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2,2′-Isopropylidenebis[(4*R*)-(1-adamantyl)-2-oxazoline] (Adam-Box). A new enantiopure C_2-symmetrical ligand: enantioselective cyclopropanations, Diels–Alder reactions, and allylic oxidations

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Abstract—The title bisoxazoline (Box) featuring two adamantane skeletons (Adam-Box) is a ligand of (*R*,*R*)-configuration, which combined with copper sources makes excellent catalysts for enantioselective cyclopropanations, Diels–Alder reactions, and allylic oxidations. © 2002 Published by Elsevier Science Ltd.

1. Introduction

Metal complexes of C_2-symmetric enantiopure ligands have gained a reputation as efficient chiral inductors. In particular, bisoxazolines (Box) have found broad use due to their versatility and easy preparation.[1] Particular attention has been drawn to Box ligands of general formula **1** derived from malonic acid (Fig. 1). The preparation of compounds **1** rely upon enantiomerically pure amino alcohols, which in general derive from the related amino acids.[2] The easily accessible bis(oxazolines) have (*S*,*S*)-configuration at the stereogenic centers.

The nitrogen atoms of **1** are excellent coordinating centres for many metals and the resulting complexes are useful in enantioselective reactions,[3] such as cyclopropanations,[1c] Diels–Alder reactions,[1c,e] allylic oxidations,[1c,f,g] and other processes.[1c]

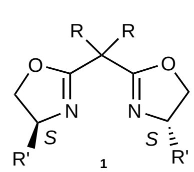

Figure 1. General formula of the Box ligands.

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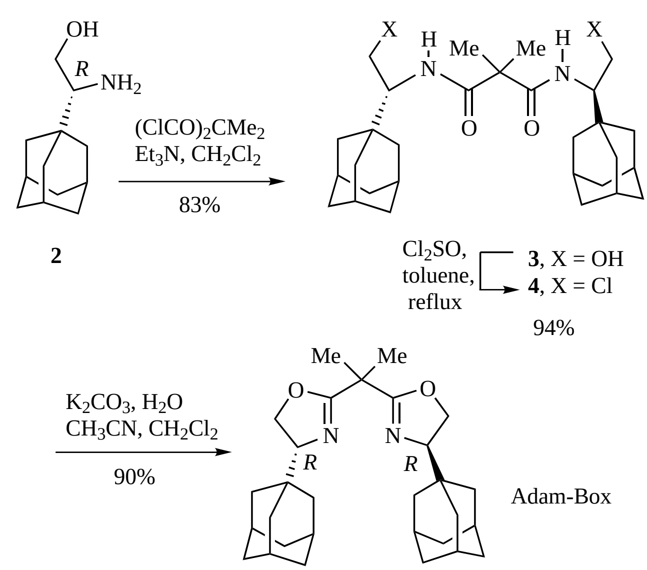
We present herein some preliminary results on highly enantioselective cyclopropanations,[4] Diels–Alder reactions,[5,6] and allylic oxidations[7] using (*R*,*R*)-Adam-Box, **5**, as an ancilliary coordinating agent (Scheme 1). (*R*,*R*)-Adam-Box, bearing bulky adamantyl groups, allows access to highly pure enantiomers with the opposite configuration compared to the ones normally obtained in literature. The required (*R*)-2-(1-adamantyl)-2-aminoethanol, **2**, was prepared by enzymatic resolution.[8] Reaction of **2** with dimethylmalonyl



Scheme 1. Preparation of (*R*,*R*)-Adam-Box, **5**.

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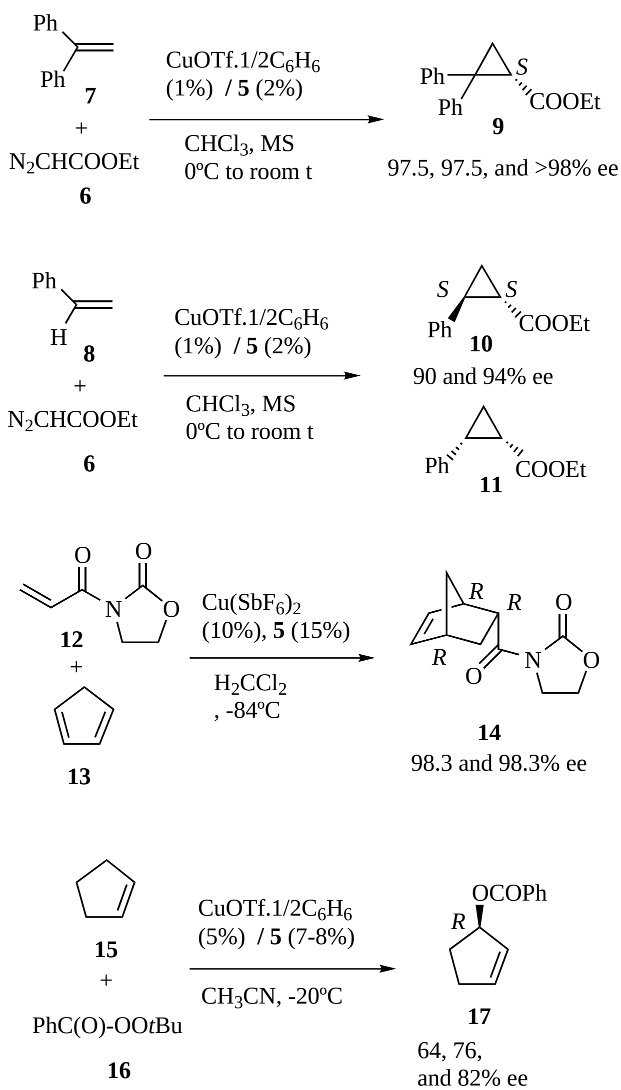
dichloride afforded diamide **3** (83%), which reacts with purified thionyl chloride to afford dichlorodiamide **4** in 94% yield. The best conditions, giving high yields in the cyclization step (90%), were achieved with K_2CO_3 in the appropriate mixture of solvents as indicated.

The results obtained in different enantioselective reactions are shown in Scheme 2. Original protocols were followed for all reactions in order to compare the new (*R*,*R*)-Adam-Box with the very efficient (*S*,*S*)-*t*-Bu-Box.

The cyclopropanation of 1,1-diphenylethene afforded ethyl (*S*)-2,2-diphenylcyclopropanecarboxylate, **9**, in 97.5, 97.5, and >98% enantiomeric excesses (ee) in three independent reactions as determined by HPLC. The product from one of the reactions was isolated in 75% yield. The method used to prepare the catalyst was as described by Mosset et al.[9] Addition of molecular sieves was essential for successful cyclopropanations. Saponification gave the corresponding acid which presented $[\alpha]_D = +163$ (*c* 1.16, CH_2Cl_2) to confirm the (*S*)-configuration.[4c] An ee value superior to 99% has been reported



Scheme 2. Enantioselective reactions.

for cyclopropane **9** (70% chemical yield) in the presence of the catalytic system CuOTf-(*R*,*R*)-*t*-Bu-Box.[4c]

Next, we studied the cyclopropanation of styrene, which delivered, in two different runs, mixtures **10**/**11** in a 75:25 ratio and 56% chemical yield. The *trans*-(*S*,*S*)-compound **10** had ee of 90 and 94% ($[\alpha]_D = +298$ (*c* 0.25, CH_2Cl_2). Evans reported 98% ee for the same (*S*,*S*)-isomer ($[\alpha]_D = +296$, $CHCl_3$) when using (*R*,*R*)-*t*-Bu-Box,[4c] and 98% ee for the (*R*,*R*)-isomer ($[\alpha]_D = -279$ in chloroform for 96% ee) when using (*S*,*S*)-*t*-Bu-Box.[4d] Although our ee values are slightly lower than those achieved by Evans group, other authors reported 80%[10] and 94% ee[11] for (*R*,*R*)-**10** when using (*S*,*S*)-*t*-Bu-Box.

The Diels–Alder reaction of *N*-acryloyloxazolidin-2-one, **12**, with cyclopentadiene was tested with (*R*,*R*)-Adam-Box, **5**, as well as with (*S*,*S*)-*t*-Bu-Box with identical results. Thus, two reactions with **5** as chiral auxiliary afforded a mixture of isomers in 66% chemical yield with an *endo*/*exo* ratio of 92:8 (the *exo*-isomer is not represented in Scheme 2). The *endo*-isomer **14** (with (*R*,*R*,*R*)-configuration) had 98.3% ee in both determinations. Two experiments using (*S*,*S*)-*t*-Bu-Box gave the (*S*,*S*,*S*)-isomer (*ent*-**14**) in 97.8% ee and an *endo*/*exo* ratio of 92:8. A ratio of 96:4 with >98% ee for *ent*-**14** has been reported.[12] Our **14** showed $[\alpha]_D = +146$ (*c* 0.53, CH_2Cl_2) in agreement with literature values: +172 in chloroform for **14**,[13] and −160 in chloroform for *ent*-**14**.[6b]

Finally, allylic oxidation of cyclopentene afforded **17** ((*R*)-configuration) in 64, 76, and 82% ee in three independent experiments. Pfaltz[7a] and Andrus[7b] reported 74 and 84% ee at rt and at −20°C in CH_3CN/chloroform (3:1 v/v),[7a] and 70% ee at −20°C in acetonitrile.[7b] Both groups worked with (*S*,*S*)-*t*-Bu-Box to afford *ent*-**17** with (*S*)-configuration. Our benzoate **17** presented $[\alpha]_D = +93$ (*c* 0.30, CH_2Cl_2) (lit.[14] $[\alpha]_D = -98.9$, chloroform, for *ent*-**17**).

2. Conclusions

In conclusion, we have prepared (*R*,*R*)-Adam-Box, **5**, bearing the bulky adamantyl group, which is not common in chiral ligands.[15] We have explored its enantioselective induction properties in three model reactions with excellent results. Under otherwise identical conditions it behaves in the same way as (*S*,*S*)-*t*-Bu-Box but affords enantiomeric final products.

3. Experimental

3.1. Preparation of *N*,*N*′-bis[(1*R*)-(1-adamantyl)-2-hydroxyethyl]-2,2-dimethyl-1,3-propanodiamide, 3

Triethylamine (1 mL, 7.4 mmol) and dimethylmalonyl dichloride (0.239 g, 1.41 mmol)[16] in dichloromethane (4 mL) were sequentially added to a stirred, ice-cooled solution of **2** (0.524 g, 2.69 mmol)[8] in dichloromethane

(12 mL). The mixture was stirred at rt for 2 h. Additional dichloromethane (15 mL) was added to dissolve all solids. The solution was partitioned with 1 M HCl, then with saturated aqueous sodium hydrogen carbonate and finally with saturated aqueous sodium chloride. The organic layer was dried and evaporated to afford **3** (83%) as a white solid, mp 210–212°C (ethyl acetate); IR (KBr) 3366, 2899, 2847, 1656, 1645, 1551, 1519, 1463, 1170, 1065 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.53–1.73 (complex absorption, 30H, 24 from adamantane+2×CH_3), 1.97 (apparent s, 6H from adamantane), 3.48 (dd, J=9.0 and 11.2 Hz, 2H, H-CHOH), 3.71 (m, 2H, CHN), 3.87 (dd, J=11.2 and 3.3 Hz, 2H, HCHOH), 6.42 (d, J=9.7 Hz, 2H, NH); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 23.8, 28.2, 35.5, 36.9, 39.1, 50.4, 60.0, 61.5, 174.0; $[\alpha]_D$=−36 (c 0.55, dichloromethane).

3.2. Preparation of *N*,*N*′-bis[(1*R*)-(1-adamantyl)-2-chloroethyl]-2,2-dimethyl-1,3-propanodiamide, 4

Purified thionyl chloride (2.1 mL)[17] was added to a stirred solution of **3** (0.574 g, 1.18 mmol) in anhydrous toluene (22 mL). The solution was heated under reflux for 24 h, and volatile products were evaporated. The solid residue was digested with pentane to afford **4** (94%) as a white solid, mp 149–151°C (toluene), IR (KBr) 3333, 2904, 2849, 1645, 1522, 1446, 1255 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.69–1.75 (complex absorption, 30H, 24H from adamantane+2×CH_3), 1.99 (apparent s, 6H from adamantane), 3.55 (dd, J=9.2 and 11.3 Hz, 2H, H-CHCl), 3.85 (dd, J=11.3 and 3.5 Hz, 2H, HCHCl), 4.00 (m, 2H, CHN), 6.73 (d, J=10.2 Hz, 2H, NH); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 24.6, 28.1, 36.7, 36.8, 38.9, 44.6, 50.0, 58.5, 173.0; $[\alpha]_D$= −28.3 (c 0.92, dichloromethane).

3.3. Preparation of 2,2′-isopropylidenebis[(4*R*)-(1-adamantyl)-2-oxazoline] (Adam-Box, 5)

To dichlorodiamide **7** (0.580 g, 1.11 mmol) in a mixture of acetonitrile (34 mL) and dichloromethane (40 mL) was added potassium carbonate (9.70 g, 70.3 mmol) in water (30 mL). The mixture was heated under reflux under stirring for 4 days (only one layer was apparent). The mixture was evaporated and then extracted with dichloromethane (3×25 mL). The organic layer was dried and evaporated to afford **5** (90%) as a white solid, mp 165–169°C (dichloromethane); IR (KBr) 2961, 2906, 2847, 1658, 1449, 1262, 1103 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.40–1.75 (complex absorption, 30H, 24H from adamantane+2×CH_3), 1.99 (apparent s, 6H from adamantane), 3.70 (dd, J=7.1 and 9.6 Hz, 2H, CHN), 4.17 (m, 4H, CH_2O); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 24.5, 28.2, 35.6, 37.2, 38.3, 67.5, 75.4, 168.0; $[\alpha]_D$=+116.4 (c 0.55, dichloromethane); HRMS calcd for $C_{29}H_{42}N_2O_2$ 450.324629, found 450.326159.

3.4. Enantiomeric purity analyses of 9, 10, 14, and 17

Analysis of **9**: HPLC, Chiracel Daicel-OD column, eluent hexane–isopropanol (99.5:0.5), flow rate 0.5 mL/min, t_r (*R*)-isomer): 23.18 min, t_r ((*S*)-isomer): 26.19 min.

Analysis of **10** and **11**: HPLC, Chiracel Daicel-OD column, eluent hexane–isopropanol (99:1), flow rate 0.5 mL/min, *trans* **10**, t_r 11.48 min (*R*,*R*) isomer, t_r 15.88 min (*S*,*S*) isomer. Under these conditions *cis* isomer **11** could not be resolved.

Analysis of **14**: HPLC, Chiracel Daicel-OD column, eluent hexane–isopropanol (95:5), flow rate 0.8 mL/min, t_r 39.0 min ((*S*,*S*,*S*)-isomer), t_r 42.0 ((*R*,*R*,*R*)-isomer). Under these conditions *exo* isomer could not be resolved.

Analysis of **17**: HPLC, Chiracel Daicel-OD column, eluent hexane–isopropanol (99.9:0.1), flow rate 0.5 mL/min, t_r ((*S*)-isomer): 17.6 min, t_r ((*R*)-isomer): 20.5 min.

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