JOC The Journal of Organic Chemistry

Article

Azotides as Modular Peptide-Based Ligands for Asymmetric Lewis Acid Catalysis

Christian Borch Borch Jacobsen, Daniel Steen Nielsen, Morten Meldal, and Frederik Diness

J. Org. Chem., **Just Accepted Manuscript** • Publication Date (Web): 29 Apr 2019

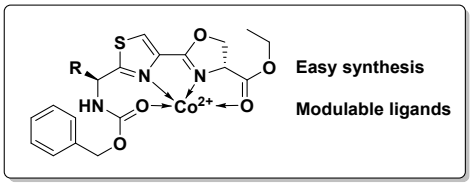
ACS Publications

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Azotides as Modular Peptide-Based Ligands for Asymmetric Lewis Acid Catalysis

Christian Borch Jacobsen, Daniel Steen Nielsen, Morten Meldal* and Frederik Diness*

Center for Evolutionary Chemical Biology, Department of Chemistry, University of Copenhagen, Universitetsparken 5, 2100 Copenhagen, Denmark



ABSTRACT: Synthesis of azotides and evaluation of these as ligands for enantioselective Lewis Acid catalysis is reported. The ligands were readily prepared from the chiral pool of amino acids. The ligands perform well in the cobalt(II) catalyzed formation of asymmetric hetero Diels-Alder adducts. A rational for the observed enantioselectivity and conversion rate supported by computational calculations is provided.

Introduction

Azotides,[1] peptides with azole or azoline moieties in the backbone, are commonly found natural products (Figure 1) produced by a broad range of cyanobacteria and other microorganisms.[2] Despite their abundance, little is known about their functions, though, several of the naturally occurring azotides has been found to have potent antibacterial or anticancer activity.[3] Since the first gene clusters responsible for their biosynthesis were discovered in 2009,[4] interest in this class of compounds has increased as their ribosomal origin facilitates bioengineering of analogues being potential pharmaceuticals.[5] In relation to this we have previously reported on the synthesis of natural azotides and their oral bioavailability.[1] Another interesting property of the azotides, is their versatile ability to coordinate metal ions (Figure 1).[6] Thus, it has been suggested that metal binding is involved in the biological function of some azotides.[7] Many synthetic chiral oxazolines derived from amino acid also bind metal ions and the (Py)BOX type ligands (Figure 1) have found broad applications in metal catalyzed asymmetric transformations.[8] From a green chemistry perspective, application of natural products as chiral ligands is attractive. Compounds such as single amino acids, tartaric acid, quinine and other cinchona alkaloids have been applied as chiral ligands; however, these are very difficult to engineer on the biosynthetic level.[9] In contrast, azotides are readily diversified by simple editing of their genetic encoded lead sequences. As they contain azoles and azolines that can act as metal-coordinating moieties, this class of compounds does appear to be intriguing starting points for developing green ligands for asymmetric metal catalysis.

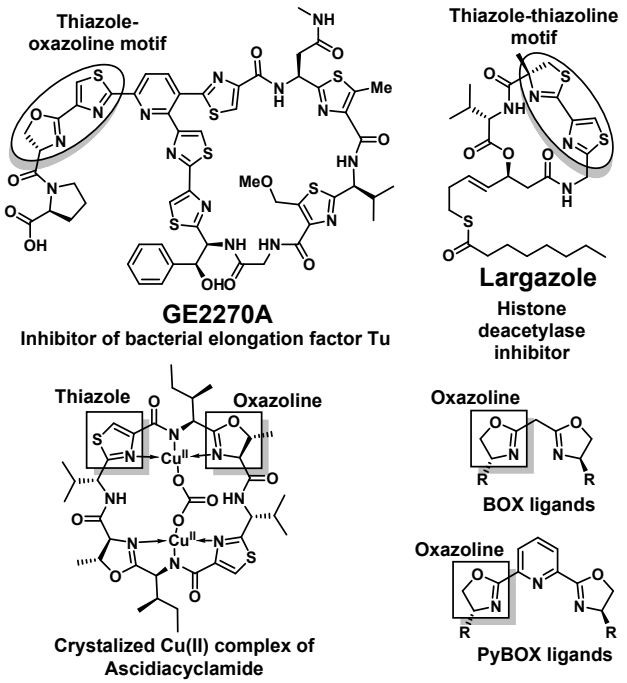
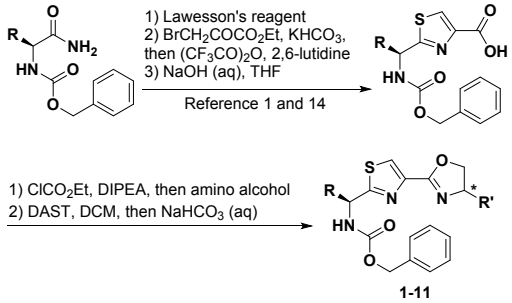


Figure 1. Natural azotides and amino acid-derived metal ligands.

In this communication, the feasibility of this concept is demonstrated through the use of azotides as cobalt(II) ligands for a Lewis acid catalyzed asymmetric hetero Diels-Alder reaction. Hetero Diels-Alder reactions are powerful tools for building heterocyclic structures,[10] and constitute a common platform for evaluation of ligand-metal catalysts' ability to control enantioselectivity, including the BOX type ligands (Figure 1).[11] Hetero Diels-Alder reactions are a part of Nature's own chemical toolbox and it is well recognized that the pyridine substructure in GE2270A (Figure 1) and other thiopeptides originate from such reactions.[12] In nature, the transformation has been demonstrated to be enzyme catalyzed, however, it is unknown if metal coordination plays a role in this process. In this work we took inspiration from the core oxazoline-thiazole structural motif in GE2270A (Figure 1). This motif comprises structural elements from the (Py)BOX ligands and is relative simple to generate chemically.[1,13]

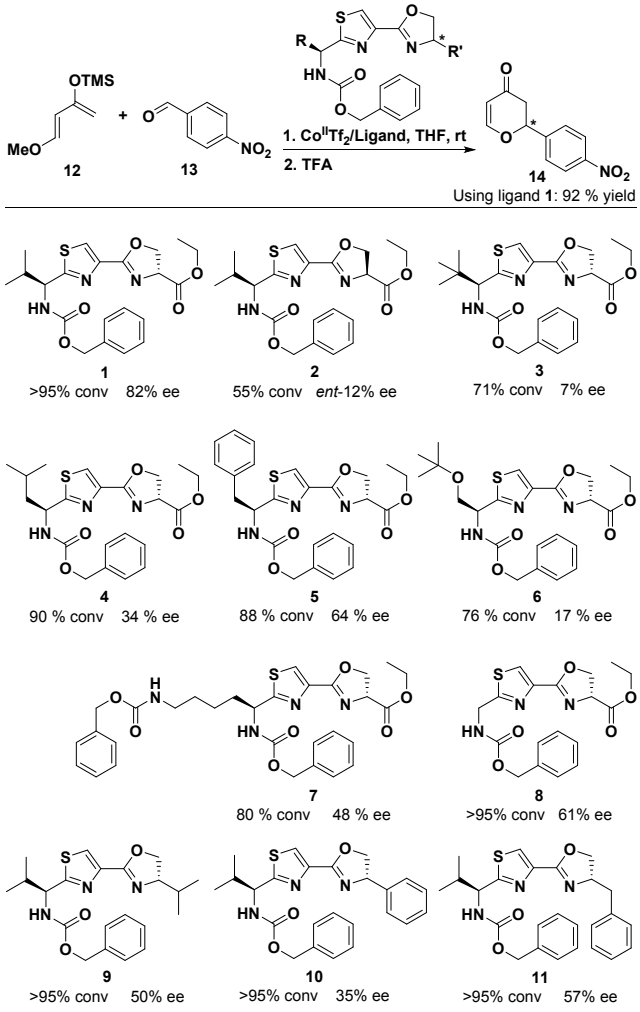
Results and Discussion

All the azotide ligands (**1-11**) were synthesized via a modified Hantzsch thiazole synthesis followed by an amide coupling and oxazoline formation. Starting from Cbz-protected amino acid amides these were converted to thioamides by reaction with Lawesson's reagent followed by alkylation and cyclization with ethyl bromo pyruvate finalized by dehydration with trifluoroacetic anhydride (Scheme 1).[1,14] The previously reported method was slightly modified for synthesis of the bulky *tert*-butyl glycine thioamide as this (CH_2Cl_2, 12 h, rt) led to poor conversion. The obstacle was solved by rising the reaction temperature to 60°C which demanded using THF instead of CH_2Cl_2. We attribute the sluggishness of this reaction to the sterically bulkiness of the *tert*-butyl group when combined with the relative bulky Lawesson's reagent. All of the obtained thiazole building blocks were then saponified, coupled to serine, or other amino alcohols followed by oxazoline formation through DAST-mediated cyclization (Scheme 1).[15]



Scheme 1: Synthesis of the azotide ligands.

Initially, the two L-valine-(D- or L)-serine derived ligands (**1** and **2**) in combination with cobalt(II) triflate were studied as catalysts for a hetero Diels-Alder reaction.[16] This revealed a high degree of cooperation between the two stereocenters in dictating the enantioselectivity. Applying the L-valine-D-serine adduct (**1**) provided full conversion of the starting material and led to a high enantioselectivity of 82% ee (Scheme 2). On the other hand, the combination of L-valine thiazole and L-serine oxazoline (**2**) gave the opposite enantiomer, but only in 12% ee and with modest conversion. Several other Lewis acidic metal salts were also tested under identical conditions. Exchanging the counter anion by using cobalt(II) acetylacetonate gave high conversion of >90 %, whereas cobalt(III) acetylacetonate lead to minimal conversion. However, both catalytic systems provided no enantioselectivity. Applying other metal triflate salts had a large effect on the conversion rates. Copper(II) triflate gave <10 % conversion, whereas zinc(II) triflate led to high conversion of >90 %. Copper(I) triflate led to a complex mixture of products which indicates that this acted not only as Lewis acid catalyst. All these other metal triflate salts provided no or negligible enantioselectivity. Hence, cobalt(II) triflate was selected for further studies of the ligands.



Scheme 2. Ligand **1-11** investigated as ligands in a cobalt catalyzed asymmetric Diels-Alder reaction.

The impact on conversion rate and enantioselectivity of the side chain on the thiazole building was investigated. Inspired by the Jacobsen thiourea catalysts[17] introduction of an additional methyl group on the β-carbon (**3**) was tested, but this led to only negligible stereoselectivity and reduced rate of conversion. Various other modifications at the β-carbon (**4**-**7**) also led to reduced stereoselectivity and

incomplete conversion. Interestingly, it was found that omitting a substituent at the α-carbon in the thiazole amino acid building block (**8**), and thereby having one less stereo center in the ligand, led to only 21% reduction of enantiomeric excess as compared to ligand **1**, while full conversion was still achieved. These results demonstrated that the substituent on the oxazoline stereo center plays a major role in dictating the enantioselectivity. A small series of azotide ligands (**9**-**11**) without coordinating groups in this position was synthesized and investigated in order to explore if the effect was mediated through steric bulk or via the additional coordination of the ester carbonyl to the cobalt(II) ion. All of these ligands (**9**-**11**) led to only modest ee as compared to the parent ligand **1**, while complete conversion was maintained.

In order to understand the observed effects of ligand variations, computational studies of the ligand-cobalt-complexes were performed by molecular dynamic simulations combined with structure energy minimizations. All the generated structures maintained a stable coordination of the cobalt(II) ion to the nitrogen atoms of the two azoles as well as to the carbonyl of the carbamate group (Figure 2). Structures displaying metal coordination to the ester carbonyl were retrieved from the dynamics of all serine derived ligands (**1**-**8**) although this coordination was less prevalent. The structure populations segregated into two major conformations with the cobalt(II) ion orientated either slightly above or slightly below the thiazole-oxazoline plane (see e.g. **11,** Figure 2), with the carbamate group coordinating from below or above, respectively. Only the D-serine derived ligand (**1**) of the two initial valine-serine derived ligands (**1** and **2**) yield low energy structures with all the four heteroatoms coordinating to cobalt (Figure 2, compound **1**).

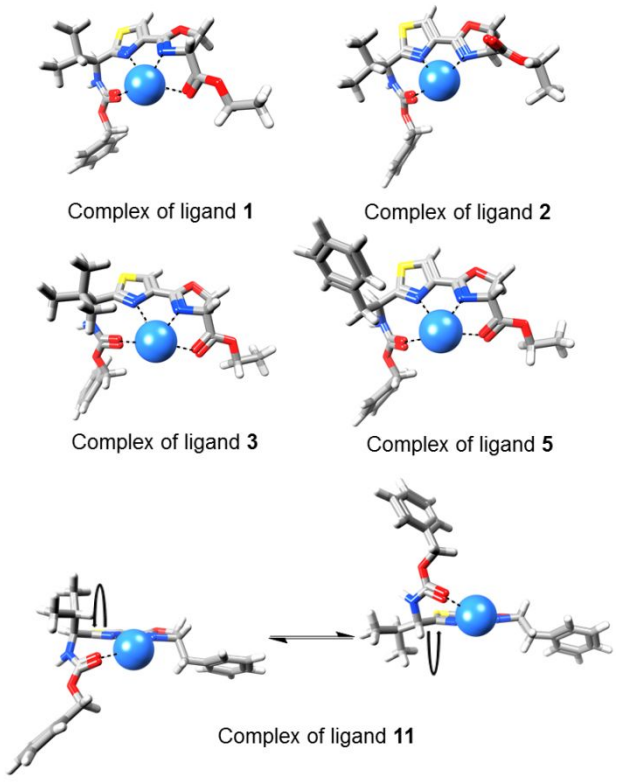


Figure 2. Computational investigation of the ligand structures' influence on cobalt coordination. Examples of low energy structures of ligands with three or four coordinating groups. Example of the two structure populations depicted for ligand **11**.

Hence, the L-serine derived ligand (**2**) give rise to a less stable cobalt(II) complex, compared to the corresponding D-serine derived ligand (**1**) which is supported by the molecular dynamics (Figure 3). The relatively high flexibility of **2** observed *in silico* may contribute to the reduced stereoselectivity observed with this ligand as compared to **1**.

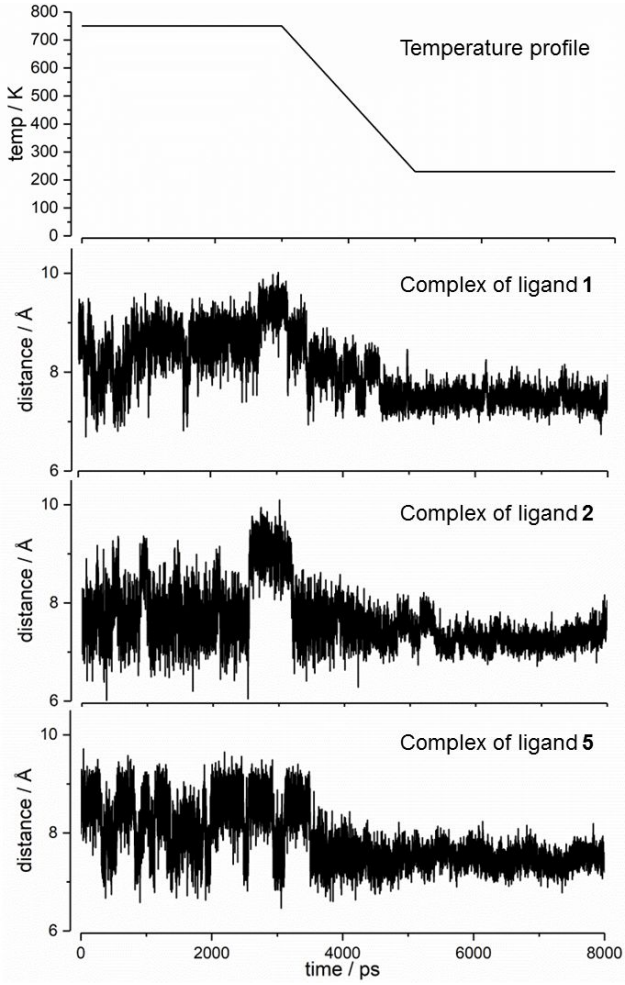


Figure 3. Simulated molecular dynamics annealing of complexes of ligand **1**, **2** and **5** represented by distance variation between the β-carbon of the amino acid in the thiazole part and the carbon equivalent to the carbonyl carbon in the serine residue (see complex structures in Figure 2). The simulation was maintained at 750 K for 3000 ps and then cooled to 230 K over 2000 ps and then equilibrated at 230 K for 3000 ps (see also supporting information).

It was noted that the L-valine-D-serine derived ligand (**1**) has the most stable structure *in silico*, as compared to compounds where the thiazole moiety were generated from other amino acids than L-valine (e.g. **5**, Figure 2). This is likely adding to the superior enantioselectivity of ligand **1**. Hence, a major disadvantage of the extended side chain found in ligand **4**-**7** may be reduced conformation stability as a consequence of the random rotations of the relative heavy flexible α-carbon substituent. This is in line with the general trend of efficient ligands for asymmetric synthesis which rarely have large substituent with connected rotational bonds.[8,9,10,11] The coordination of the cobalt(II) ion to the carbonyl substituent on the oxazoline is clearly imperative in guiding the enantioselectivity. Absence of this carbonyl leads to a less shielded catalytic site with the substituent on the 4-position on the oxazoline pointing away from the cobalt (see **11,** Figure 2). Interestingly, even the complex of **1** appears to have a relative open face with the isopropyl side chain pointing away from the cobalt(II) ion. The less hindered access to the cobalt could be crucial in order to accommodate both the aldehyde and the diene close to the catalytic center. As it was found that cobalt(II) triflate catalyzed the reaction well even in the absence of ligand, it is possible that the modest selectivity of some of the ligands including the more steric congested ligands **3** (Figure 2) originate from competing background reaction with minute amounts of the free cobalt(II) ions. Hence, several factors may be the origin of that the isopropyl substituent is the optimal structural motif among the tested amino acid side chains. In ligand **1** this balances shielding sides of the cobalt(II) ion in order to induce enantioselectivity, while still leaving room for substrate binding and high catalytic turnover.

In conclusion, inspired by a structural motif in the naturally occurring azotide GE2270A (Figure 1), we have synthesized a library of azotides and demonstrated their enantio-selectivity inducing capacity when used as ligands in a cobalt(II)-catalyzed hetero Diels-Alder reaction. These readily available chiral ligands can be easily diversified and take advantage of the inherent chirality of α-amino acids. The relative enantioselectivity and catalytic capacity has been correlated to computational studies of the ligand-metal complexes. The results provide an optimal base for developing more advanced synthesized or expressed azotide ligands, and apply these in green and benign enantioselective catalysis.

Experimental details

All purchased chemicals were used without further purification. All solvents were HPLC-grade. Flash chromatography (FC) was carried out on Merck silica gel 60 (0.040-0.063 mm). NMR spectra were recorded on a Bruker ADVANCE III 500 MHz CRYO probe instrument. Chemical shifts are reported in ppm relative to residual solvent signals ($CHCl_3$, 7.26 ppm; DMSO-d_6, 2.50 ppm) for ^{1}H NMR spectra and relative to the central solvent resonance ($CDCl_3$, 77.0 ppm; DMSO-d_6, 39.5 ppm) for ^{13}C NMR spectra. The following abbreviations are used to indicate the multiplicity in ^{1}H and ^{13}C NMR spectra: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; ddd, doublet of doublet of doublets; dt, doublet of triplets; tt, triplet of triplets; m, multiplet. ^{13}C NMR spectra were acquired in broadband decoupled mode. High resolution mass spectrometry (HRMS) was performed on a Bruker micro-TOF using positive electrospray ionization. Enantiomeric excesses were determined by chiral HPLC on a Waters 600 system (Waters 60F solvent pump; Waters 2996 photodiode array detector) using a Lux 5 μm Cellulose-1 LC column 250 x 4.6 mm from Phenomenex and eluting with an isocratic eluent of 60% isopropanol in heptane with a flow-rate of 1.0 mL/min. The reference racemic sample was prepared using $Co(OTf)_2$ without ligand as a catalyst.

General procedure for the formation of ligands 1 - 11

The Cbz-protected thiazole building blocks (Cbz-X-Thz-OH, where X indicates the designated amino acid) were prepared as their ethyl esters by a literature procedure, followed by ester hydrolyzed as previously described.[1] The ligands **1** - **11** were all isolated as clear viscous oils and

prepared by the following procedure using Ligand **1** as an example: DIPEA (610 µL, 3.5 mmol) was added to a stirred solution of Cbz-Val-Thz-OH (334 mg, 1.0 mmol) in THF (10 mL) then ethyl chloroformate (190 µL, 2.0 mmol) was added. The solution was stirred for 30 minutes prior to addition of D-serine ethyl ester hydrochloride (339 mg, 2.0 mmol) as a solid. The reaction was stirred at room temperature overnight. Citric acid (20% aq., 20 mL) was added and the product was extracted with EtOAc (2x 10 mL). The combined organic phases were concentrated and the residual Cbz-Val-Thz-D-Ser-OEt was purified by column chromatography (369 mg, 82% yield). The intermediate (369 mg, 0.82 mmol) was dissolved in CH_2Cl_2 (5.0 mL) and cooled to -40 °C. Diethylaminosulfur trifluoride (145 µL, 1.1 mmol) was added to the stirred solution. The reaction was stirred at -20 °C for 1 hour. $NaHCO_3$ (sat. aq., 2.0 mL) was added and the reaction allowed to reach room temperature. The solution was extracted with EtOAc (2x10 mL). The solvent was removed in vacuo and the product was purified by flash column chromatography using a gradient of EtOAc in heptane, from 1:4 to 1:1. The product (**1**) was collected as a clear syrup upon evaporation (332 mg, 0.76 mmol, 94% yield). The yields (unoptimized) for the remaining ligands 2-11 are reported below as the overall yields for the combined synthetic steps on a 1.0 mmol scale.

Procedure for the formation of (*S/R*)-2-(4-nitrophenyl)-2,3-dihydro-4H-pyran-4-one (14) by a cobalt-catalyzed hetero-Diels-Alder reaction:

$Co(OTf)_2$ was synthesized by dissolving anhydrous $CoCl_2$ (65 mg, 0.5 mmol) in acetonitrile (25 mL) and adding AgOTf (257 mg, 1.0 mmol) to the mixture. A white solid formed that was filtered off after 1 h. The light pink $Co(OTf)_2$ catalyst was isolated by evaporation of the solvent and stored under nitrogen. A vial containing $Co(OTf)_2$ (3.6 mg, 10 mol%, 0.01 mmol) and the ligand (one of compound **1** – **11**) (15 mol%, 0.015 mmol) in dry THF (0.20 mL) was heated in an oil bath to 50 °C under nitrogen for 10 min to allow complex formation. The vial was cooled to room temperature then 4-nitrobenzaldehyde (0.10 mmol) and Danishefsky´s diene (0.15 mmol) was added. The reaction was stirred under nitrogen for 16 h at room temperature. Trifluoroacetic acid (0.10 mL) was added and the reaction stirred for 1 hour. The mixture was loaded direct onto a silica column and the product eluted with EtOAc/heptane 1:4. The product (**14**) was obtained in a maximum yield of 92% (20.2 mg, 0.092 mmol), and enantiomeric excess of 83% using ligand **1.** The enantiomeric excess was assessed by chiral HPLC analysis of a sample in isopropanol/heptane 3:2 as described above.

Ethyl (*R*)-2-(2-((*S*)-1-(((benzyloxy)carbonyl)amino)-2-methylpropyl)thiazol-4-yl)-4,5-dihydrooxazole-4-carboxylate (1):

Yield: 332 mg, 0.76 mmol, 76%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.43 – 7.29 (m, 5H), 5.58 (d, J = 9.2 Hz, 1H), 5.12 (d, J = 2.7 Hz, 2H), 4.94 (ddd, J = 10.3, 8.0, 3.7 Hz, 2H), 4.69 (t, J = 8.4 Hz, 1H), 4.62 (dd, J = 10.5, 8.7 Hz, 1H), 4.40 – 4.14 (m, 2H), 2.43 (dq, J = 10.4, 5.2, 3.8 Hz, 1H), 1.32 (t, J = 7.1 Hz, 3H), 0.95 (d, J = 6.8 Hz, 3H), 0.93 (d, J = 6.8 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 172.3, 170.9, 161.3, 156.0, 143.6, 136.2, 128.5, 128.2, 128.1, 124.1, 70.0, 68.7, 67.1, 61.8, 58.6, 33.5, 19.5, 17.6, 14.2. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{26}N_3O_5S^+$ 432.1588; Found 432.1558.

Ethyl (*S*)-5-(2-((*S*)-1-(((benzyloxy)carbonyl)amino)-2-methylpropyl)thiazol-4-yl)-3,4-dihydro-*2H*-pyrrole-2-carboxylate (2):

Yield: 296 mg, 0.69 mmol, 69%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.42 – 7.29 (m, 5H), 5.56 (d, J = 9.3 Hz, 1H), 5.17 – 5.06 (m, 2H), 5.01 – 4.87 (m, 2H), 4.70 (t, J = 8.4 Hz, 1H), 4.61 (dd, J = 10.5, 8.7 Hz, 1H), 4.26 (p, J = 7.2 Hz, 2H), 2.44 (dt, J = 13.6, 6.8 Hz, 1H), 1.32 (t, J = 7.1 Hz, 3H), 0.97 (d, J = 6.9 Hz, 3H), 0.92 (d, J = 6.8 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 172.6, 170.9, 161.4, 156.0, 143.7, 136.2, 128.5, 128.2, 128.1, 124.0, 70.1, 68.8, 67.2, 61.9, 58.6, 33.4, 19.5, 17.5, 14.2. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{26}N_3O_5S^+$ 432.1588; Found 432.1556.

Ethyl (*R*)-2-(2-((*S*)-1-(((benzyloxy)carbonyl)amino)-2,2-dimethylpropyl)thiazol-4-yl)-4,5-dihydrooxazole-4-carboxylate (3):

Yield: 170 mg, 0.38 mmol, 38%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.40-7.31 (m, 1H), 5.89 (d, J = 9.7 Hz, 1H), 5.16-5.07 (m, 2H), 4.97 (dd, J = 10.5, 8.1 Hz, 1H), 4.93 (d, J = 9.6 Hz, 1H), 4.70 (t, J = 8.4 Hz, 1H), 4.63 (dd, J = 10.5, 8.7 Hz, 1H), 4.29 (t, J = 6.8 Hz, 2H), 1.34 (t, J = 7.1 Hz, 3H), 1.04 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 170.9, 169.8, 161.4, 156.1, 143.3, 136.3, 128.5, 128.1, 128.0, 124.1, 70.0, 68.8, 67.0, 61.9, 61.1, 35.7, 26.6, 14.2. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{28}N_3O_5S^+$ 446.1744; Found 446.1750.

Ethyl (*R*)-2-(2-((*S*)-1-(((benzyloxy)carbonyl)amino)-3-methylbutyl)thiazol-4-yl)-4,5-dihydrooxazole-4-carboxylate (4):

Yield: 272 mg, 0.61 mmol, 61%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.39 – 7.27 (m, 5H), 5.50 (d, J = 9.0 Hz, 1H), 5.17 – 5.03 (m, 3H), 4.92 (dd, J = 10.5, 8.1 Hz, 1H), 4.66 (t, J = 8.4 Hz, 1H), 4.58 (dd, J = 10.5, 8.6 Hz, 1H), 4.28 – 4.18 (m, 2H), 1.96 – 1.86 (m, 1H), 1.83 – 1.73 (m, 1H), 1.72 – 1.62 (m, 1H), 1.29 (t, J = 7.1 Hz, 3H), 0.97 – 0.89 (m, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 173.6, 170.8, 161.2, 155.6, 143.5, 136.1, 128.4, 128.0, 127.9, 124.0, 69.9, 68.7, 66.9, 61.7, 51.5, 44.4, 24.8, 22.8, 21.7, 14.0. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{28}N_3O_5S^+$ 446.1744; Found 446.1713.

Ethyl (*R*)-2-(2-((*R*)-1-(((benzyloxy)carbonyl)amino)-2-phenylethyl)thiazol-4-yl)-4,5-dihydrooxazole-4-carboxylate (5):

Yield: 254 mg, 0.53 mmol, 53%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.36 – 7.26 (m, 4H), 7.25 – 7.18 (m, 4H), 7.09 – 7.04 (m, 2H), 5.67 (d, J = 8.6 Hz, 1H), 5.33 (q, J = 7.5 Hz, 1H), 5.06 (s, 2H), 4.95 (dd, J = 10.5, 8.1 Hz, 1H), 4.69 (t, J = 8.4 Hz, 1H), 4.61 (dd, J = 10.5, 8.6 Hz, 1H), 4.30 – 4.20 (m, 2H), 3.36 – 3.29 (m, 2H), 1.31 (t, J =

7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 172.3, 170.8, 161.2, 155.5, 143.4, 136.1, 136.0, 129.3, 128.6, 128.4, 128.1, 127.9, 127.0, 124.3, 70.0, 68.7, 67.0, 61.8, 54.3, 41.6, 14.1. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{25}H_{26}N_3O_5S^+$ 480.1588; Found 480.1551.

Ethyl (*R*)-2-(2-((*R*)-1-(((benzyloxy)carbonyl)amino)-2-(tert-butoxy)ethyl)thiazol-4-yl)-4,5-dihydrooxazole-4-carboxylate (6):
Yield: 257 mg, 0.54 mmol, 54%. ^1H NMR (500 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.48 – 7.31 (m, 5H), 5.99 (s, 1H), 5.24 (s, 1H), 5.16 (s, 2H), 4.99 (dd, *J* = 10.5, 8.0 Hz, 1H), 4.75 (t, *J* = 8.4 Hz, 1H), 4.70 – 4.64 (m, 1H), 4.37 – 4.24 (m, 2H), 3.95 – 3.86 (m, 1H), 3.74 – 3.66 (m, 1H), 1.35 (t, *J* = 7.1 Hz, 3H), 1.11 (d, *J* = 1.7 Hz, 9H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 172.4, 170.8, 161.3, 161.3, 155.7, 143.0, 136.1, 128.5, 128.2, 124.5, 73.8, 69.9, 68.7, 67.1, 63.5, 61.7, 54.0, 27.2, 14.1. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{30}N_3O_6S^+$ 476.1850; Found 476.1815.

Ethyl (*S*)-2-(2-((*R*)-3,11-dioxo-1,13-diphenyl-2,12-dioxa-4,10-diazatridecan-5-yl)thiazol-4-yl)-4,5-dihydrooxazole-4-carboxylate (7):
Yield: 137 mg, 0.23 mmol, 23%. ^1H NMR (500 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.36 – 7.27 (m, 10H), 5.85 (d, *J* = 8.0 Hz, 1H), 5.18 – 4.95 (m, 5H), 4.90 (dd, *J* = 10.5, 8.1 Hz, 1H), 4.65 (t, *J* = 8.4 Hz, 1H), 4.56 (dd, *J* = 10.6, 8.6 Hz, 1H), 4.29 – 4.18 (m, 2H), 3.25 – 3.05 (m, 2H), 2.15 – 1.98 (m, 1H), 1.98 – 1.80 (m, 2H), 1.60 – 1.34 (m, 4H), 1.29 (t, *J* = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 173.5, 170.8, 161.2, 161.1, 156.6, 155.9, 143.4, 136.5, 136.1, 128.4, 128.4, 128.1, 128.0, 128.0, 124.1, 69.9, 68.6, 67.0, 66.5, 61.7, 53.2, 40.1, 34.8, 29.2, 22.4, 14.0. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{30}H_{35}N_4O_7S^+$ 595.2221; Found 595.2169.

Ethyl (*R*)-2-(2-((((benzyloxy)carbonyl)amino)methyl)thiazol-4-yl)-4,5-dihydrooxazole-4-carboxylate (8):
Yield: 238 mg, 0.61 mmol, 61%. ^1H NMR (500 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.42 – 7.31 (m, 5H), 5.53 (s, 1H), 5.15 (s, 2H), 4.94 (dd, *J* = 10.5, 8.1 Hz, 1H), 4.71 (dd, *J* = 9.6, 7.3 Hz, 3H), 4.61 (dd, *J* = 10.5, 8.7 Hz, 1H), 4.34 – 4.16 (m, 2H), 1.32 (t, *J* = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 170.7, 169.1, 161.2, 156.2, 143.2, 136.0, 128.6, 128.3, 128.1, 124.9, 70.1, 68.7, 67.3, 61.9, 42.6, 14.1. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{20}N_3O_5S^+$ 390.1118; Found 390.1093.

Benzyl ((*S*)-1-(4-((*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl)thiazol-2-yl)-2-methylpropyl)carbamate (9):
Yield: 237 mg, 0.57 mmol, 57%. ^1H NMR (500 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.47 – 7.28 (m, 5H), 5.63 (d, *J* = 9.3 Hz, 1H), 5.11 (d, *J* = 1.7 Hz, 2H), 4.95 (dd, *J* = 9.2, 6.1 Hz, 1H), 4.50 – 4.38 (m, 1H), 4.20 – 4.05 (m, 2H), 2.43 (dq, *J* = 13.5, 6.8 Hz, 1H), 1.91 (dqt, *J* = 13.1, 9.4, 4.8 Hz, 1H), 1.04 (d, *J* = 6.8 Hz, 3H), 0.95 (d, *J* = 6.7 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 6H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 172.1, 158.6, 156.0, 144.4, 136.2, 128.5, 128.1, 128.0, 122.8, 72.6, 70.3, 67.1, 58.6, 33.6, 32.5, 19.5, 19.2, 17.9, 17.5. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{28}N_3O_3S^+$ 402.1846; Found 402.1820.

Benzyl ((*S*)-2-methyl-1-(4-((*S*)-4-phenyl-4,5-dihydrooxazol-2-yl)thiazol-2-yl)propyl)carbamate (10):
Yield: 166 mg, 0.38 mmol, 38%. ^1H NMR (500 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.43 – 7.27 (m, 10H), 5.64 (d, *J* = 9.3 Hz, 1H), 5.41 (dd, *J* = 10.2, 8.3 Hz, 1H), 5.12 (d, *J* = 1.1 Hz, 2H), 4.96 (dd, *J* = 9.0, 6.0 Hz, 1H), 4.82 (dd, *J* = 10.2, 8.4 Hz, 1H), 4.32 (t, *J* = 8.4 Hz, 1H), 2.45 (dq, *J* = 13.3, 6.6 Hz, 1H), 0.97 (d, *J* = 6.7 Hz, 3H), 0.94 (d, *J* = 6.9 Hz, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 172.2, 159.8, 156.0, 144.2, 141.8, 136.2, 128.7, 128.5, 128.1, 128.0, 127.7, 126.8, 123.3, 75.0, 70.2, 67.0, 58.6, 33.5, 19.5, 17.6. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{26}N_3O_3S^+$ 436.1689; Found 436.1659.

Benzyl ((*S*)-1-(4-((*S*)-4-benzyl-4,5-dihydrooxazol-2-yl)thiazol-2-yl)-2-methylpropyl)carbamate (11):
Yield: 207 mg, 0.46 mmol, 46%. ^1H NMR (500 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.40 – 7.28 (m, 6H), 7.25 – 7.16 (m, 4H), 5.62 (d, *J* = 9.2 Hz, 1H), 5.12 (d, *J* = 1.9 Hz, 2H), 4.95 (dd, *J* = 9.3, 6.2 Hz, 1H), 4.67 – 4.56 (m, 1H), 4.36 (t, *J* = 8.9 Hz, 1H), 4.19 – 4.10 (m, 1H), 3.34 (dd, *J* = 13.8, 4.7 Hz, 1H), 2.73 (dd, *J* = 13.8, 9.5 Hz, 1H), 2.44 (dq, *J* = 13.5, 6.7 Hz, 1H), 0.95 (dd, *J* = 9.8, 6.8 Hz, 6H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 172.1, 159.2, 156.0, 144.3, 137.8, 136.2, 129.1, 128.6, 128.5, 128.1, 128.0, 126.5, 122.9, 72.2, 68.0, 67.1, 58.5, 41.6, 33.6, 19.4, 17.6. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{25}H_{28}N_3O_3S^+$ 450.1846; Found 450.1813.

Molecular dynamics annealing of Co^{2+} triflate in complex with ligands 1 – 11.
The dynamic behavior of the catalyst complexes obtained from the ligands and $Co^{2+}OTf_2$ was studied by performed MD-annealing in suite Molecular Operating Environment (MOE from CCG) of the complexes from 750 K to 230 K by empirical methods using the Amber 10 force field[18] in the default Amber 10:ETH setting. The solvated complexes (in a droplet of $CHCl_3$, 12 layers) were constructed in the molecule builder and all major conformations of each complex were visited and energy minimized. Based on potential energy calculation low energy conformers of the complexes were extracted. In order to follow the dynamics of the interchange between these conformers a distance between the carbonyl carbon of the ester (or equivalent carbon in ligand **9-11**) and the C^β of the chiral center connected to the thiazole was monitored during a simulated MD-annealing process. The process started at 750 K for 3000 ps in order to establish the population of the two conformers as well as the relative barrier of interchange. This was followed by a cooling period of 2000 ps to 230 K and an equilibration period of 3000 ps at this temperature to find the low energy conformations at low temperature. The distance in Å between the two carbon atoms (one carbon and one hydrogen for ligand **8**) over time are depicted for each ligand complex.

ASSOCIATED CONTENT

Supporting Information

NMR spectra and computational data (PDF). The Supporting Information is available free of charge on the ACS Publications website.

AUTHOR INFORMATION

Corresponding Author

* Email: meldal@nano.ku.dk, fdi@chem.ku.dk

ORCID

Christian Borch Jacobsen: 0000-0002-7502-9831

Daniel S. Nielsen: 0000-0001-7851-1538

Morten Meldal: 0000-0001-6114-9018

Frederik Diness: 0000-0001-5098-7198

Notes

The authors declare no competing financial interest

ACKNOWLEDGMENT

The University of Copenhagen is acknowledged for funding of the Center for Evolutionary Chemical Biology (CECB). The authors are grateful to the Villum Foundation for postdoctoral grants to C.B.J. and D.S.N.

REFERENCES

(1) (a) Diness, F.; Nielsen, D. S.; Fairlie, D. P. Synthesis of the thiazole-thiazoline fragment of largazole analogues. *J. Org. Chem.* **2011**, *76*, 9845-9851. (b) Nielsen, D. S.; Hoang, H.; Lohmann, R.-J.; Diness, F.; Fairlie, D. P. Total Synthesis, Structure, and Oral Absorption of a Thiazole Cyclic Peptide, sanguinamide A. *Org. Lett.* **2012**, *14*, 5720-5723.

(2) Arnison, P. G. et al. Ribosomally Synthesized and Post-translationally Modified Peptide Natural Products: Overview and Recommendations for a Universal Nomenclature. *Nat. Prod. Rep.*, **2013**, *30*, 108-160.

(3) (a) Tan, L. T. Bioactive Natural Products from Marine Cyanobacteria for Drug Discovery. *Phytochemistry* **2007**, *68*, 954-979. (b) Just-Baringo, X.; Albericio, F.; Álvarez, M. Thiopeptide Antibiotics: Retrospective and Recent Advances. *Mar. Drugs* **2014**, *12*, 317-351.

(4) (a) Kelly, W. L.; Pan L.; Li C. Thiostrepton Biosynthesis: Prototype for a New Family of Bacteriocins. *J. Am. Chem. Soc.* **2009**, *131*, 4327-4334. (b) Liao, R.; Duan, L.; Lei, C.; Pan, H.; Ding, Y.; Zhang, Q.; Chen, D.; Shen, B.; Yu, Y.; Liu, W. Thiopeptide Biosynthesis Featuring Ribosomally Synthesized Precursor Peptides and Conserved Posttranslational Modifications. *Chem. Biol.* **2009**, *16*, 141-147. (c) Brown, L. C. W.; Acker, M. G.; Clardy, J.; Walsh, C. T.; Fischbach, M. A. Thirteen Posttranslational Modifications Convert a 14-residue Peptide into the Antibiotic Thiocillin. *Proc. Natl. Acad. Sci. USA* **2009**, *106*, 2549-2553.

(5) (a) Li, C.; Kelly, W. L. Recent Advances in Thiopeptide Antibiotic Biosynthesis. *Nat. Prod. Rep.* **2010**, *27*, 153. (b) Bagley, M. C.; Dale, J. W.; Meritt, E. A.; Xiong, X. Thiopeptide Antibiotics. *Chem. Rev.* **2005**, *105*, 685. (c) Melby, J. O.; Nard, N. J.; Mitchell, D. A. Thiazole/oxazole-modified Microcins: Complex Natural Products from Ribosomal Templates. *Curr. Opin. Chem. Biol.* **2011**, *15*, 369-378. (d) Ortega, M. A.; van der Donk, W. A. New Insights into the Biosynthetic Logic of Ribosomally Synthesized and Post-translationally Modified Peptide Natural Products**.** *Cell Chem. Biol.* **2016**, *23*, 31-44. (e) Goto, Y.; Ito, Y.; Kato, Y.; Tsunoda, S.; Suga, H. One-Pot Synthesis of Azoline-containing Peptides in a Cell-free Translation System Integrated with a Posttranslational Cyclodehydratase. *Chem. Biol.* **2014**, *21*, 766-774. (f) Donia, M. S.; Hathaway, B. J.; Sudek, S.; Haygood, M. G.; Rosovitz, M. J.; Ravel, J.; Schmidt, E. W. Natural Combinatorial Peptide Libraries in Cyanobacterial Symbionts of Marine Ascidians. *Nat. Chem. Biol.*, **2006**, *2*, 729-735. (g) Schmidt, E. W.; Nelson, J. T.; Rasko, D. A.; Sudek, S.; Eisen, J. A.; Haygood, M. G.; Ravel, J. Patellamide A and C Biosynthesis by a Microcin-like Pathway in Prochloron Didemni, the Cyanobacterial Symbiont of Lissoclinum patella. *Proc. Natl. Acad. Sci. USA*, **2005**, *102*, 7315-7320.

(6) (a) Brenk, A. L.; Fairlie, D. P.; Hanson, G. R.; Gahan, L. R.; Hawkins, C. J.; Jones, A. Binding of Copper(II) to the Cyclic Octapeptide Patellamide D. *Inorg. Chem.*, **1994**, *33*, 2280-2289. (b) Cusack, R. M.; Grøndahl, L.; Fairlie, D. P.; Gahan, L. R.; Hanson, G. R. Cyclic Octapeptides Containing Thiazole. Effect of Stereochemistry and Degree of Flexibility on Calcium Binding Properties. *J. Chem. Soc., Perkin Trans. 2*, **2002**, 556-563. (c) Brenk, A. L.; Tyndall, J. D. A.; Cusack, R. M.; Jones, A.; Fairlie, D. P.; Gahan, L. R.; Hanson, G. R. Formation of Mononuclear and Chloro-bridged Binuclear Copper(II) Complexes of Patellamide D, a Naturally Occurring Cyclic Peptide: Influence of Anion and Solvent. *J. Inorg. Biochem.*, **2004**, *98*, 1857-1866.

(7) Donia, M. S.; Schmidt, E. W. Cyanobactins – Ubiquitous Cyanobacterial Ribosomal Peptide Metabolites. In *Comprehensive Natural Products II: Chemistry and Biology,* Mander, L., Liu, H. W., Eds.; Elsevier, Amsterdam, Netherlands. **2010**, pp 539-558.

(8) (a) Babu, S. A.; Krishnan, K. K.; Ujwaldev, S. M.; Anilkumar, G. Applications of Pybox Complexes in Asymmetric Catalysis. *Asian J. Org. Chem.* **2018**, *7*, 1033-1053. (b) Desimoni, G.; Faita, G.; Jørgensen, K. A. C(2)-Symmetric Chiral

Bis(oxazoline) Ligands in Asymmetric Catalysis. *Chem. Rev.* **2006**, *106*, 3561-3651.
(9) Blaser, H. U. C2 Symmetry and Asymmetric Induction. *Chem. Rev.* **1992**, *92*, 935-952.
(10) (a) Jørgensen, K. A. Catalytic Asymmetric Hetero-Diels-Alder Reactions of Carbonyl Compounds and Imines. *Angew. Chem. Int. Ed.* **2000***, 39*, 3558-3588. (b) Pellissier, H. Asymmetric Hetero-Diels–Alder Reactions of Carbonyl Compounds. *Tetrahedron* **2009**, *65*, 2839–2877. (c) Held, F. E.; Tsogoeva, S. B. Asymmetic Cycloaddition Reactions Catalyzed by Bifunctional Thiourea and Squareamide Organocatalysts: Recent Advances. *Catal. Sci. Technol.* **2016**, *6*, 645-667.
(11) (a) Rajaram, S.; Sigman, M. S. Design of Hydrogen Bond Catalysts Based on a Modular Oxazoline Template: Application to an Enantioselective Hetero Diels-Alder Reaction. *Org. Lett.* **2005**, *7*, 5473-5475. (b) White, J. D.; Shaw, S. Cis-2,5-Diaminobicyclo[2.2.2]octane, a New Scaffold for Asymmetric Catalysis via Salen-metal complexes. *Org. Lett.* **2011**, *13*, 2488-2491.
(12) Zhang, Q.; Liu, W. Biosynthesis of Thiopeptide Antibiotics and Their Pathway Engineering. *Nat. Prod. Rep.* **2013**, *30*, 218-226.
(13) Nicolaou, K. C.; Safina, B. S.; Zak, M.; Lee, S. H.; Nevalainen, M.; Bella, M.; Estrada, A. A.; Funke, C.; Zécri, F. J.; Bulat, S. Total Synthesis of Thiostrepton. Retrosynthetic Analysis and Construction of Key Building Blocks. *J. Am. Chem. Soc.* **2005**, *127,* 11159-11175.
(14) (a) Brendenkamp, M. W.; Holzapfel, C. W.; van Zyl, W. The Chiral Synthesis of Thiazole Amino Acid Enantiomers. Synth. Commun. **1990**, 20, 2235-2249. (b) Bredenkamp, M. W.; Holzapfel, C. W.; Snyman, R. M.; van Zyl, W. J. Observations on the Hantzsch Reaction: Synthesis of *N*-^{t}Boc-*S*-Dolaphenine. Synth. Commun. **1992**, *22*, 3029-3039.
(15) (a) Burrell, G.; Evans, J. M.; Jones, G. E.; Stemp, G. The Action of Diethylaminosulphur Trifluoride (dast) on Trans-4-amido- 3-Chromanols: Preparation of Cis-amidoalcohols via Oxazolines. *Tetrahedron Lett.* **1990**, *31*, 3649-3652. (b) Phillips, A. J., Uto, Y., Wipf, P., Reno, M. J., Williams, D. R. Synthesis of Functionalized Oxazolines and Oxazoles with DAST and Deoxo-Fluor. *Org. Lett.* **2000**, *2*, 1165-1168.
(16) Kezuka, S., Mita, T., Ohtsuki, N., Ikeno, T., Yamada, T. Optically Active Cationic Cobalt(III) Complexes: Highly Efficient Catalysts for Enantioselective Hetero Diels–Alder Reaction. *Chem. Lett.*, **2000**, *29*, 824-825.
(17) Matthew, S. S.; Jacobsen, E. N. Schiff Base Catalysts for the Asymmetric Strecker Reaction Identified and Optimized from Parallel Synthetic Libraries. *J. Am. Chem. Soc.* **1998**, *120*, 4901-4902.
(18) Case, D. A.; Darden, T. A.; Cheatham, III, T.E.; Simmerling, C. L.; Wang, J.; Duke, R. E.; Luo, R.; Crowley, M.; Walker, R. C.; Zhang, W.; Merz, K. M.; Wang, B.; Hayik, S.; Roitberg, A.; Seabra, G.; Kolossvary, I.; Wong, K. F.; Paesani, F.; Vanicek, J.; Wu, X.; Brozell, S. R.; Steinbrecher, T.; Gohlke, H.; Yang, L.; Tan, C.; Mongan, J.; Hornak, V.; Cui, G.; Mathews, D. H.; Seetin, M. G.; Sagui, C.; Babin, V.; Kollman, P. A. AMBER 10, **2008**, University of California, San Francisco.