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Tying a Molecular Overhand Knot of Single Handedness and Asymmetric Catalysis with the Corresponding Pseudo-*D*₃-Symmetric Trefoil Knot

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Supporting Information Placeholder

ABSTRACT: We report the stereoselective synthesis of a left-handed trefoil knot from а tri(2,6pyridinedicarboxamide) oligomer with six chiral centers using a lanthanide(III) ion template. The oligomer folds around the lanthanide ion to form an overhand knot complex of single handedness. Subsequent joining of the overhand knot end groups by ring-closing olefin metathesis affords a single stereoisomer of the trefoil knot in 90% yield. The knot topology and handedness was confirmed by NMR spectroscopy, mass spectrometry and X-ray crystallography. The pseudo- D_3 -symmetric knot was employed as an asymmetric catalyst in Mukaiyama aldol reactions, generating enantioselectivities of up to 83:17 er, significantly higher than those obtained with a comparable unknotted ligand complex.

Knotted regions of proteins can play a significant role in ligand binding¹ and alter enzymatic activity compared to unknotted homologues.² The chemical effects of knotting in synthetic molecular systems, however, have to date been less explored.³ The simplest non-trivial knot, the trefoil knot, has three crossing points and is topologically chiral.⁴ Although a number of synthetic strategies to racemic trefoil knots have been developed,^{5,6} there are few examples of their stereose-lective synthesis.⁷ Here we describe the assembly of a trefoil knot of single handedness by entwining a ligand strand with six asymmetric carbon atoms around a lanthanide ion template.⁸ We find that the chiral trefoil knot is an effective catalyst for the asymmetric Mukaiyama aldol reaction. As far as we are aware this is the first example of a chiral molecular knot being utilized in asymmetric catalysis.^{9,10}

We recently described^{7d} the assembly of three chiral 2,6pyridinedicarboxamide ligands about a lanthanide metal ion to form a circular helicate.¹¹ By joining the ligands' end groups a trefoil knot of single handedness was obtained, the point chirality of the ligands determining the topological handedness of the knot. Following Hunter's synthesis of a racemic trefoil knot by entwining a flexible bipyridine oligomer about a zinc(II) ion template to form a racemic overhand knot,^{5g,12} we envisioned that it might be possible to tie an overhand knot of defined stereochemistry in a molecular strand using a chiral tri(2,6-pyridinedicarboxamide) oligomer and a lanthanide(III) ion template. Subsequently joining the ends of the overhand knot together would give a chiral trefoil knot.

Scheme 1. Synthesis of Molecular Overhand Knots, Λ -Lu/Eu(R^6)-1(CF₃SO₃)₃, and Trefoil Knots, Λ -Lu/Eu(R^6)-2, of Single Handedness^{*a*}



^{*a*} Reagents and conditions: (a) $Eu(CF_3SO_3)_3$, CH_3CN , 80 ^oC, 12 h, 85% or $Lu(CF_3SO_3)_3$, 80 ^oC, 12 h, 90%; (b) Hoveyda-Grubbs 2nd generation catalyst (15 mol%), CH_2Cl_2/CH_3NO_2 , 50 ^oC, 18 h, 88% Λ -Lu(R^6)-2(CF_3SO_3)₃, 90% Λ -Eu(R^6)-2(CF_3SO_3)₃.

Our previous Ln-template chiral trefoil knot was prepared^{7d} using ring closing olefin metathesis (RCM) to simultaneously form ten-atom linkers between each pair of the three 2,6-pyridinedicarboxamide units. To maintain a similar spacer length¹³ in the tri(2,6-pyridinedicarboxamide) oligomer we used triethylene glycol groups to connect the end sections to the central ligand set, generating ligand (R^6)-1 (see Supporting Information).

Ligand (R^6)-1 was treated with Lu(CF₃SO₃)₃ in CD₃CN and the overhand knot tying process (Scheme 1, step a) followed by ¹H NMR spectroscopy (Figure 1). Although the assembly of discrete 2,6-pyridinedicarboxamide ligands about a lanthanide(III) ion is typically fast, even at room temperature,^{7d,14} the ¹H NMR spectrum of (R^6)-1 in the presence of Lu(CF₃SO₃)₃ was initially broad (Figure 1b). However, heating the solution at 80 °C led to a sharp ¹H NMR spectrum after several hours (Figure 1c) indicating slow equilibration to predominantly a single species. This was shown to be the overhand knot complex, Λ -Lu(R^6)-1(CF₃SO₃)₃, by a combination of electrospray ionization mass spectrometry (ESI-MS; m/z 1074 [Lu(R^6)-1][CF₃SO₃]²⁺, 666 [Lu(R^6)-1]³⁺) and ¹H NMR spectroscopy (Figure 1c). (a)

Figure 1. Selected regions of the ¹H NMR spectra (600 MHz, CD₃CN, 295 K [345 K for (a) and (c)]) of: (a) ligand strand (R^6) -1; (b) equimolar mixture of oligomer (R^6) -1 and Lu(CF₃SO₃)₃ after 5 min at rt; (c) left-handed overhand knot complex Λ -Lu(R^6)-1(CF₃SO₃)₃; (d) left-handed trefoil knot complex Λ -Lu(R^6)-2(CF₃SO₃)₃. The signals shown in red correspond to the protons in the pyridine rings and -NHCHCH₃-fragments. The lettering refers to the proton assignments shown in Scheme 1. * = water

The ¹H NMR spectrum of Λ -Lu(R°)-1(CF₃SO₃)₃ (Figure 1c) features several different environments for each set of protons H_a, H_b, H_c, H_d and H_e, consistent with the pronounced asymmetric environment provided by the overhand knot. Pyridine ring protons H_a and H_b are significantly shifted up-

field with respect to those in (R^6) -1 ($\Delta\delta_{H_a} = 0.89$ and 1.96 ppm), indicative of π - π stacking between the pyridine and naphthalene rings. The H_d protons are also upfield shifted ($\Delta\delta = 0.63$ and 0.73 ppm) and split into two different signals.

To join the two end groups of the overhand knot, Λ -Lu(R^6)-1(CF₃SO₃)₃ was treated with the second generation Hoveyda-Grubbs catalyst in CH₂Cl₂/CH₃NO₂ (3:1, v/v) at 50 °C for 18 h (Scheme 1, step b). Quenching of the reaction with ethyl vinyl ether, followed by addition of dichloromethane, precipitated trefoil knot complex Λ -Lu(R^6)-2(CF₃SO₃)₃. The ¹H NMR spectrum (Figure 1d) lacks the terminal alkene protons of Λ -Lu(R^6)-1(CF₃SO₃)₃ (Figure 1c) and features fewer sets of resonances than the overhand knot, a reflection of the trefoil knot being essentially D_3 -symmetric other than for one of the three linker groups being different to the other two. Electrospray ionization mass spectrometry confirmed the intramolecular ring closure (ESI-MS; m/z 1060 [Lu(R^6)-2][CF₃SO₃]²⁺, 657 [Lu(R^6)-2]³⁺).

Substituting Eu(CF₃SO₃)₃ for Lu(CF₃SO₃)₃ in the reactions shown in Scheme 1 generated the corresponding europium trefoil knot complex, Λ -Eu(R^6)-2(CF₃SO₃)₃ (see Supporting Information). Slow diffusion of diethyl ether into a saturated methanolic solution of Λ -Eu(R^6)-2(CF₃SO₃)₃ afforded single crystals suitable for X-ray diffraction. The solid state X-ray structure confirmed the molecular topology and showed that the trefoil knot is of Λ -handedness (Figure 2 and Supporting Information). The knotted ligand wraps around the europium ion to give a trigonal prismatic coordination geometry with the Eu-O (2.33 and 2.39 Å) and Eu-N (2.52 Å) distances ranges for europium-2,6the expected in pyridinedicarboxamide complexes.^{7d,15} Aromatic stacking between each pyridine ring and two naphthalene groups hold the ligand in a compact arrangement around the metal ion. The solid state structure is consistent with the ¹H NMR shielding observed in solution (Figure 1).



Figure 2. (a) X-Ray crystal structure of Λ -Eu(R^6)-2(CF₃SO₃)₃ shown in framework representation. Hydrogen atoms, solvent molecules and counter-anions are omitted for clarity. Selected metal-donor atom bond lengths (Å): Eu-O 2.33(2) x 3, 2.39(2) x 3; Eu-N 2.52(2) x 2, 2.52(1).

Ligand **2** is a rare example of an enantiomerically pure trefoil knot.^{6,7} A pentafoil knot was recently employed in anion binding catalysis¹⁶ but the chirality of molecular knots has 1 2

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59 60 not previously been exploited in asymmetric catalysis. As lanthanide salts have been widely used as Lewis acids to promote asymmetric Mukaiyama aldol reactions, in some cases with high enantioselectivies,¹⁷ we first investigated the efficacy of Λ -Eu(R^6)-2(CF₃SO₃)₃ as a chiral catalyst for the reaction of 4-nitrobenzaldehyde 3 with silyl enol ether 4 (Figure 3).¹⁸ Solvent choice proved crucial for the catalysis;¹⁹ methanol:acetonitrile (5:2) giving both the highest conversions and the most promising levels of enantioenrichment. In comparison to both open complex A-Eu-6 (Figure 3 table, entry 2) and the previously reported^{7d} trefoil knot, Λ -Eu-7 (Figure 3 table, entry 3), Λ -Eu(R^6)-2 generated product 5 with improved (65:35 er) enantiomeric enrichment (Figure 3 table, entry 1). In each case enrichment was observed only in the syn-diastereomer,²⁰ with the anti-diastereomer formed racemically.²¹ Introducing additional steric bulk into the enol ether (8) improved the enantioselectivity (83:17 er for syn-9, Figure 4). Less activated aldehydes (replacing NO₂ with H or Me) gave lower yields and favored the anti-adduct (10 and 11, Figure 4), although the degree of enantioselectivity in the syn-diastereomer was maintained. p-Bromoaldehyde proved essentially unreactive under the reaction conditions employed (12, Figure 4).



Entry	Catalyst	Solvent	Conv. (%) ^a	syn:anti ^a	<i>syn-</i> er (%) ^b
1	Λ -Eu(R^6)-2	MeOH/CH ₃ CN	61	1:1	65:35
2	Λ-Eu- 6	MeOH/CH ₃ CN	61	1:1	58:42
3	Λ-Eu-7	MeOH/CH ₃ CN	65	1:1.4	54:46
4	-	MeOH/CH ₃ CN	17	1:1	-

Figure 3. Europium-ligand catalyzed Mukaiyama aldol reactions. Reaction conditions: 4-nitrobenzaldehyde (1.0 equiv.), trimethyl(1-phenylpropenyloxy)silane (1.0 equiv.) at -10 °C for 4 d. ^aDetermined by ¹H NMR. ^bDetermined by chiral HPLC.

To probe the mechanism of enantioselective knot catalysis we determined the accessibility of the lanthanide ion bound within the chiral pocket of the knot. Luminescence decay lifetime measurements²² in MeOH and MeOD were used to determine the number of solvent molecules bound to the lanthanide core of complexes Λ -Eu(R^6)-2, Λ -Eu-6 and Λ -Eu-7 (see Supporting Information). For the trefoil knots, Λ -Eu(R^6)-2 and Λ -Eu-7, q values of o.8 and 1.1 were obtained, respectively, indicating that a solvent molecule rapidly and reversibly binds to the lanthanide ion despite it being at the center of the trefoil knot.²² As the metal ion remains accessible whilst bound within the chiral pocket of the knot it may be that the Mukaiyama aldol reaction is promoted through coordination of the aldehyde to the lanthanide.²³ In contrast, Λ -Eu-6 gave *q* values of 0.9 and 3.3, indicative of two species in slow exchange, one bound to one solvent molecule and one bound to three. Presumably the more highly solvated lanthanide ion results from transient loss of one of the 2,6pyridinedicarboxamide groups. The continuous covalent backbone of the knotted ligand thus helps to maintain the well-defined chiral environment around the lanthanide ion which, in turn, may help to maximize the enantiomeric enrichment of the *syn*- product.



Figure 4. Chiral trefoil knot Λ -Eu(R^6)-2(CF₃SO₃)₃ catalyzed asymmetric Mukaiyama aldol reactions. Reaction conditions: 1.0 equiv. of aldehyde and 1.5 equiv. trimethyl(3-methyl-1-phenylbutenyloxy)silane at –10 °C for 4 d. ^{*a*}Determined by 'H NMR. ^{*b*}Determined by chiral HPLC. In all cases the relative stereochemistry of the most enantioenriched diastereomer is shown.

In summary, the stereochemistry of chiral centers within a ligand strand has been used to control the handedness of an overhand knot tied in the strand through complexation with a lanthanide ion. Joining the ends of the overhand knot by RCM resulted in a trefoil knot of single handedness in 90% yield. The chiral trefoil knot-lanthanide complex is an effective catalyst for the asymmetric Mukaiyama aldol reaction. The ability to tie knots of single handedness in molecular strands should facilitate the investigation of topological stereochemistry in fields where the transfer of chiral information is important (such as asymmetric catalysis, chiral recognition, chiral liquid crystal phases and materials for nonlinear optics).

ASSOCIATED CONTENT

Supporting Information

Synthetic procedures, X-ray, NMR and MS characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

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