q).

Using the procedure described above, (11*S*,12*S*)-9,10-ethane-11,12-dimenthyl carboxylate-9,10-dihydro anthracene was similarly prepared from (L) dimenthyl fumarate (5.66 g, 14.4 mmol) as a white solid (5.89 g, 71% yield): mp 168.5–170°C; $[\alpha]_D$=−30.0 (c=5.02, $CHCl_3$).

Preparation of (11R,12R)-9,10-ethane-11,12-dicarboxylic acid-9,10-dihydro anthracene[18]

A mixture of (11*R*,12*R*)-9,10-ethane-11,12-dimenthyl carboxylate-9,10-dihydro anthracene (9.60 g, 16.8 mmol) and 170 mL of 0.6 N sodium hydroxide (4.0 g, 100 mmol) in 9:1 ethanol:water was heated to reflux. After 16 hours, the mixture was concentrated via rotovap, then diluted with water (100 mL) and further concentrated. The residue was slurried in water (100 mL) and the precipitated white solid (menthol) separated by filtration. The filtrate was acidified with hydrochloric acid until pH<2, then extracted with diethyl ether (3×75 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. The residue was recrystallized from acetonitrile to give the title compound (3.13 g, 63% yield) as a white powder: mp 253–254.5°C [literature[19] mp 252.5°C]; $[\alpha]_D$=+12.1 (c 5.22, 1,4-dioxane) [literature[19] $[\alpha]_{578}$=+11.7 (c 5.00, 1,4-dioxane)]; ^1H NMR (300 MHz, acetone-d_6) δ 10.87 (br s, 2 H), 7.39 (s, 2 H), 7.29 (s, 2 H), 7.09 (m, 4 H), 4.83 (s, 2 H), 3.38 (s, 2 H); ^{13}C NMR (75

MHz, acetone-d_6) δ 173.5 (s), 143.6 (s), 141.6 (s), 126.8 (d), 126.7 (d), 125.5 (d), 124.2 (d), 48.2 (d), 47.3 (d).

Using the procedure described above, (11*S*,12*S*)-9,10-ethane-11,12-dimenthyl carboxylate-9,10-dihydro anthracene (8.40 g, 14.7 mmol) was hydrolyzed to afford (11*S*,12*S*)-9,10-ethane-11,12-dicarboxylic acid-9,10-dihydro anthracene (2.28 g, 53% yield) as a white powder: mp 252–253.5°C [literature[19] mp 252.5°C]; $[\alpha]_D=-15.05$ (c=2.06, 1,4-dioxane) [literature[19] $[\alpha]_{578}=-15.3$ (c=2.00, 1,4-dioxane)].

Preparation of box ligands 7a and 7c

To a cooled (−5°C) solution of (11*R*,12*R*)-9,10-ethane-11,12-dicarboxylic acid-9,10-dihydro anthracene (1.00 g, 3.40 mmol) and Et_3N (0.99 mL, 7.1 mmol) in THF (40 mL) was added isobutyl chloroformate (0.96 mL, 7.4 mmol). The resulting slurry was stirred for 30 minutes (ca. −5°C), then filtered directly into a solution of (*R*)-phenylglycinol (1.0 g, 7.4 mmol) in cold (ca. −5°C) THF (70 mL). The resulting mixture was stirred and slowly warmed to room temperature. After 16 hours, the mixture was concentrated and the residue partitioned between CH_2Cl_2 (75 mL) and 10% aq HCl (75 mL). The organic layer was washed sequentially with 10% aq HCl (75 mL), satd aq NaCl (75 mL), and then dried ($MgSO_4$) and concentrated to give a crude bis(hydroxyamide) which was used without further purification.

The crude bis(hydroxyamide) was dissolved in CH_2Cl_2 (100 mL) and treated with $SOCl_2$ (4.9 mL, 67 mmol). After 15 min, the resulting solution was heated at reflux for 3 h, then recooled to RT and washed sequentially with cold water (100 mL), 0.1 M aq K_2CO_3 (2×120 mL), and satd aq NaCl (100 mL). The organic layer was dried (Na_2SO_4) and concentrated. Chromatography on silica (EtOAc–hexanes) gave crude bisamide dichloride which was used without further purification: TLC analysis (60:40 CH_2Cl_2:Et_2O) R_f 0.76.

A mixture of the bisamide dichloride and NaOH (4.3 g, 108 mmol) in 50% aq MeOH (200 mL) was heated under reflux for 4 hours, then cooled and the methanol removed via rotovap. NaCl was added to saturate the aqueous residue, and the resulting mixture extracted with CH_2Cl_2 (4×90 mL). The combined extracts were washed with 2% aq NaOH, dried (Na_2SO_4) and concentrated. Chromatography on silica (EtOAc–hexanes) yielded the *meso backbone* (1,4)-box ligand **7c** (189 mg, 11% yield) as a pale yellow solid and the desired (1,4)-box ligand **7a** (358 mg, 21% yield).

Spectral data for **7c**: TLC analysis (60:40 CH_2Cl_2:Et_2O) R_f 0.71; mp 87–89°C; $[\alpha]_D=+40.6$ (c 1.06, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.35 (m, 4 H), 7.26 (m, 6 H), 7.15 (m, 4 H), 7.06 (m, 4 H), 4.99 (dd, J=7.9, 9.8 Hz, 2 H), 4.82 (s, 2 H), 4.57 (dd, J=8.6, 10.0 Hz, 2 H), 4.01 (t, J=8.0 Hz, 2 H), 3.68 (s, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5 (s), 143.2 (s), 141.1 (s), 129.2 (d), 127.2 (d), 127.0 (d), 124.5 (d), 75.9 (t), 69.9 (d), 47.6 (d), 43.5 (d); FT-IR (ZnSe, ATR) 3024, 2962, 1657 cm^{-1}; Combustion analysis ($C_{34}H_{28}N_2O_2$=82.23% C, 5.68% H) found 82.42% C, 5.72% H.

Spectral data for **7a**: TLC analysis (60:40 CH_2Cl_2:Et_2O) R_f 0.64; mp 147–149°C; $[\alpha]_D=-27.4$ (c 1.03, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.35 (m, 14 H), 6.50 (m, 4 H), 5.02 (t, J=8.9 Hz, 2 H), 4.89 (s, 2 H), 4.60 (dd, J=8.1, 10.1 Hz, 2 H), 3.97 (t, J=8.2 Hz, 2 H), 3.93 (s, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9 (s), 142.8 (s), 141.6 (s), 129.1 (d), 127.1 (d), 125.5 (d), 125.2 (d), 76.6 (t), 69.7 (d, Ph–CH–N), 47.2 (d), 43.8 (d); FT-IR (ZnSe, ATR) 3026, 2964, 1657 cm^{-1}; Combustion analysis ($C_{34}H_{28}N_2O_2$=82.23% C, 5.68% H) found 81.96% C, 5.46% H.

Preparation of box ligands 7b (and 7c)

Condensation of (11*S*,12*S*)-9,10-ethane-11,12-dicarboxylic acid-9,10-dihydro anthracene (1.00 g, 3.40 mmol) with (*R*)-phenylglycinol according to the procedure described above afforded the (1,4)-box ligand **7c** (122 mg, 7% yield) as a pale yellow solid and the desired (1,4)-box ligand **7b** (154 mg, 9% yield) Spectral data for **7b**: TLC analysis (60:40 CH_2Cl_2:Et_2O) R_f 0.64; mp 158–159.5°C; $[\alpha]_D=-33.2$ (c 0.99, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.54 (m, 2 H), 7.24 (m, 12 H), 6.49 (m, 4 H), 5.02 (t, J=9.3 Hz, 2 H), 4.87 (s, 2 H), 4.60 (dd, J=8.1, 10.1 Hz, 2 H), 3.96 (t, J=8.1 Hz, 2

H), 3.92 (s, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9 (s), 142.8 (s), 141.6 (s), 129.1 (d), 127.1 (d), 125.5 (d), 125.2 (d), 76.6 (t), 69.8 (d), 47.2 (d), 43.8 (d); FT IR (ZnSe, ATR) 2966, 2895, 1656 cm^{-1}; Combustion analysis ($C_{34}H_{28}N_2O_2$=82.23% C, 5.68% H) found 82.06% C, 5.46% H.

Acknowledgements

Financial support by the UNL Research Council and the NIH is gratefully acknowledged. We thank the NIH (SIG 1-S10-RR06301) and NSF (CHE-93000831) for instrumentation funding, and M. J. Reno and K. L. Reiman for preparing some of the compounds used in this study.

References

1. Takacs, J. M.; Lawson, E. C.; Reno, M. J.; Youngman, M. A.; Quincy, D. A. *Tetrahedron: Asymmetry* **1997**, *8*, 3073–78.
2. Corey, E. J.; Ishihara, K. *Tetrahedron Lett.* **1992**, *33*, 6807–10.
3. Evans, D. A.; Miller, S. J.; Lectka, T. *J. Am. Chem. Soc.* **1993**, *115*, 6460–1.
4. Bolm, C.; Weickhardt, K.; Zehnder, M.; Ranff, T. *Chem. Ber.* **1991**, *124*, 1173–80.
5. The crystal structure of the bicyclo[2.2.2]-1,4-box ligand **7a** as determined by X-ray methods is shown below in stereoview. The dihedral angle defined by C(2) of the two oxazoline moieties is 113°.

6. Davies, I. W.; Gerena, L.; Castonguay, L.; Sennayake, C. H.; Larson, R. D.; Verhoeven, T. R.; Reider, P. J. *Chem. Commun.* **1996**, 1753–4.
7. Harm, A. M.; Knight, J. G.; Stemp, G. *Synlett* **1996**, 677–8.
8. Bedekar, A. V.; Andersson, P. G. *Tetrahedron Lett.* **1996**, *37*, 4073–6.
9. Imai, Y.; Zhang, W.; Kida, T.; Nakatsuji, Y.; Ikeda, I. *Tetrahedron: Asymmetry* **1996**, *7*, 2453–6.
10. Furuta, K.; Iwanaga, K.; Yamamoto, H. *Tetrahedron Lett.* **1986**, *27*, 4507–4510.
11. Heathcock, C. H.; Davis, B. R.; Hadley, C. R. *J. Med. Chem.* **1989**, *32*, 197.
12. The bis(hydroxyamide) intermediates synthesized in the course of this study often proved difficult to handle due to poor solubility and/or the tendency to form gels in common organic solvents.
13. Denmark, S. E.; Makajima, N.; Nicase, O. J.-C.; Faucher, A.-M.; Edwards, J. P. *J. Org. Chem.* **1995**, *60*, 4884–92; and references cited therein.
14. Vorbruggen, H.; Krolikiewicz, K. *Tetrahedron Lett.* **1981**, *22*, 4471–4.
15. Johannsen, M.; Jørgensen, K. A. *J. Org. Chem.* **1995**, *60*, 5757–62.
16. See also: Davies, I. W.; Gerena, L.; Cai, D.; Larson, R. D.; Verhoeven, T. R.; Reider, P. J. *Tetrahedron Lett.* **1997**, *38*, 1145–8.
17. Scharf, H.-D.; VaBen, R.; Runsink, J. *Chem. Ber.* **1986**, *119*, 3492–7.
18. Matsuda, H.; Kanai, H. *J. Mol. Catal.* **1985**, *29*, 157–64.
19. Jacques, J.; Brienne, M.-J. *Bull. Soc. Chim. Fr.* **1973**, 190–7.

(Received in USA 7 July 1997)