Tetrahedron 69 (2013) 57–68

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

# Synthesis of a $C_1$-symmetric Box macrocycle and studies towards active-template synthesis of mechanically planar chiral rotaxanes

Pauline E. Glen, James A.T. O'Neill, Ai-Lan Lee *

*Institute of Chemical Sciences, Heriot-Watt University, Edinburgh EH14 4AS, United Kingdom*

ARTICLE INFO

*Article history:*
Received 1 August 2012
Received in revised form 3 October 2012
Accepted 22 October 2012
Available online 30 October 2012

*Keywords:*
Macrocycles
Bis-oxazolines
Oxidative Heck
CuAAC click
Cadiot–Chodkiewicz
Rotaxane

ABSTRACT

A $C_1$-symmetric Box macrocycle has been synthesized for the first time. The Box macrocycle along with other $C_1$ and $C_2$-symmetric Box ligands were evaluated and compared as ligands in the Cadiot–Chodkiewicz, oxidative Heck and CuAAC 'click' reactions as part of our studies towards achieving active-metal template synthesis of mechanically planar chiral rotaxanes. This study constitutes the first report of Cadiot–Chodkiewicz and CuAAC 'click' reactions using Box ligands, as well as the first dedicated study of oxidative Heck reactions using Box ligands.



## 1. Introduction

The synthesis of interlocked molecules such as catenanes and rotaxanes is of great contemporary interest to chemists due not only to their peculiar structures but also their potential applications in nanotechnology—for example, as molecular machines, switches, wires and motors.[1] Additionally, rotaxanes and knots found in nature exhibit remarkable activities compared with linear analogues.[2] So far, however, much less attention has been paid to one of the most interesting and yet least exploited features of interlocked architectures: their chirality—a rotaxane can possess *mechanical planar chirality* (sometimes referred to as 'cyclochirality')[3] even if both the wheel and axle are achiral themselves.[3] This inherent chirality arises if there is dissymmetry in both the ring and the thread, for example, if both the axle and the wheel bear groups, which impart directionality (Fig. 1). Planar chiral rotaxanes have seen application as chiral sensors for amino acids,[4c] and other chiral rotaxanes have shown promise in asymmetric catalysis applications.[5] To date, however, only one attempt at an enantioselective synthesis of mechanically planar chiral rotaxanes has been reported, yielding an optically active rotaxane in only 4.4% ee.[6] Prior to that, optically active planar chiral rotaxanes have been isolated by preparative chiral stationary phase HPLC separation of a racemic mixture.[4] In addition, Lacour et al. attempted the diastereoselective synthesis of an inherently chiral pseudorotaxane, achieving a de of <8%.[7] Thus, the goal of efficiently synthesizing and investigating the asymmetric induction properties of planar chiral rotaxanes, especially ones with no other element of chirality, remains a major challenge.

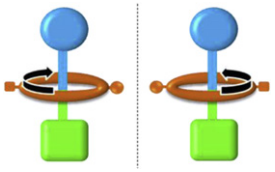
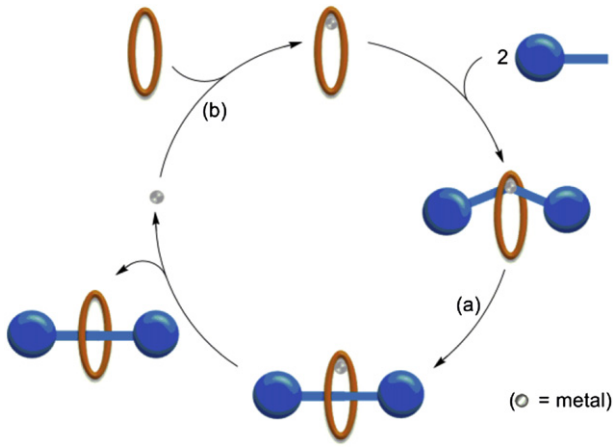


**Fig. 1.** Mechanical planar chirality in rotaxanes.

Recently, Leigh and co-workers pioneered the use of the active-template metal strategy as an efficient way of synthesising interlocked molecules.[8] The active-metal template strategy utilises the metal to play a dual role of template for entwining or threading the components and as a catalyst for covalent bond formation for capturing the final interlocked product. For rotaxane formation, the macrocycle thus acts as a ligand to coordinate a metal, which in turn acts as a catalyst to mediate the covalent bond formation between two half-threads in the cavity of the macrocycle, leading to a rotaxane (Scheme 1). The use of a metal–ligand complex in such a way opens the possibility of combining asymmetric catalysis with rotaxane bond formation.

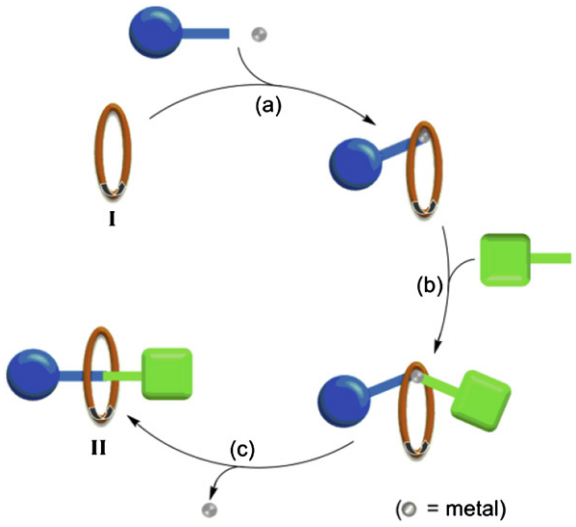
* Corresponding author. E-mail address: A.Lee@hw.ac.uk (A.-L. Lee).

0040-4020/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2012.10.069




**Scheme 1.** Active-metal template strategy for forming rotaxanes. (a) Metal-catalyzed covalent bond formation. (b) Metal template turnover in catalytic active-metal template synthesis of rotaxanes.

To this end, we were interested in investigating an asymmetric active-template method to form planar chiral rotaxanes (Scheme 2). If a cross-coupling reaction of two distinct half-threads is used with a macrocycle that lacks any element of symmetry (i.e., $C_1$-symmetric), and the faces of the metal macrocycle complex are designed to be sterically different (e.g., by having point chirality), the approach of the first fragment should be selectively from the less sterically hindered face of the macrocycle. Approach of the second fragment from the opposite face followed by the metal-catalysed bond formation to form the [2]rotaxane should lead to an optically active, planar chiral rotaxane. If the point chirality within the macrocycle is then removed, the resulting rotaxane will be left solely with mechanical planar chirality.



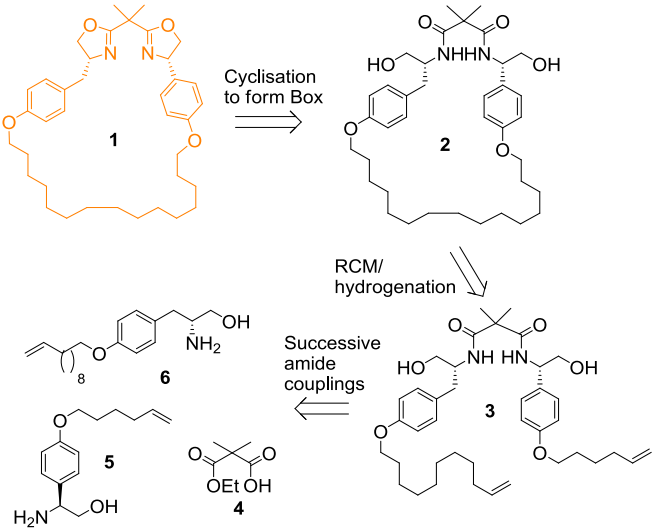

**Scheme 2.** Proposed asymmetric active-metal template for rotaxane formation. (a) Approach of first fragment to less sterically hindered face of asymmetric macrocycle **I**. (b) Approach of second fragment to opposite face. (c) Covalent bond-forming reaction and demetallation to furnish chiral rotaxane **II**.

In this article, we present the synthesis of the first $C_1$-symmetric Box macrocycle and its application, along with other model $C_1$- and $C_2$-symmetric Box ligands, in the Cadiot–Chodkiewicz, oxidative Heck and CuAAC 'click' reactions as part of our studies towards achieving the active-metal template synthesis of chiral rotaxanes.

## 2. Results and discussion

### 2.1. Synthesis of $C_1$-symmetric Box macrocycle 1

Our first aim was thus to synthesize a suitable $C_1$-symmetric macrocycle with sterically different faces, which can act as a ligand for various metal-catalyzed reactions, and whose point chirality could be removed after the rotaxane forming process. With this in mind, we chose to synthesize bis-oxazoline (Box) macrocycle **1**.[9] While examples of $C_2$-symmetric Box macrocycles have been reported by Žinić, Šunjić and co-workers as chiral ligands for Cu-catalyzed reactions,[10] there are no examples of $C_1$-symmetric Box macrocycles in the literature.[11–15] Our retrosynthetic plan involves ring closing metathesis/hydrogenation of **3** as the key macrocyclisation step, followed by cyclisation of **2** to the bis-oxazoline (Scheme 3). The unsymmetrical fragment **3** will in turn be assembled through successive amide couplings of dimethyl malonic acid monomethylester **4** with amino alcohols **5** and **6**.

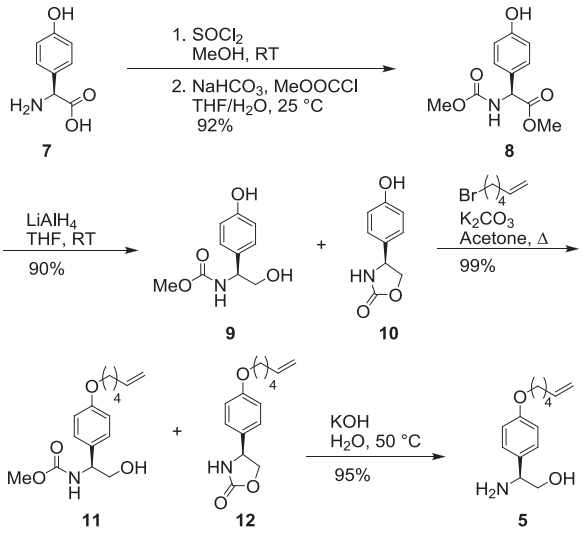



**Scheme 3.** Retrosynthetic analysis of macrocycle **1**.

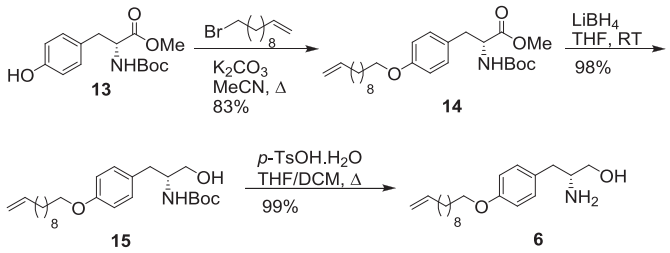
Amino alcohol **5** was prepared as outlined in Scheme 4. Esterification followed by N-protection of 4-hydroxy-L-phenylglycine **7** furnished **8** in high yield (92%). Reduction of ester **8** with $LiAlH_4$ afforded both alcohol **9** as expected, but also oxazolidinone **10**, resulting from reaction between the alcohol and carbamate protecting group. As both products **9** and **10** can be taken forward in the synthetic scheme both were alkylated with 6-bromo-1-hexene under standard conditions to yield ethers **11** and **12**. A mixture of these ethers was then subjected to basic conditions in order to attain amino alcohol **5** in excellent yield (95%).

Synthesis of the other amino alcohol portion **6** began with the alkylation of Boc-D-tyrosine methyl ester **13** with 11-bromoundecene to provide ether **14** in an 83% yield (Scheme 5). Alcohol **15** was produced by reduction of **14** with $LiBH_4$ (98%). Subsequent deprotection of the Boc group gave amino alcohol **6** in almost quantitative yield.

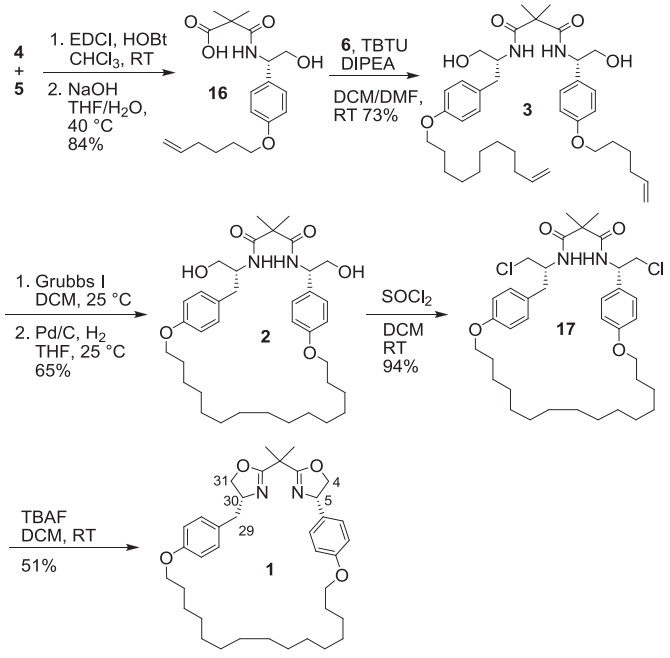
With both amino alcohols in hand, assembly of macrocycle **1** was carried out (Scheme 6). The EDCI-promoted coupling of dimethyl malonic acid monomethylester **4** with amino alcohol **5** followed by hydrolysis afforded amide **16** in an 84% yield. Coupling of amino alcohol **6** with **16**, in a TBTU-promoted reaction, provided unsymmetrical diene **3** in a 73% yield. Treatment of diene **3** with Grubbs' first generation catalyst under high dilution conditions and




**Scheme 4.** Synthesis of amino alcohol **5**.




**Scheme 5.** Synthesis of amino alcohol **6**.




**Scheme 6.** Synthesis of macrocycle **1**.

subsequent reduction of the alkene with Pd/C under a hydrogen atmosphere furnished macrocycle **2** in a good 65% yield over two steps. Finally, Box macrocycle **1** was synthesized from bis-amide **2** in two steps. Reaction of diol **2** with thionyl chloride gave dichloride **17** in high yield (94%). Cyclisation to the Box macrocycle **1** was then achieved by treatment of **17** with TBAF.[16] At this point, we discovered that the Box macrocycle **1** is unstable to silica gel chromatography, forming decomposition products as well as reverting to the uncyclised **2**. Eventually, alumina chromatography techniques were developed for successful purification of **1**. Thus, the synthesis of the first $C_1$-symmetric bis-oxazoline macrocycle **1** was achieved in a gram scale.

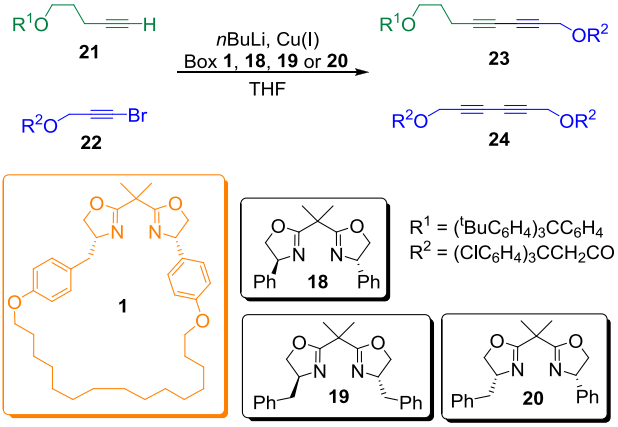
## 2.2. Catalysis studies

Following the successful synthesis of macrocycle **1**, we set out to study the applicability of Box ligands in the Cadiot–Chodkiewicz,[17] oxidative Heck[18] and CuAAC 'click'[19] reactions as these reactions have been shown to perform well in the active-template synthesis of rotaxanes, and are suitable for heterocoupling of two different half-threads, required to form a dissymmetric thread.[20–22,23] However, since only pyridine and/or bipyridine-based macrocycles have been utilized in these rotaxane forming reactions, and Box ligands have either not been evaluated (Cadiot–Chodkiewicz, CuAAC) or have only seen limited study (oxidative Heck),[24] it was necessary for us to carry out model studies in order to understand how bis-oxazoline ligands will perform for these reactions. Thus, non-macrocyclic $C_2$-Box ligands **18** and **19**, model $C_1$-Box ligand **20** as well as macrocycle **1** were utilized in these investigations for comparison purposes between macrocyclic/non-macrocyclic/$C_1$/$C_2$ ligands.

In order to emphasize the asymmetry of any planar chiral rotaxanes produced, half-threads with significantly different stopper groups were utilized in our studies. In the Cu(I)-catalysed Cadiot–Chodkiewicz alkyne cross-coupling reaction, stopper fragments **21** and **22** were employed. When the reaction was carried out with $C_2$-Box ligand **18** (Table 1, entry 1), heterocoupled thread **23** was obtained, along with homocoupled product **24** in a 74:26 ratio and with a 74% conversion from bromoalkyne **22**. With this encouraging result in hand, efforts were made to improve the conversion of the reaction. Running the reaction for 5 days and changing the Cu(I) source to CuCl allowed for full conversion of bromoalkyne **22** to threads **23** and **24** without a change in the heterocoupled:homocoupled thread ratio (Table 1, entry 2).

Once we had our optimised conditions for the reaction using $C_2$-Box ligand **18**, we turned our attention to model $C_1$-Box ligand **20** and $C_1$-macrocycle **1** (Table 1, entries 3 and 4). To our surprise, neither of the reactions gave any indication of either heterocoupled thread **23** or homocoupled bromide **24**. As a control reaction run in the absence of any ligand (Table 1, entry 5) gives us a conversion to heterocoupled thread **23** of 34%, it would appear that the non-macrocycle $C_1$-Box ligand **20** and $C_1$-macrocycle **1** are actually *inhibiting* the reaction. This is in direct contrast with $C_2$-Box ligand **18**, which promotes the reaction to complete conversion. There are two possible causes for this outcome. Either the benzyl (vs Ph) group is inhibiting the reaction or the steric hindrance of having both groups on the same face of the ligand is too great for the reaction to occur. To ascertain the cause, the reaction was carried out with commercially available $C_2$-symmetric *dibenzyl* Box ligand **19** (Table 1, entry 6). The conversion of bromoalkyne **22** to thread **23** was significantly lower for the dibenzyl Box ligand **19** than for the diphenyl Box compound **18** (22% vs 100%) and was also lower than for the ligand-free reaction (22% vs 34%). This would imply that the dibenzyl Box ligand **19** actively inhibits the Cadiot–Chodkiewicz reaction. It would appear, therefore, that the presence of a benzyl group in conjunction with the $C_1$-nature of the ligand, with its steric crowding of one face of the compound, completely prevents the

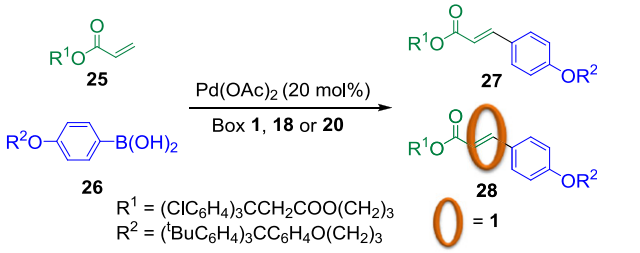
**Table 1**
Optimization studies for the Cadiot–Chodkiewicz reaction




| Entry | Cu(I) | Box | Time | Conv. of **22** to **23**+**24**[a] (%) | Ratio **23**/**24**[a] |
|---|---|---|---|---|---|
| 1 | CuI | **18** | 24 h | 74 | 74:26 |
| 2 | CuCl | **18** | 5 days | 100 | 74:26 |
| 3 | CuCl | **20** | 5 days | 0 | — |
| 4 | CuCl | **1** | 5 days | 0 | — |
| 5 | CuCl | — | 5 days | 34 | 100:0 |
| 6 | CuCl | **19** | 5 days | 22 | 100:0 |

[a] Determined by $^1$H NMR spectroscopic analysis of the reaction mixture.

**Table 2**
Optimization studies for the oxidative Heck reaction




| Entry | Box | $Pd(OAc)_2$[a] (%) | Oxidant | Solvent | Conv. of **25** to **27**[b] (%) |
|---|---|---|---|---|---|
| 1 | **18** | 20 | BQ | $DMF/CHCl_3$ | 100 |
| 2 | **20** | 20 | BQ | $DMF/CHCl_3$ | 59 |
| 3 | **20** | 20 | $BQ/O_2$ | $DMF/CHCl_3$ | 100 |
| 4 | — | 20 | $BQ/O_2$ | $DMF/CHCl_3$ | 24 |
| 5 | **1** | 20 | $BQ/O_2$ | $DMF/CHCl_3$ | 21 |
| 6 | **1** | 100 | — | $DMF/CHCl_3$ | 50[c] |
| 7 | — | 100 | $BQ/O_2$ | $DMF/CHCl_3$ | 47 |
| 8 | — | 20 | $BQ/O_2$ | $CHCl_3$ | 31 |
| 9 | **20** | 20 | $BQ/O_2$ | $CHCl_3$ | 20 |
| 10 | **1** | 20 | $BQ/O_2$ | $CHCl_3$ | 5 |

BQ=benzoquinone.
[a] With respect to alkene **25**.
[b] Determined by $^1$H NMR spectroscopic analysis of the reaction mixture.
[c] No evidence of rotaxane **28** by mass spectrometry.

Cadiot–Chodkiewicz reaction from occurring in the presence of Box ligand **20** and macrocycle **1**.

Our investigation into the compatibility of Box ligands in reactions known for active-metal template synthesis of rotaxanes continued with the study into Pd(II) oxidative Heck reactions. Reports of bis-oxazolines as ligands for oxidative Heck reactions are limited to only a couple of rare examples as part of ligand screens,[23] so once again, model studies had to be carried out.

Alkene **25** and boronic acid **26** were employed in the oxidative Heck reactions to synthesise **27** as the unsymmetrical thread (Table 2). To our delight, complete conversion of alkene stopper fragment **25** to thread **27** was obtained when the reaction was carried out with benzoquinone as the oxidant in 1:1 $DMF/CHCl_3$, as the components of the reaction were not soluble in DMF alone (Table 2, entry 1). When the ligand was changed from $C_2$-Box ligand **18** to $C_1$-Box ligand **20** a lower than expected conversion of 59% was obtained (Table 2, entry 2). However, running the reaction under an oxygen atmosphere (Table 2, entry 3) successfully promotes complete conversion to thread **27**. Comparison with a ligand-free control reaction (Table 2, entry 4) confirms that the non-macrocyclic Box ligands **18** and **20** accelerate the reaction under these conditions.

Encouraged by the complete conversion of alkene **25** to thread **27** by the non-macrocyclic $C_1$-Box ligand **20**, the synthesis of rotaxane **28** was attempted. However, a conversion to non-interlocked thread **27** of only 21% was achieved (Table 2, entry 5), similar to that of the ligand-free reaction (Table 2, entry 4). It is also in the region of what would be expected if the palladium catalyst was not turning over in the reaction (20%). Therefore, the reaction was repeated with stoichiometric amounts of $Pd(OAc)_2$ in order to determine if the macrocycle was sequestering the palladium and preventing turnover (Table 2, entry 6). The conversion of alkene **25** to non-interlocked thread **27** achieved under these conditions was only 50%, similar to the conversion obtained from the ligand-free stoichiometric control reaction (Table 2, entry 7, 47%). This similarity, when coupled with the lack of rotaxane **28** in the reaction, implies that the Box macrocycle **1** is not bound to the palladium throughout the reaction and only the background reaction is being observed.

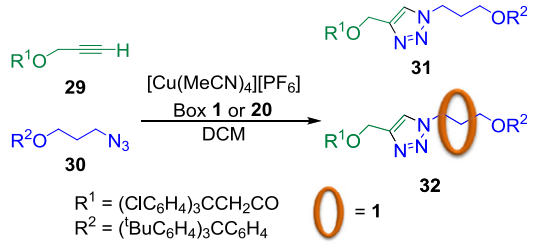
Suspecting competition between the macrocycle **1** and DMF in ligating to the palladium catalyst, the reaction was repeated in chloroform alone as this has a lower binding affinity to transition metals than DMF.[25] A ligand-free control reaction indicated that chloroform was a suitable solvent for the oxidative Heck reaction between alkene **25** and boronic acid **26**, achieving a better conversion than the ligand-free control in $DMF/CHCl_3$, though still quite low at 31% (Table 2, entry 8). When the reaction was carried out with non-macrocyclic $C_1$-Box ligand **20** and macrocycle **1** (Table 2, entries 9 and 10) the conversions were lower than those obtained in the control reaction; 20% and 5%, respectively. It is apparent from these results that both the non-macrocyclic Box ligand **20** and macrocycle **1** are ligated to the metal catalyst throughout the reaction and are slowing down the reaction compared to the ligand-free control. This supports our conjecture that the DMF is competing with the Box macrocycle in ligating with the palladium. It would appear from our results that there is a series in binding affinity to palladium between the solvent and Box ligands, which runs as follows: non-macrocyclic $C_2$-Box 18 ~ non-macrocyclic $C_1$-Box 20<DMF<Box macrocycle **1**.

With the failure to form rotaxane **28**, we turned to investigate the third known active-metal template reaction for compatibility with Box ligands: the CuAAC 'click' reaction of an azide with an acetylene. The reaction is known to work well with bipyridine macrocycles[19] but there are no known examples for the use of bis-oxazoline ligands.

Pleasingly, complete reaction of acetylene **29** with azide **30** was observed at 80 °C[20b] to form triazole thread **31** using model $C_1$-Box ligand **20** (Table 3, entry 1). Substituting **20** with our macrocycle **1** under the same conditions also resulted in full conversion of acetylene **29**, but disappointingly there was no evidence of rotaxane **32** in either $^1$H NMR spectroscopy or mass spectrometry. We speculated that the macrocycle may no longer be bound to the copper species at the high temperatures used in the reaction (80 °C). We therefore decided to optimise the CuAAC reaction at room temperature. Unfortunately, initial attempts to optimise the reaction proved irreproducible. The unreliability of the reaction turned out to be related to the concentration, which was subject to change through evaporation of the DCM solvent over the long period of the reaction. The

reactions were therefore carried out in a sealed vial instead, which proves that concentration is key to the observing reactivity (Table 3, entries 3 and 4). Complete conversion of acetylene **29** to thread **31** was achieved in only 48 h through further concentration of the reaction mixture and with the use of additional azide **30** as this was found to be a limiting factor (Table 3, entry 5).

**Table 3**
Optimization studies for CuAAC click reaction




| Entry | Box | Temp (°C) | Concn[a] (mM) | Time | Conv. of **29** to **31**[b] (%) |
|---|---|---|---|---|---|
| 1 | **20** | 80[c] | 10 | 68 h | 100 |
| 2 | **1** | 80[c] | 10 | 72 h | 100[d] |
| 3 | **20** | 25 | 10 | 7 days | 0 |
| 4 | **20** | 25 | 60 | 4 days | 40 |
| 5[e] | **20** | 25 | 400 | 48 h | 100 |
| 6[e] | **1** | 25 | 400 | 48 h | 100[f] |
| 7[e] | — | 25 | 400 | 19 h | 100 |

[a] With respect to Box.
[b] Determined by $^1$H NMR spectroscopic analysis of the reaction mixture.
[c] Reaction carried out in a sealed vessel.
[d] No evidence of rotaxane **32** by mass spectrometry.
[e] With 1.5 equiv azide **30**.
[f] Trace amounts of rotaxane **32** detected by mass spectrometry.

Finally, rotaxane synthesis using macrocycle **1** was attempted again, using the optimised RT conditions and full conversion of acetylene **29** was achieved (Table 3, entry 6). Regrettably, however, rotaxane **32** remained elusive; although detected by mass spectrometry, it was present in only trace amounts. The most likely explanation for the lack of rotaxane, that the Box ligands are not in fact bound to the metal throughout the reaction, is refuted by the result of the ligand-free control reaction (Table 3, entry 7). Like Leigh and co-workers,[22b] we found that the ligand-free reaction reached complete conversion of acetylene **29** into non-interlocked thread **31** in only 19 h, compared to the 48 h required for the reactions with the bis-oxazoline ligands. The Box ligands must inhibit the reaction in some fashion, possibly, as postulated by Leigh et al.,[22b] by preventing a faster, ligand-free pathway for the reaction. The lack of rotaxane in our CuAAC 'click' reaction with macrocycle **1** must therefore be due to some hindrance in carrying out the reaction *through* the macrocycle cavity, with only a small percentage of the thread being formed within the cavity. Redesign of the Box macrocycle **1** to provide a more rigid structure may be necessary for the successful asymmetric synthesis of planar chiral rotaxanes via the active-template method.

## 3. Conclusions

The synthesis of the first $C_1$-symmetric bis-oxazoline macrocycle **1** was successfully achieved in gram scale. Macrocycle **1**, along with model $C_2$ bis-oxazoline ligands **18** and **19**, and $C_1$-Box ligand **20** were investigated as ligands for the Cadiot–Chodkiewicz, oxidative Heck and CuAAC 'click' reactions. This study constitutes the first report of Cadiot–Chodkiewicz and CuAAC 'click' reactions using Box ligands, as well as the first dedicated study of oxidative Heck reactions using Box ligands. In the Cadiot–Chodkiewicz reaction, $C_2$-Box ligand **18** successfully promotes the reaction to completion, but in contrast, $C_1$-Box ligands **20** and **1** surprisingly inhibit the reaction. Pd(II)-catalysed oxidative Heck reaction with Box macrocycle **1** succeeds in forming the coupled thread **27**, but not the rotaxane **28**. Our investigations suggest that DMF competes with Box macrocycle **1** as a ligand for Pd under oxidative Heck conditions. The CuAAC reaction with Box ligands **20** and **1** once again successfully forms the non-interlocked thread **31** under mild conditions, but the desired rotaxane was formed in only trace quantities. Control studies suggest that the macrocycle ligand **1** is bound to the metal during the CuAAC reaction, making it the most promising reaction of the three investigated, although a more rigid macrocycle design is probably necessary for successful rotaxane formation in the future. Although macrocycle **1** proved unsuitable for our ultimate aim of synthesizing mechanically planar chiral rotaxanes, the results of our model studies nevertheless provide valuable insight into the behaviour of $C_1$ and $C_2$ bis-oxazolines as ligands in these copper- and palladium-catalyzed reactions.

## 4. Experimental

### 4.1. General experimental section

Unless otherwise stated, all reactions were performed under nitrogen atmosphere. $^1$H NMR spectra were recorded on Bruker AC200, AV 300, DPX 400 and AV 400 spectrometers at 200, 300 and 400 MHz, respectively, and referenced to residual solvent. $^{13}$C NMR spectra were recorded using the same spectrometers at 50, 75 and 101 MHz, respectively. Chemical shifts ($\delta$ in parts per million) were referenced to tetramethylsilane (TMS) or to residual solvent peaks. *J* values are given in Hertz and s, d, dd, dt, ddt, t, tdd, quin. and m abbreviations correspond to singlet, doublet, doublet of doublet, doublet of triplet, doublet of doublet of triplet, triplet, triplet of doublet of doublet, quintet and multiplet. The numbers for the peak assignment of macrocycle **1** are referred to the system in Scheme 6. Mass spectra were obtained at the EPSRC National Mass Spectrometry Service Centre in Swansea. Infrared spectra were obtained on Perkin–Elmer Spectrum 100 FT-IR Universal ATR Sampling Accessory, deposited neat or as a chloroform solution onto a diamond/ZnSe plate. Optical rotations were recorded on a Bellingham & Stanley ADP410 polarimeter. Starting compounds 3-ethoxy-2,2-dimethyl-3-oxopropanoic acid **4**,[26] 4,4′,4″-((4-(pent-4-ynyloxy) phenyl)methanetriyl)tris(*tert*-butyl benzene) **21**,[27] 4-(3-(4-(tris(4-*tert*-butyl-phenyl)methyl)phenoxy) propoxy)phenylboronic acid **26**,[21] 1-(3-azido-propoxy)-4-(tris-(4-*tert*-butyl-phenyl)-methyl)-benzene **30**[22a] and (*S*)-3-(2-hydroxy-1-phenylethylamino)-2,2-dimethyl-3-oxopropanoic acid **33**[11d] were synthesized according to literature procedures. All other reagents used were purchased from commercial suppliers and were used without any further purification unless otherwise stated. *N*-Bromosuccinimide (NBS) was recrystallised from water. Dichloromethane (DCM) was distilled over $CaH_2$ and stored over 4 Å molecular sieves. Acetone was stored over 3 Å sieves. Tetrahydrofuran (THF) was dried by distillation from sodium-benzophenone under nitrogen. Anhydrous *N*,*N* dimethylformamide (DMF) was used as supplied (Sureseal®). Petrol ether refers to petroleum ether (40–60). All glassware was heat gun dried. Flash column chromatography, unless otherwise stated, was carried out using Matrix silica gel 60 from Fisher Chemicals. Alumina flash column chromatography was carried out using activated neutral aluminium oxide Brockmann I 150 mesh from Aldrich. TLC was performed using Merck silica gel 60 F254 precoated sheets and visualized by UV (254 nm) or stained by the use of aqueous acidic $KMnO_4$ or aqueous acidic ammonium molybdate as appropriate.

*4.1.1. (S)-Methyl 2-(4-hydroxyphenyl)-2-(methoxycarbonylamino) acetate (**8**).* Thionyl chloride (41.0 mL, 560 mmol) was added dropwise to a stirring solution of (*S*)-2-amino-2-(4-hydroxyphenyl)

acetic acid **7** (52.5 g, 310 mmol) in methanol (1.1 L). The resulting mixture was stirred at 25 °C for 16 h. The reaction was concentrated under reduced pressure and the resulting residue washed with diethyl ether. The resulting crude product was dissolved in 1:1 THF/$H_2O$ (1 L) and $NaHCO_3$ (79 g, 940 mmol) added. Methyl chloroformate (26.6 mL, 340 mmol) was added dropwise and the resulting mixture stirred at 25 °C for 16 h. The reaction was quenched with water (500 mL) and the aqueous layer extracted with ethyl acetate. The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The resulting residue was recrystallised from ethyl acetate/hexane to yield the title compound **8** (68.8 g, 92%) as a white solid. Mp 138–139 °C; $R_f$ 0.29 (1:1 ethyl acetate/petrol ether); $[\alpha]_D^{21}$ +153.5 (*c* 0.99, MeOH); $\nu_{max}/cm^{-1}$ 3371 (NH), 3279 br (OH), 3000 (CH), 2951 (CH), 2845 (CH), 1756 (C=O), 1698 (C=O), 1616 (Ar C=C), 1598 (Ar C=C), 1510 (Ar C=C), 1440 (Ar C=C), 1264 (N–CO–O), 1213 (C–OH), 1171 (Ar CH), 1059 (N–CO–O), 1011 (C–OH), 780 (Ar CH); $\delta_H$ (200 MHz, $C_2D_6SO$) 8.00 (1H, d, *J* 7.5, N*H*), 7.29–7.04 (2H, m, Ar–*H*), 6.79–6.60 (2H, m, Ar–*H*), 5.08 (1H, d, *J* 7.5, C*H*COOMe), 3.60 (3H, s, OC$H_3$), 3.55 (3H, s, OC$H_3$); $\delta_C$ (50 MHz, $C_2D_6SO$) 171.8 (*C*), 157.4 (*C*), 156.5 (*C*), 129.1 (*C*H), 126.4 (*C*), 115.3 (*C*H), 57.5 (*C*H), 52.1 ($CH_3$), 51.6 ($CH_3$); HRMS (ESI) $[M+H]^+$ calcd for $C_{11}H_{14}NO_5$ 240.0866, found 240.0869.

*4.1.2. (S)-Methyl 2-hydroxy-1-(4-hydroxyphenyl)ethylcarbamate (**9**).* $LiAlH_4$ (7.60 g, 200 mmol) was added portionwise to a stirring solution of (*S*)-methyl 2-(4-hydroxyphenyl)-2-((methoxycarbonyl) amino)acetate **8** (24.0 g, 100 mmol) in THF (1.5 L) at 0 °C. The resulting mixture was stirred at 0 °C for 1 h then warmed to RT over 24 h. The reaction was cooled to 0 °C and ice-cold water (16 mL) added. The mixture was stirred at 0 °C for 10 min then 15% aq NaOH (16 mL) was added and the reaction stirred at 0 °C for a further 10 min. Ice-cold water (48 mL) was added and the reaction stirred at 0 °C for 30 min. The resulting suspension was filtered and the filtrate dried ($MgSO_4$) then concentrated under reduced pressure. The resulting residue was purified by column chromatography (petrol ether to 1:1 petrol ether/ethyl acetate to ethyl acetate) to yield the title compound **9** (12.7 g, 60%) as a white solid. Mp 112–115 °C; $R_f$ 0.20 (2:1 ethyl acetate/petrol ether); $[\alpha]_D^{18}$ +70.6 (*c* 1.02, MeOH); $\nu_{max}/cm^{-1}$ 3339 (OH/NH), 2944 (CH), 1685 (C=O), 1600 (NH), 1534 (Ar C=C), 1517 (Ar C=C), 1452 (Ar C=C), 1360 (OH), 1218 (Ar C–O), 1173 (N–CO–O), 1058 (N–CO–O), 1013 (C–O); $\delta_H$ (300 MHz, $C_2D_6SO$) 7.40 (1H, d, *J* 8.1, N*H*), 7.13–7.03 (2H, m, Ar–*H*), 6.78–6.53 (2H, m, Ar–*H*), 4.75 (1H, t, *J* 5.5, O*H*), 4.46 (1H, dt, *J* 8.1, 6.2, C*H*$CH_2$OH), 3.50 (3H, s, OC$H_3$), 3.44 (2H, t, *J* 6.2, CHC$H_2$OH); $\delta_C$ (75 MHz, $C_2D_6SO$) 156.8 (*C*), 156.7 (*C*), 132.1 (*C*), 128.3 (*C*H), 115.2 (*C*H), 65.3 (*C*$H_2$), 57.0 (*C*H), 51.6 ($CH_3$); HRMS (ESI) $[M+H]^+$ calcd for $C_{10}H_{14}NO_4$ 212.0917, found 212.0919.

*4.1.3. (S)-4-(4-Hydroxyphenyl)oxazolidin-2-one (**10**).*[28] Compound **10** was also formed as a side-product (5.40 g, 30%) as a white solid. Mp 203–205 °C [lit.[28] mp 201–204 °C]; $R_f$ 0.32 (4:1 ethyl acetate/petrol ether); $[\alpha]_D^{20}$ +48.6 (*c* 1.48, MeOH) [lit.[28] $[\alpha]_D^{20}$ +41.4 (*c* 1.70, EtOH)]; $\nu_{max}/cm^{-1}$ 3304 (NH), 3226 br (OH), 2925 (CH), 2833 (CH), 1724 (C=O), 1614 (Ar C=C), 1601 (NH), 1513 (Ar C=C), 1487 (Ar C=C), 1374 (OH), 1238 (N–CO–O), 1212 (C–O), 1029 (N–CO–O), 825 (Ar CH); $\delta_H$ (300 MHz, $C_2D_6SO$) 8.04 (1H, s, N*H*), 7.19–7.09 (2H, m, Ar–*H*), 6.82–6.72 (2H, m, Ar–*H*), 4.81 (1H, dd, *J* 8.6, 7.0, CHC*H*HO), 4.60 (1H, dd, *J* 8.6, 8.6, C*H*CHHO), 3.95 (1H, dd, *J* 8.6, 7.0, CHCH*H*O); $\delta_C$ (75 MHz, $C_2D_6SO$) 158.9 (*C*), 157.2 (*C*), 131.0 (*C*), 127.4 (*C*H), 115.4 (*C*H), 71.6 (*C*$H_2$), 54.8 (*C*H); HRMS (ESI) $[M+H]^+$ calcd for $C_9H_{10}NO_3$ 180.0655, found 180.0654.

*4.1.4. (S)-Methyl 1-(4-(hex-5-enyloxy)phenyl)-2-hydroxyethyl carbamate (**11**).* 6-Bromohex-1-ene (5.00 mL, 37.7 mmol) was added dropwise to a stirring suspension of (*S*)-methyl 2-hydroxy-1-(4-hydroxyphenyl)ethylcarbamate **9** (7.42 g, 35.1 mmol) and $K_2CO_3$ (5.36 g, 38.8 mmol) in acetone (80 mL). The resulting mixture was heated at reflux for 43 h. After cooling, the reaction was quenched with water (80 mL) and the aqueous layer extracted with ethyl acetate. The combined organic layers were washed with water, brine, dried ($MgSO_4$) and concentrated under reduced pressure. The resulting residue was purified by column chromatography (1:1 ethyl acetate/petrol ether to 9:1 ethyl acetate/petrol ether) to yield the title compound **11** (6.94 g, 68%) as a white solid. Mp 73–74 °C; $R_f$ 0.48 (4:1 ethyl acetate/petrol ether); $[\alpha]_D^{20}$ +64.0 (*c* 1.00, $CHCl_3$); $\nu_{max}/cm^{-1}$ 3337 br (OH, NH), 2945 (CH), 2867 (CH), 1692 (C=O), 1641 (C=C), 1613 (Ar C=C), 1586 (Ar C=C), 1533 (NH), 1513 (Ar C=C), 1478 (Ar C=C), 1460 (OH), 1265 (N–CO–O), 1241 br (C–O–C), 1178 (Ar CH), 1114 (C–O–C), 1089 (C–O), 1056 (N–CO–O), 1030 (C–OH), 997 (=CH), 915 (=CH), 825 (Ar CH), 779 (OH); $\delta_H$ (200 MHz, $CDCl_3$) 7.25–7.16 (2H, m, Ar–*H*), 6.96–6.72 (2H, m, Ar–*H*), 5.83 (1H, ddt, *J* 17.0, 10.4, 6.6, C*H*=$CH_2$), 5.37 (1H, d, *J* 7.1, N*H*), 5.11–4.92 (2H, m, =C$H_2$), 4.77 (1H, dd, *J* 7.1, 5.4, C*H*$CH_2$OH), 3.95 (2H, t, *J* 6.2, OC$H_2$), 3.84 (2H, t, *J* 5.4, CHC$H_2$OH), 3.68 (3H, s, OC$H_3$), 2.31–2.04 (3H, m, alkyl-H, O*H*), 1.90–1.69 (2H, m, alkyl-*H*), 1.68–1.46 (2H, m, alkyl-*H*); $\delta_C$ (50 MHz, $CDCl_3$) 158.8 (*C*), 157.1 (*C*), 138.5 (*C*H), 130.9 (*C*), 127.7 (*C*H), 114.8 (*C*H and *C*$H_2$ overlapping), 67.8 (*C*$H_2$), 66.6 (*C*$H_2$), 56.6 (*C*H), 52.4 ($CH_3$), 33.4 (*C*$H_2$), 28.6 (*C*$H_2$), 25.3 (*C*$H_2$); HRMS (ESI) $[M+H]^+$ calcd for $C_{16}H_{24}NO_4$ 294.1700, found 294.1703.

Cyclic compound **12** was also formed as a side-product (2.83 g, 32%) as a white solid. Mp 96–97 °C; $R_f$ 0.68 (2:1 ethyl acetate/petrol ether); $[\alpha]_D^{22}$ +28.6 (*c* 0.14, $CHCl_3$); $\nu_{max}/cm^{-1}$ 3233 (NH), 3139 (Ar CH), 2936 (CH), 2921 (CH), 1740 (C=O), 1640 (Ar C=C), 1614 (NH), 1586 (Ar C=C), 1512 (Ar C=C), 1393 (=CH), 1239 (C–O), 1061 (C–O), 1025 (N–CO–O), 925 (=CH), 828 (Ar CH); $\delta_H$ (200 MHz, $CDCl_3$) 7.33–7.21 (2H, m, Ar–*H*), 6.98–6.85 (2H, m, Ar–*H*), 5.84 (1H, ddt, *J* 17.0, 10.0, 6.6, C*H*=$CH_2$), 5.50 (1H, s, N*H*), 5.14–4.84 (3H, m, CHC*H*HO, =C$H_2$), 4.67 (1H, dd, *J* 8.3, 8.3, CHCH*H*O), 4.17 (1H, dd, *J* 8.3, 7.1, C*H*$CH_2$O), 3.97 (2H, t, *J* 6.4, OC$H_2$$CH_2$), 2.16–2.04 (2H, m, alkyl-*H*), 1.90–1.72 (2H, m, alkyl-*H*), 1.61–1.48 (2H, m, alkyl-*H*); $\delta_C$ (50 MHz, $CDCl_3$) 159.5 (*C*), 138.4 (*C*), 131.0 (*C*), 127.4 (2×CH overlapping), 115.0 (*C*H), 114.8 (*C*$H_2$), 72.7 (*C*$H_2$), 67.9 (*C*$H_2$), 55.9 (*C*H), 33.4 (*C*$H_2$), 28.6 (*C*$H_2$), 25.2 (*C*$H_2$); HRMS (ESI) $[M+H]^+$ calcd for $C_{15}H_{20}NO_3$ 262.1438, found 262.1441.

*4.1.5. (S)-2-Amino-2-(4-(hex-5-enyloxy)phenyl)ethanol (**5**).* A suspension of (*S*)-methyl 1-(4-(hex-5-enyloxy)phenyl)-2-hydroxyethylcarbamate **11** (8.71 g, 29.7 mmol) and (*S*)-4-(4-(hex-5-enyloxy)phenyl)oxazolidin-2-one **12** (2.86 g, 10.9 mmol) in a solution of KOH (25% aq, 365 mL) was stirred at 50 °C for 27 h. After cooling, the reaction was quenched with water (365 mL) and extracted with ethyl acetate. The combined organic layers were washed with water, brine, dried ($MgSO_4$) and concentrated under reduced pressure to yield the title compound **5** (9.12 g, 95%) as a pale yellow solid. Mp 72–73 °C; $R_f$ 0.03 (20:1 DCM/methanol); $[\alpha]_D^{20}$ +28.3 (*c* 1.27, $CHCl_3$); $\nu_{max}/cm^{-1}$ 3500 br (OH), 3323 (NH), 3067 (Ar CH), 2936 (CH), 2865 (CH), 1713 (Ar C–H), 1642 br (C=C, $NH_2$), 1611 (Ar C=C), 1559 (Ar C=C), 1512 (Ar C=C), 1469 (Ar C=C), 1389 (C–N), 1245 (C–O–C), 1176 (C–N), 1155 (C–N), 1065 (Ar CH), 1028 (C–OH), 993 (=CH), 907 (=CH), 827 (Ar CH, $NH_2$), 809 ($NH_2$); $\delta_H$ (200 MHz, $CDCl_3$) 7.26–7.19 (2H, m, Ar–*H*), 6.97–6.70 (2H, m, Ar–*H*), 6.00–5.68 (1H, m, C*H*=$CH_2$), 5.14–4.84 (2H, m, =C$H_2$), 4.09–3.84 (3H, m, OC$H_2$, C*H*$CH_2$O), 3.69 (1H, dd, *J* 10.8, 4.6, CHC*H*HOH), 3.52 (1H, dd, *J* 10.8, 8.3, CHCH*H*OH), 2.40 (3H, s, N$H_2$, O*H*), 2.22–2.00 (2H, m, alkyl-*H*), 1.91–1.69 (2H, m, alkyl-*H*), 1.68–1.39 (2H, m, alkyl-*H*); $\delta_C$ (50 MHz, $CDCl_3$) 158.4 (*C*), 138.5 (*C*H), 134.4 (*C*), 127.5 (*C*H), 114.7 (*C*H), 114.5 (*C*$H_2$), 67.9 (*C*$H_2$), 67.7 (*C*$H_2$), 56.7 (*C*H), 33.4 (*C*$H_2$), 28.6 (*C*$H_2$), 25.2 (*C*$H_2$); HRMS (ESI) $[M+Na]^+$ calcd for $C_{14}H_{21}NNaO_2$ 258.1465, found 258.1467.

*4.1.6. (R)-Methyl 2-(tert-butoxycarbonylamino)-3-(4-(undec-10-enyloxy)phenyl)propanoate (**14**).* A solution of 11-bromoundec-1-ene (53.4 g, 230 mmol) in acetonitrile (100 mL) was added

dropwise to a stirring suspension of (*R*)-methyl 2-((*tert*-butoxycarbonyl)amino)-3-(4-hydroxyphenyl)propanoate **13** (56.4 g, 190 mmol) and $K_2CO_3$ (32.0 g, 230 mmol) in acetonitrile (250 mL). The resulting mixture was heated at reflux for 18 h. After cooling, the reaction was quenched with water (500 mL) and the aqueous layer extracted with ethyl acetate. The combined organic layers were washed with brine, dried ($Na_2SO_4$) and concentrated under reduced pressure. The resulting residue was purified by column chromatography (petrol ether to 4:1 petrol ether/ethyl acetate) then recrystallised from toluene/petrol ether to yield the title compound **14** (70.8 g, 83%) as a white solid. Mp 59–62 °C; $R_f$ 0.30 (9:1 petrol ether/ethyl acetate); $[\alpha]_D^{20}$ −33.9 (*c* 1.12, $CHCl_3$); $\nu_{max}$/$cm^{-1}$ 3367 (NH), 2980 (Ar CH), 2920 (CH), 2851 (CH), 1737 (C=O), 1691 (C=O), 1641 (C=C), 1614 (Ar C=C), 1583 (NH), 1524 (Ar C=C), 1512 (Ar C=C), 1467 (CH), 1367 (CH), 1242 (C–O–C), 1161 (C–O–C/N–CO–O) 994 (=CH), 909 (=CH), 826 (Ar CH); $\delta_H$ (300 MHz, $CDCl_3$) 7.08–6.99 (2H, m, Ar–*H*), 6.89–6.77 (2H, m, Ar–*H*), 5.82 (1H, ddt, *J* 16.9, 10.3, 6.6, C*H*=$CH_2$), 5.06–4.90 (3H, m, =C$H_2$, N*H*), 4.61–4.46 (1H, m, C*H*COOMe), 3.93 (2H, t, *J* 6.6, OC$H_2$), 3.72 (3H, s, OC$H_3$), 3.11–2.92 (2H, m, C$H_2$CHCO), 2.11–1.98 (2H, m, alkyl-*H*), 1.84–1.68 (2H, m, alkyl-*H*), 1.51–1.25 (21H, m, alkyl-H, C(C$H_3$)$_3$); $\delta_C$ (75 MHz, $CDCl_3$) 172.4 (*C*), 158.2 (*C*), 154.9 (*C*), 139.2 (*C*H), 130.2 (*C*H), 127.7 (*C*), 114.5 (*C*H), 114.1 ($CH_2$), 79.9 (*C*), 68.0 ($CH_2$), 54.5 (*C*H), 52.2 ($CH_3$), 37.5 ($CH_2$), 33.8 ($CH_2$), 29.5 ($CH_2$), 29.4 ($CH_2$), 29.1 ($CH_2$), 28.9 ($CH_2$) (plus two overlapping peaks), 28.3 ($CH_3$), 26.0 ($CH_2$); HRMS (ESI) $[M+H]^+$ calcd for $C_{26}H_{42}NO_5$ 448.3057, found 448.3053.

*4.1.7. (R)-tert-Butyl 1-hydroxy-3-(4-(undec-10-enyloxy)phenyl) propan-2-ylcarbamate (**15**).* $LiBH_4$ (5.90 g, 270 mmol) was added portionwise to a stirring solution of (*R*)-methyl 2-((*tert*-butoxycarbonyl)amino)-3-(4-(undec-10-en-1-yloxy)phenyl)propanoate **14** (60.4 g, 130 mmol) in THF (1.2 L) at 0 °C. The resulting mixture was allowed to warm to RT over 16 h. The reaction was quenched with 1 M aq HCl until effervescing ceased and the aqueous layer extracted with ethyl acetate. The combined organic layers were washed with brine, dried ($Na_2SO_4$) and concentrated under reduced pressure. The resulting residue was triturated with ice-cold hexane (2×500 mL) and sonicated briefly. The resulting precipitate was filtered, washed with hexane and dried in vacuo to yield the title compound **15** (55 g, 98%) as a white solid. Mp 67–69 °C; $R_f$ 0.15 (4:1 petrol ether/ethyl acetate); $[\alpha]_D^{22}$ +12.3 (*c* 2.11, $CHCl_3$); $\nu_{max}$/$cm^{-1}$ 3358 br (NH, OH), 2974 (Ar CH), 2920 (CH), 2852 (CH), 1689 (C=O), 1642 (Ar C=C), 1614 (Ar C=C), 1582 (NH), 1528 (Ar C=C), 1510 (Ar C=C), 1268 (N–CO–O), 1241 (C–O–C), 1171 (N–CO–O), 1061 (C–OH), 1035 (C–OH), 1004 (=CH), 906 (=CH); $\delta_H$ (300 MHz, $CDCl_3$) 7.16–7.08 (2H, m, Ar–*H*), 6.89–6.80 (2H, m, Ar–*H*), 5.82 (1H, ddt, *J* 13.2, 10.3, 6.6, C*H*=$CH_2$), 5.07–4.90 (2H, m, =C$H_2$), 4.73 (1H, d, *J* 7.7, N*H*), 3.93 (2H, t, *J* 6.6, OC$H_2$), 3.88–3.72 (1H, m, C*H*C$H_2$OH), 3.72–3.48 (2H, m, C$H_2$OH), 2.78 (2H, d, *J* 7.3, C$H_2$CHC$H_2$), 2.41 (1H, br s, O*H*), 2.11–1.98 (2H, m, alkyl-*H*), 1.85–1.71 (2H, m, alkyl-*H*), 1.52–1.24 (21H, m, alkyl-*H*, C(C$H_3$)$_3$); $\delta_C$ (75 MHz, $CDCl_3$) 157.9 (*C*), 156.2 (*C*), 139.2 (*C*H), 130.1 (*C*H), 129.4 (*C*), 114.6 (*C*H), 114.1 ($CH_2$), 79.7 (*C*), 68.0 ($CH_2$), 64.4 ($CH_2$), 53.9 (*C*H), 36.2 ($CH_2$), 33.8 ($CH_2$), 29.5 ($CH_2$), 29.4 ($CH_2$), 29.3 ($CH_2$), 28.9 ($CH_2$) (plus two overlapping peaks), 28.3 ($CH_3$), 26.0 ($CH_2$); HRMS (ESI) $[M+H]^+$ calcd for $C_{25}H_{42}NO_4$ 420.3108, found 420.3101.

*4.1.8. (R)-2-Amino-3-(4-(undec-10-enyloxy)phenyl)propan-1-ol (**6**).* *p*-Toluenesulfonic acid monohydrate (53.9 g, 280 mmol) was added portionwise to a stirring solution of (*R*)-*tert*-butyl 1-hydroxy-3-(4-(undec-10-en-1-yloxy)phenyl)propan-2-ylcarbamate **15** (59.4 g, 140 mmol) in 1:1 THF/$H_2O$ (1.5 L). The resulting mixture was heated at reflux for 18 h. After cooling, the reaction was quenched with 2 M aq NaOH (500 mL) and the aqueous layer extracted with ethyl acetate (250 mL) and then DCM (250 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure to yield the title compound **6** (44.7 g, 99%) as a white solid. Mp 75–78 °C; $R_f$ 0.03 (9:1 petrol ether/ethyl acetate); $[\alpha]_D^{20}$ +7.7 (*c* 1.04, $CHCl_3$); $\nu_{max}$/$cm^{-1}$ 3355 (NH), 3298 (NH), 3077 (Ar CH), 2923 br (OH), 2851 (CH), 1613 (Ar C=C), 1582 (Ar C=C), 1509 (Ar C=C), 1467 (Ar C=C), 1243 (C–O–C), 1059 (C–OH), 909 (=CH); $\delta_H$ (400 MHz, $CDCl_3$) 7.13–7.03 (2H, m, Ar–*H*), 6.90–6.79 (2H, m, Ar–*H*), 5.82 (1H, ddt, *J* 17.0, 10.3, 6.7, C*H*=$CH_2$), 5.06–4.88 (2H, m, =C$H_2$), 3.93 (2H, t, *J* 6.5, OC$H_2$), 3.63 (1H, dd, *J* 10.6, 3.2, C*H*HOH), 3.37 (1H, dd, *J* 10.6, 6.5, CH*H*OH), 3.13–3.02 (1H, m, C*H*$NH_2$), 2.73 (1H, dd, *J* 13.5, 5.3, C*H*HCH$NH_2$), 2.47 (1H, dd, *J* 13.5, 8.5, CH*H*CH$NH_2$), 2.24–1.99 (5H, m, alkyl-*H*, N$H_2$, O*H*), 1.85–1.70 (2H, m, alkyl-*H*), 1.51–1.23 (12H, m, alkyl-*H*); $\delta_C$ (101 MHz, $CDCl_3$) 157.8 (*C*), 139.2 (*C*H), 130.3 (*C*H), 130.1 (*C*), 114.6 (*C*H), 114.1 ($CH_2$), 68.0 ($CH_2$), 66.1 ($CH_2$), 54.3 (*C*H), 39.8 ($CH_2$), 33.8 ($CH_2$), 29.5 ($CH_2$), 29.4 ($CH_2$), 29.3 ($CH_2$), 29.1 ($CH_2$) (plus one overlapping peak), 27.6 ($CH_2$), 26.0 ($CH_2$); HRMS (ESI) $[M+H]^+$ calcd for $C_{20}H_{34}NO_2$ 320.2584, found 320.2588.

*4.1.9. (S)-Ethyl 3-(1-(4-(hex-5-enyloxy)phenyl)-2-hydroxyethy lamino)-2,2-dimethyl-3-oxopropanoate (**34**).* A solution of EDCI (9.50 g, 50.0 mmol) in chloroform (53 mL) was added dropwise to a stirring solution of (*S*)-2-amino-(4-(hex-5-enyloxy)phenyl)ethanol **5** (12.0 g, 50.0 mmol) and HOBt (6.70 g, 50.0 mmol) in chloroform (395 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 1.5 h. A solution of 3-ethoxy-2,2-dimethyl-3-oxopropanoic acid **4** (8.50 g, 45.0 mmol) in chloroform (79 mL) was added dropwise. The resulting mixture was allowed to warm to RT for 18 h. The reaction was quenched with 3 M aq HCl (100 mL) and the aqueous layer extracted with chloroform. The combined organic layers were washed with water, dried ($Na_2SO_4$) and concentrated under reduced pressure. The resulting residue was purified by column chromatography (1:1 petrol ether/ethyl acetate) to yield the title compound **34** (16.0 g, 95%) as a white solid. Mp 73–75 °C; $R_f$ 0.35 (1:1 petrol ether/ethyl acetate); $[\alpha]_D^{19}$ +37.0 (*c* 1.08, $CHCl_3$); $\nu_{max}$/$cm^{-1}$ 3309 (NH), 3258 br (OH), 3074 (Ar CH), 2985 (CH), 2939 (CH), 2862 (CH), 1730 (C=O), 1644 (C=O), 1611 (Ar C=C), 1584 (Ar C=C), 1548 (NH), 1511 (Ar C=C), 1477 (Ar C=C), 1265 (C–N), 1246 (C–O–C), 1174 (C–O–C), 1151 (C–O), 1028 (C–OH), 997 (C=C), 917 (C=C), 827 (Ar CH); $\delta_H$ (200 MHz, $CDCl_3$) 7.24–7.09 (3H, m, Ar–*H*, N*H*), 6.89–6.78 (2H, m, Ar–*H*), 5.81 (1H, ddt, *J* 17.0, 10.4, 6.6, C*H*=$CH_2$), 5.10–4.86 (3H, m, C*H*C$H_2$OH, CH=C$H_2$), 4.15 (2H, q, *J* 7.1, OC$H_2$C$H_3$), 3.91 (2H, t, *J* 6.4, OC$H_2$C$H_2$), 3.82–3.69 (2H, m, CHC$H_2$OH), 3.47 (1H, s, O*H*), 2.20–1.96 (2H, m, alkyl-*H*), 1.88–1.68 (2H, m, alkyl-*H*), 1.64–1.48 (2H, m, alkyl-*H*), 1.45 (3H, s, C$H_3$), 1.42 (3H, s, C$H_3$′), 1.23 (3H, t, *J* 7.1, OCH$_2$C$H_3$); $\delta_C$ (50 MHz, $CDCl_3$) 174.6 (*C*), 172.2 (*C*), 158.4 (*C*), 138.3 (*C*H), 130.8 (*C*), 127.5 (*C*H), 114.6 ($CH_2$), 114.5 (*C*H), 67.5 ($CH_2$), 65.9 ($CH_2$), 61.5 ($CH_2$), 55.1 (*C*H), 49.7 (*C*), 33.2 ($CH_2$), 28.5 ($CH_2$), 25.1 ($CH_2$), 23.4 (2×$CH_3$ overlapping), 13.8 ($CH_3$); HRMS (ESI) $[M+H]^+$ calcd for $C_{21}H_{32}NO_5$ 378.2275, found 378.2275.

*4.1.10. (S)-3-(1-(4-(Hex-5-enyloxy)phenyl)-2-hydroxyethylamino)-2,2-dimethyl-3-oxopropanoic acid (**16**).* A solution of NaOH (10.6 g, 260 mmol) in 1:1 THF/$H_2O$ (300 mL) was added to a stirring solution of (*S*)-ethyl 3-(1-(4-(hex-5-enyloxy)phenyl)-2-hydroxyethylamino)-2,2-dimethyl-3-oxopropanoate **34** (10.0 g, 26.0 mmol) in 1:1 THF/$H_2O$ (500 mL). The resulting mixture was stirred at 45 °C for 4 h. The reaction was cooled to 0 °C and quenched with 6 M aq HCl until pH 1 was reached. The mixture was extracted with ethyl acetate and DCM and the combined organic layers were washed with water, brine and dried ($MgSO_4$). The resulting solution was concentrated under reduced pressure to yield the title compound **16** (8.20 g, 89%) as a white solid. Mp 118–121 °C; $R_f$ 0.05 (9:1 ethyl acetate/petrol ether); $[\alpha]_D^{21}$ +73.0 (*c* 1.26, $CHCl_3$); $\nu_{max}$/$cm^{-1}$ 3308 br (OH/NH), 2980 (Ar CH), 2935 (CH), 2865 (CH), 1715 (Ar CH), 1679 (C=O), 1655 (C=O), 1613 (Ar C=C),

1559 (NH), 1512 (Ar C=C), 1466 (Ar C=C), 1389 (C–N), 1247 (C–O–C/C–N), 1175 (C–N), 1156 (C–O), 1028 (C–OH), 992 (=CH), 900 (=CH), 827 (Ar CH), 810 (NH); $\delta_H$ (200 MHz, $CDCl_3$) 7.92 (1H, d, *J* 5.8, N*H*), 7.20 (2H, d, *J* 8.3, Ar–*H*), 6.82 (2H, d, *J* 8.3, Ar–*H*), 5.83 (1H, ddt, *J* 16.8, 10.1, 6.6, C*H*=$CH_2$), 5.22–4.92 (3H, m, C*H*$CH_2$OH, =C*H*$_2$), 4.04–3.70 (4H, m, C*H*$_2$OH, OC*H*$_2$), 2.24–2.04 (2H, m, alkyl-*H*), 1.90–1.67 (2H, m, alkyl-*H*), 1.65–1.35 (8H, m, alkyl-*H*); $\delta_C$ (50 MHz, $CDCl_3$) 177.2 (*C*), 173.8 (*C*), 158.6 (*C*), 138.5 (*C*H), 130.6 (*C*), 127.6 (*C*H), 114.7 ($CH_2$), 114.7 (*C*H), 67.7 (*C*H$_2$), 64.8 ($CH_2$), 55.4 (*C*H), 49.5 (*C*), 33.4 (*C*H$_2$), 28.6 ($CH_2$), 25.3 ($CH_2$), 23.5 ($CH_3$), 23.4 ($CH_3$); HRMS (ESI) $[M+H]^+$ calcd for $C_{19}H_{28}NO_5$ 350.1962, found 350.1965.

*4.1.11. $N^1$-((S)-1-(4-(Hex-5-enyloxy)phenyl)-2-hydroxyethyl)-$N^3$-((R)-1-hydroxy-3-(4-(undec-10-enyloxy)phenyl)propan-2-yl)-2,2-dimethylmalonamide (**3**).* (*R*)-2-Amino-3-(4-(undec-10-enyloxy)phenyl)propan-1-ol **6** (4.31 g, 13.5 mmol) was added to a stirring solution of (*S*)-3-(1-(4-(hex-5-enyloxy)phenyl)-2-hydroxyethylamino)-2,2-dimethyl-3-oxopropanoic acid **16** (4.20 g, 12.0 mmol), *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate (TBTU) (4.30 g, 13.0 mmol) and *N*,*N*-diisopropylethylamine (DIPEA) (2.30 mL, 13.4 mmol) in 4:1 DCM/DMF (400 mL). The resulting mixture was stirred at RT for 93 h. The reaction was quenched with water (400 mL) and the aqueous layer extracted with ethyl acetate. The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The resulting residue was purified by column chromatography (1:1 ethyl acetate/petrol ether to 95:5 ethyl acetate/methanol) to yield the title compound **3** (5.70 g, 73%) as a white solid. Mp 77–78 °C; $R_f$ 0.47 (4:1 ethyl acetate/petrol ether); $[\alpha]_D^{20}$ +37.9 (*c* 0.95, $CHCl_3$); $\nu_{max}/cm^{-1}$ 3335 br (OH/NH), 2926 (CH), 2855 (CH), 1640 (C=O), 1613 (Ar C=C), 1583 (NH), 1510 (Ar C=C), 1471 (Ar C=C), 1243 (C–O–C), 1176 (C–O), 1034 (C–OH), 994 (=CH), 909 (=CH), 829 (Ar CH); $\delta_H$ (400 MHz, $CDCl_3$) 7.22–7.04 (5H, m, Ar–*H*, N*H*), 6.89–6.78 (4H, m, Ar–*H*), 6.65 (1H, d, *J* 7.9, N*H*), 5.89–5.77 (2H, m, C*H*=$CH_2$, C*H*=$CH_2$′), 5.08–4.90 (5H, m, C*H*$CH_2$OH, =C*H*$_2$, =C*H*$_2$′), 4.16–4.05 (1H, m, C*H*$(CH_2)_2$), 3.96–3.88 (4H, m, OC*H*$_2$, OC*H*$_2$′), 3.85–3.72 (2H, m, C*H*$_2$OH), 3.63 (1H, dd, *J* 11.2, 3.8, $CH_2$CHC*H*HOH), 3.55 (1H, dd, *J* 11.2, 5.6, $CH_2$CHCH*H*OH), 2.94 (2H, br s, O*H*), 2.82 (1H, dd, *J* 13.8, 6.7, C*H*HCHC$H_2$OH), 2.73 (1H, dd, *J* 13.8, 7.6, CH*H*CHC$H_2$OH), 2.18–2.00 (4H, m, alkyl-*H*), 1.84–1.72 (4H, m, alkyl-*H*), 1.61–1.51 (2H, m, alkyl-*H*), 1.49–1.28 (18H, m, C*H*$_3$, C*H*$_3$′, alkyl-*H*); $\delta_C$ (101 MHz, $CDCl_3$) 174.1 (*C*=O), 173.8 (*C*=O), 158.7 (Ar–*C*), 157.9 (Ar–*C*), 139.2 (*C*H=$CH_2$), 138.5 (*C*H=$CH_2$′), 130.5 (Ar–*C*, Ar–*C*H), 130.1 (Ar–*C*H), 129.2 (Ar–*C*), 127.6 (Ar–*C*H), 114.8 (=*C*H$_2$), 114.7 (Ar–*C*H), 114.6 ($CH_2$), 114.1 (Ar–*C*H), 68.0 (O*C*H$_2$), 67.8 (O*C*H$_2$′), 66.2 (*C*H$_2$OH), 64.0 ($CH_2$CH*C*H$_2$OH), 55.4 (*C*HCH$_2$OH), 53.3 (*C*H$(CH_2)_2$), 49.8 (*C*$(CH_3)_2$), 35.9 (*C*H$_2$CHCH$_2$OH), 33.8 (alkyl-*C*H$_2$), 33.4 (alkyl-*C*H$_2$), 29.5 (alkyl-*C*H$_2$), 29.4 (alkyl-*C*H$_2$), 29.3 (alkyl-*C*H$_2$), 29.1 (alkyl-*C*H$_2$), 28.9 (alkyl-*C*H$_2$) (plus one overlapping peak), 28.7 (alkyl-*C*H$_2$), 26.0 (alkyl-*C*H$_2$), 25.3 (alkyl-*C*H$_2$), 23.8 (*C*H$_3$), 23.6 (*C*H$_3$′); HRMS (ESI) $[M+H]^+$ calcd for $C_{39}H_{59}N_2O_6$ 651.4368, found 651.4362.

*4.1.12. Macrocycle **2**.* A solution of $N^1$-((*S*)-1-(4-(hex-5-enyloxy) phenyl)-2-hydroxyethyl)-$N^3$-((*R*)-1-hydroxy-3-(4-(undec-10-enyloxy) phenyl)propan-2-yl)-2,2-dimethylmalonamide **3** (2.30 g, 3.53 mmol) in DCM (130 mL) was added dropwise to a stirring solution of Grubbs first generation catalyst (0.29 g, 0.35 mmol) in DCM (930 mL) under an argon atmosphere. The resulting mixture was heated at reflux for 7 days. The reaction was cooled to RT and concentrated under reduced pressure. The resulting residue was passed through a silica column (9:1 petrol ether/ethyl acetate to 5% methanol/ethyl acetate) to remove unreacted **3**. The resulting crude product was dissolved in THF (200 mL) and 10% w/w Pd/C (0.87 g) added. The resulting mixture was placed under a hydrogen atmosphere and stirred at RT for 6 h. The mixture was then flushed through a plug of Celite with THF and the resulting solution concentrated under reduced pressure. The resulting residue was purified by column chromatography (1:1 ethyl acetate/petrol ether to 5% methanol/ethyl acetate) to yield the title compound **2** (1.42 g, 65%) as a white solid. Mp 186–190 °C; $R_f$ 0.08 (4:1 ethyl acetate/petrol ether); $[\alpha]_D^{21}$ +68.7 (*c* 0.99, $CHCl_3$); $\nu_{max}/cm^{-1}$ 3428 (NH), 3368 br (OH), 2924 (CH), 2854 (CH), 1655 (C=O), 1633 (NH), 1611 (Ar C=C), 1582 (Ar C=C), 1530 (N–C=O), 1513 (Ar C=C), 1470 (Ar C=C), 1243 (C–N, C–O–C), 1179 (C–OH), 1073 (C–O–C), 1038 (C–O–C, C–OH), 826 (Ar CH); $\delta_H$ (400 MHz, $CDCl_3$) 7.16–7.07 (4H, m, Ar–*H*), 6.94 (1H, d, *J* 7.0, N*H*), 6.88–6.81 (4H, m, Ar–*H*), 6.56 (1H, d, *J* 7.9, N*H*), 4.92–4.84 (1H, m, C*H*$CH_2$OH), 4.15–4.03 (1H, m, C*H*$(CH_2)_2$), 4.00–3.90 (4H, m, OC*H*$_2$, OC*H*$_2$′), 3.79 (1H, dd, *J* 11.2, 4.4, CHC*H*HOH), 3.74 (1H, dd, *J* 11.2, 6.2, CHCH*H*OH), 3.57 (1H, dd, *J* 10.9, 3.8, $CH_2$CHC*H*HOH), 3.51 (1H, dd, *J* 10.9, 5.0, $CH_2$CHCH*H*OH), 2.79 (2H, d, *J* 7.3, C*H*$_2$CHC$H_2$OH), 1.83–1.871 (4H, m, alkyl-*H*), 1.60–1.10 (28H, m, alkyl-*H*); $\delta_C$ (101 MHz, $CDCl_3$) 174.1 (*C*=O), 173.8 (*C*=O), 159.0 (Ar–*C*), 158.2 (Ar–*C*), 130.8 (Ar–*C*), 130.3 (Ar–*C*H), 129.5 (Ar–*C*), 127.7 (Ar–*C*H), 115.1 (Ar–*C*H), 115.0 (Ar–*C*H), 68.2 (O*C*H$_2$), 66.3 (CH*C*H$_2$OH), 63.9 ($CH_2$CH*C*H$_2$OH), 55.7 (*C*HCH$_2$OH), 53.3 (*C*H$(CH_2)_2$), 50.1 (*C*$(CH_3)_2$), 36.0 ($CH_2$CHCH$_2$OH), 29.1 (alkyl-*C*H$_2$), 29.1 (alkyl-*C*H$_2$), 29.0 (alkyl-*C*H$_2$), 28.9 (alkyl-*C*H$_2$) (plus six overlapping peaks), 28.8 (alkyl-*C*H$_2$), 28.7 (alkyl-*C*H$_2$), 25.9 (alkyl-*C*H$_2$), 25.7 (alkyl-*C*H$_2$), 24.2 (*C*H$_3$), 23.2 (*C*H$_3$′); HRMS (ESI) $[M+H]^+$ calcd for $C_{37}H_{57}N_2O_6$ 625.4211, found 625.4205.

*4.1.13. Macrocycle **17**.* Thionyl chloride (2.00 mL, 27.0 mmol) was added to a stirring suspension of macrocycle **2** (1.42 g, 2.27 mmol) in DCM (50 mL). The resulting mixture was stirred at RT for 23 h, then concentrated under reduced pressure and the resulting residue purified by column chromatography (49:1 DCM/ethyl acetate) to yield the title compound **17** (1.43 g, 94%) as a white solid. Mp 145–148 °C; $R_f$ 0.25 (49:1 DCM/ethyl acetate); $[\alpha]_D^{21}$ +37.9 (*c* 0.58, $CHCl_3$); $\nu_{max}/cm^{-1}$ 3376 (NH), 2924 (CH), 2854 (CH), 1652 (C=O), 1612 (Ar C=C), 1584 (NH), 1510 (N–C=O), 1471 (Ar C=C), 1240 (C–O–C), 1179 (Ar CH), 1033 (C–O–C), 836 (Ar CH), 749 (C–Cl); $\delta_H$ (400 MHz, $CDCl_3$) 7.17–7.10 (4H, m, Ar–*H*), 7.08 (1H, d, *J* 7.6, N*H*), 6.94–6.71 (4H, m, Ar–*H*), 6.47 (1H, d, *J* 8.2, N*H*), 5.17–5.09 (1H, m, C*H*$CH_2$Cl), 4.37–4.22 (1H, m, C*H*$(CH_2)_2$), 4.04–3.87 (4H, m, OC*H*$_2$, OC*H*$_2$′), 3.75 (2H, d, *J* 5.6, CHC*H*$_2$Cl), 3.44 (1H, dd, *J* 11.4, 3.5, $CH_2$CHC*H*HCl), 3.38 (1H, dd, *J* 11.4, 4.4, $CH_2$CHCH*H*Cl), 2.87 (1H, dd, *J* 13.5, 5.9, C*H*HCHCH$_2$Cl), 2.79 (1H, dd, *J* 13.5, 8.8, CH*H*CHCH$_2$Cl), 1.87–1.66 (4H, m, alkyl-*H*), 1.57–1.25 (28H, m, alkyl-*H*); $\delta_C$ (101 MHz, $CDCl_3$) 173.3 (*C*=O), 172.3 (*C*=O), 158.9 (Ar–*C*), 158.2 (Ar–*C*), 130.2 (Ar–*C*), 130.1 (Ar–*C*H), 128.4 (Ar–*C*), 127.6 (Ar–*C*H), 114.9 (Ar–*C*H), 114.8 (Ar–*C*H), 67.9 (O*C*H$_2$), 67.8 (O*C*H$_2$′), 53.6 (*C*HCH$_2$Cl), 51.5 (*C*H$(CH_2)_2$), 49.8 (*C*$(CH_3)_2$), 47.2 (CH*C*H$_2$Cl), 45.9 ($CH_2$CH*C*H$_2$Cl), 36.2 ($CH_2$CHCH$_2$Cl), 29.2 (alkyl-*C*H$_2$), 29.1 (alkyl-*C*H$_2$), 29.1 (alkyl-*C*H$_2$), 28.9 (alkyl-*C*H$_2$), 28.8 (alkyl-*C*H$_2$) (plus six overlapping peaks), 25.8 (alkyl-*C*H$_2$), 25.7 (alkyl-*C*H$_2$), 24.6 (*C*H$_3$), 22.3 (*C*H$_3$); HRMS (ESI) $[M+H]^+$ calcd for $C_{37}H_{55}{}^{35}Cl_2N_2O_4$ 661.3533, found 661.3533.

*4.1.14. Macrocycle **1**.* Tetrabutylammonium fluoride (TBAF) (1.0 M in THF, 7.60 mL, 7.60 mmol) was added to a stirring solution of macrocycle **17** (1.25 g, 1.89 mmol) in DCM (100 mL). The resulting mixture was stirred at RT for 43 h. The mixture was concentrated under reduced pressure and the resulting residue dissolved in DCM (100 mL). The solution was washed with satd aq sodium citrate (3×100 mL), brine, dried ($MgSO_4$) and concentrated under reduced pressure. The resulting residue was purified by alumina column chromatography (7:1 hexane/ethyl acetate, 0.4% $Et_3N$) to yield the title compound **1** (0.57 g, 51%) as a white gum. Mp 62–65 °C; $R_f$ 0.18 (1:1 ethyl acetate/petrol ether); $[\alpha]_D^{21}$ −45.4 (*c* 0.44, $CHCl_3$); $\nu_{max}/cm^{-1}$ 2926 (CH), 2855 (CH), 1656 (C=N), 1612 (Ar C=C), 1583 (Ar C=C), 1512 (Ar C=C), 1472 (Ar C=C), 1247 (C–O–C), 1116 (C–O–C), 831 (Ar CH); $\delta_H$ (400 MHz, $CDCl_3$) 7.19–7.08 (4H, m, Ar–*H*), 6.87–6.82 (4H, m, Ar–*H*), 5.12 (1H, dd, *J* 10.0, 6.5, H-5), 4.55 (1H, dd,

*J* 10.0, 8.5, H-4a), 4.51–4.43 (1H, m, H-30), 4.23 (1H, dd, *J* 9.4, 8.5, H-31a), 4.14 (1H, dd, *J* 8.5, 6.5, H-4b), 4.04 (1H, dd, *J* 8.5, 7.2, H-31b), 3.97 (4H, t, *J* 6.5, OC*H*$_2$, OC*H*$_2$′), 3.09 (1H, dd, *J* 13.8, 5.0, H-29a), 2.69 (1H, dd, *J* 13.8, 8.2, H-29b), 1.83–1.73 (4H, m, alkyl-*H*), 1.60 (3H, s, C*H*$_3$), 1.59 (3H, s, C*H*$_3$′), 1.54–1.26 (22H, m, alkyl-*H*); $\delta_C$ (101 MHz, $CDCl_3$) 169.8 (N=*C*O), 169.6 (N=*C*O′), 158.5 (Ar–*C*), 157.8 (Ar–*C*), 134.8 (Ar–*C*), 130.5 (Ar–*C*H), 129.2 (Ar–*C*), 127.8 (Ar–*C*H), 114.8 (Ar–*C*H), 114.6 (Ar–*C*H), 75.7 (C-4), 71.7 (C-31), 68.9 (C-5), 68.0 (O*C*H$_2$), 67.8 (O*C*H$_2$′), 67.1 (C-30), 40.1 (C-29), 38.6 (*C*(CH$_3$)$_2$), 29.3 (alkyl-*C*H$_2$), 29.3 (alkyl-*C*H$_2$), 29.2 (alkyl-*C*H$_2$), 29.1 (alkyl-*C*H$_2$), 29.1 (alkyl-*C*H$_2$), 29.0 (alkyl-*C*H$_2$), 29.0 (alkyl-*C*H$_2$), 29.0 (alkyl-*C*H$_2$) (plus four overlapping peaks), 25.9 (alkyl-*C*H$_2$), 24.6 (*C*H$_3$), 23.6 (*C*H$_3$′); HRMS (ESI) $[M+H]^+$ calcd for $C_{37}H_{53}N_2O_4$ 589.4000, found 589.3987.

The following three-step procedure forms $C_1$-Box ligand **20** via **35** and **36**.

*4.1.15. N$^1$-((S)-2-Hydroxy-1-phenylethyl)-N$^3$-((R)-1-hydroxy-3-phenylpropan-2-yl)-2,2-dimethylmalonamide (**35**).* A solution of *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbo diimide hydrochloride (EDCI) (84.1 mg, 4.39 mmol) in $CHCl_3$ (5 mL) was added dropwise to a stirring solution of (*S*)-3-(2-hydroxy-1-phenylethylamino)-2,2-dimethyl-3-oxopropanoic acid **33** (99.9 mg, 3.97 mmol), 1-hydroxybenzotriazole hydrate (HOBt) (62.6 mg, 4.63 mmol) and $Et_3N$ (1.40 mL, 10.0 mmol) in $CHCl_3$ (37 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 1 h. A solution of (*R*)-2-amino-3-phenylpropan-1-ol (66.2 mg, 4.38 mmol) in $CHCl_3$ (7 mL) was added dropwise. The resulting solution was warmed to RT and stirred for 41 h. The reaction was quenched with 3 M aq HCl (12 mL) and the aqueous layer extracted with $CHCl_3$. The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The resulting residue was purified by column chromatography (9:1 ethyl acetate/petrol ether) to yield the title compound **35** (1.05 g, 69%) as a pale yellow solid. Mp 119–122 °C; $R_f$ 0.30 (9:1 ethyl acetate/petrol ether); $[\alpha]_D^{20}$ +54.9 (*c* 1.02, $CHCl_3$); $\nu_{max}/cm^{-1}$ 3315 (OH/NH), 3275 (OH/NH), 3062 (Ar CH), 2942 (CH), 1633 (C=O), 1523 (N–C=O), 1495 (Ar C=C), 1453 (Ar C=C), 1285 (C–N), 1056 (C–OH), 1032 (C–OH), 911 (Ar CH), 735 (Ar CH), 698 (Ar CH); $\delta_H$ (300 MHz, $CDCl_3$) 7.38–7.15 (11H, m, Ar–*H*, N*H*), 6.67 (1H, d, *J* 8.1, N*H*), 5.07–4.93 (1H, m, C*H*CH$_2$OH), 4.23–4.06 (1H, m, C*H*CH$_2$OH′), 3.85 (1H, dd, *J* 11.4, 4.0, CHC*H*HOH), 3.77 (1H, dd, *J* 11.7, 6.6, CHC*H*HOH′), 3.63 (1H, dd, *J* 11.7, 4.0, CHCH*H*OH′), 3.54 (1H, dd, *J* 11.4, 5.1, CHCH*H*OH), 2.89 (1H, dd, *J* 13.6, 6.6, C*H*HCHCH$_2$), 2.80 (2H, dd, *J* 13.6, 7.7, CH*H*CHCH$_2$), 1.41 (3H, s, C*H*$_3$), 1.35 (3H, s, C*H*$_3$′); $\delta_C$ (75 MHz, $CDCl_3$) 174.0 (*C*), 173.8 (*C*), 138.8 (*C*), 137.5 (*C*), 129.2 (*C*H), 128.8 (*C*H), 128.5 (*C*H), 127.8 (*C*H), 126.6 (*C*H), 126.5 (*C*H), 66.0 (*C*H$_2$), 63.9 (*C*H$_2$), 55.8 (*C*H), 53.2 (*C*H), 49.8 (*C*), 36.7 (*C*H$_2$), 23.6 (*C*H$_3$), 23.5 (*C*H$_3$); HRMS (ESI) $[M+H]^+$ calcd for $C_{22}H_{29}N_2O_4$ 385.2122, found 385.2122.

*4.1.16. N$^1$-((S)-2-Chloro-1-phenylethyl)-N$^3$-((R)-1-chloro-3-phenylpropan-2-yl)-2,2-dimethylmalonamide (**36**).* Thionyl chloride (1.60 mL, 21.9 mmol) was added to a stirring suspension of N$^1$-((*S*)-2-hydroxy-1-phenylethyl)-N$^3$-((*R*)-1-hydroxy-3-phenylpropan-2-yl)-2,2-dimethylmalonamide **35** (74.0 mg, 1.92 mmol) in DCM (40 mL). The resulting mixture was stirred at RT for 19 h, then concentrated under reduced pressure and the resulting residue purified by column chromatography (49:1 DCM/ethyl acetate) to yield the title compound **36** (0.681 g, 85%) as a white solid. Mp 157–160 °C; $R_f$ 0.64 (49:1 DCM/ethyl acetate); $[\alpha]_D^{21}$ +42.3 (*c* 1.04, $CHCl_3$); $\nu_{max}/cm^{-1}$ 3310 (NH), 3063 (Ar CH), 3028 (Ar CH), 2972 (CH), 1637 (C=O), 1554 (N–C=O), 1526 (N–C=O), 1496 (Ar C=C), 1455 (Ar C=C), 699 (C–Cl); $\delta_H$ (300 MHz, $CDCl_3$) 7.43–7.22 (11H, m, Ar–*H*, N*H*), 6.68 (1H, d, *J* 8.1, N*H*), 5.33–5.25 (1H, m, C*H*CH$_2$Cl), 4.46 (1H, tdd, *J* 7.7, 4.4, 3.7, CH$_2$C*H*CH$_2$Cl), 3.85 (1H, dd, *J* 11.4, 5.1, CHC*H*HCl), 3.78 (1H, dd, *J* 11.4, 6.2, CHCH*H*Cl), 3.60 (1H, dd, *J* 11.4, 4.4, CH$_2$CHC*H*HCl), 3.51 (1H, dd, *J* 11.4, 3.7, CH$_2$CHCH*H*Cl), 2.95 (2H, d, *J* 7.7, C*H*$_2$CHCH$_2$Cl), 1.50 (3H, s, C*H*$_3$), 1.45 (3H, s, C*H*$_3$'); $\delta_C$ (75 MHz, $CDCl_3$) 173.3 (*C*), 172.8 (*C*), 138.3 (*C*), 136.7 (*C*), 129.2 (*C*H), 128.9 (*C*H), 128.8 (*C*H), 128.2 (*C*H), 127.0 (*C*H), 126.5 (*C*H), 54.1 (*C*H$_2$), 51.1 (*C*H$_2$), 49.5 (*C*), 47.5 (*C*H), 46.3 (*C*H), 37.4 (*C*H$_2$), 24.0 (*C*H$_3$), 23.7 (*C*H$_3$); HRMS (ESI) $[M+H]^+$ calcd for $C_{22}H_{27}{}^{35}Cl_2N_2O_2$ 421.1444, found 421.1442.

*4.1.17. (R)-4-Benzyl-2-(2-((S)-4-phenyl-4,5-dihydrooxazol-2-yl) propan-2-yl)-4,5-dihydrooxazole (**20**).* TBAF (1.0 M in THF, 5.50 mL, 5.50 mmol) was added to a stirring solution of N$^1$-((*S*)-2-chloro-1-phenylethyl)-N$^3$-((*R*)-1-chloro-3-phenylpropan-2-yl)-2,2-dimethylmalonamide **36** (56.3 mg, 1.34 mmol) in THF (50 mL). The resulting mixture was stirred at RT for 18 h, concentrated under reduced pressure and the resulting residue dissolved in DCM (100 mL). The solution was washed with satd aq sodium citrate (3×100 mL), brine, dried ($MgSO_4$) and concentrated under reduced pressure. The resulting residue was purified by alumina column chromatography (7:3 hexane/ethyl acetate, 0.4% $Et_3N$) to yield the title compound **20** (36.2 mg, 80%) as a colourless oil. $R_f$ 0.10 (3:7 hexane/ethyl acetate); $[\alpha]_D^{20}$ −51.9 (*c* 1.31, $CHCl_3$); $\nu_{max}/cm^{-1}$ 3059 (Ar CH), 3028 (Ar CH), 2984 (CH), 2936 (CH), 2901 (CH), 1651 (N=C), 1604 (Ar C=C), 1495 (Ar C=C), 1455 (Ar C=C), 1145 (C–O), 1116 (C–O), 979 (C–N), 921 (Ar CH), 756 (Ar CH), 700 (Ar CH); $\delta_H$ (300 MHz, $CDCl_3$) 7.40–7.20 (10H, m, Ar–*H*), 5.22 (1H, dd, *J* 9.9, 7.7, OCH$_2$C*H*N), 4.65 (1H, dd, *J* 10.1, 8.3, OC*H*HCHN′), 4.54–4.41 (1H, m, OCH$_2$C*H*N′), 4.26 (1H, dd, *J* 9.9, 8.8, OC*H*HCHN), 4.18–4.03 (2H, m, OCH*H*CHN, OCH*H*CHN′), 3.16 (1H, dd, *J* 13.8, 5.0, ArC*H*HCH), 2.72 (1H, dd, *J* 13.8, 8.6, ArCH*H*CH), 1.63 (3H, s, C*H*$_3$), 1.59 (3H, s, C*H*$_3$′); $\delta_C$ (75 MHz, $CDCl_3$) 170.3 (*C*), 169.4 (*C*), 142.5 (*C*), 137.7 (*C*), 129.5 (*C*H), 128.7 (*C*H), 128.5 (*C*H), 127.6 (*C*H), 126.7 (*C*H), 126.5 (*C*H), 75.5 (*C*H$_2$), 72.1 (*C*H$_2$), 69.5 (*C*H), 67.1 (*C*H), 41.4 (*C*H$_2$), 38.7 (*C*), 24.4 (2×*C*H$_3$ overlapping); HRMS (ESI) $[M+H]^+$ calcd for $C_{22}H_{25}N_2O_2$ 349.1911, found 349.1908.

*4.1.18. Prop-2-ynyl 3,3,3-tris(4-chlorophenyl)propanoate (**29**).* EDCI (1.98 g, 10.3 mmol) was added to a solution of propargyl alcohol (0.600 mL, 10.3 mmol) and 3,3,3-tris(4-chlorophenyl)propionic acid (4.03 g, 9.93 mmol) in DCM (100 mL). 4-(Dimethylamino) pyridine (DMAP) (13.3 mg, 1.09 mmol) was added and the resulting mixture was stirred at RT for 5 h. The reaction was quenched with water (100 mL) and the aqueous layer extracted with DCM. The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The resulting residue was purified by column chromatography (4:1 hexane/ethyl acetate) to yield the title compound **29** (3.83 g, 83%) as a white solid. Mp 88–89 °C; $R_f$ 0.55 (4:1 hexane/ethyl acetate); $\nu_{max}/cm^{-1}$ 3290 (≡CH), 3282 (≡CH), 3075 (Ar CH), 2948 (CH), 2129 (C≡C), 1729 (C=O), 1589 (Ar C=C), 1490 (Ar C=C), 1441 (Ar C=C), 1269 (≡CH), 1219 (Ar CH), 1137 (C–O), 1093 (Ar C–Cl), 803 (Ar CH), 688 (≡CH); $\delta_H$ (400 MHz, $C_2D_6O$) 7.28–7.08 (6H, m, Ar–*H*), 7.12–6.94 (6H, m, Ar–*H*), 4.36 (2H, d, *J* 2.5, C*H*$_2$C≡CH), 3.61 (2H, s, C*H*$_2$COO), 2.33 (1H, t, *J* 2.5, ≡C*H*); $\delta_C$ (101 MHz, $C_3D_6O_2$) 169.4 (*C*), 143.9 (*C*), 132.7 (*C*), 130.3 (*C*H), 128.3 (*C*H), 77.2 (*C*H), 74.9 (*C*), 54.6 (*C*), 52.0 (*C*H$_2$), 45.8 (*C*H$_2$); HRMS (ESI) $[M+Na]^+$ calcd for $C_{24}H_{17}{}^{35}Cl_3NaO_2$ 465.0186, found 465.0183.

*4.1.19. 3-Bromoprop-2-ynyl 3,3,3-tris(4-chlorophenyl)propanoate (**22**).* Silver nitrate (28.8 g, 1.69 mmol) was added to a stirring suspension of prop-2-ynyl 3,3,3-tris(4-chlorophenyl)propanoate **29** (2.00 g, 4.51 mmol) and NBS (90.0 mg, 5.06 mmol) in acetone (50 mL). The flask was protected from light and the mixture stirred at RT for 1 h. The reaction was diluted with petrol ether (50 mL) and washed with water. The aqueous layer was extracted with 1:1 petrol ether/diethyl ether. The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to yield the title compound **22** (2.5 g, 100%) as a white solid. Mp 116–188 °C; $R_f$ 0.75

(9:1 petrol ether/ethyl acetate); $\nu_{max}/cm^{-1}$ 3083 (Ar CH), 2934 (CH), 2873 (CH), 2229 (C≡C), 1748 (C=O), 1591 (Ar C=C), 1490 (Ar C=C), 1326 (C–O), 1195 (Ar CH), 1183 (Ar CH), 1137 (C–O), 1092 (Ar C–Cl), 1012 (C–Br), 817 (Ar CH); $\delta_H$ (300 MHz, $CDCl_3$) 7.34–7.23 (6H, m, Ar–*H*), 7.19–7.05 (6H, m, Ar–*H*), 4.48 (2H, s, C*H*$_2$C≡CBr), 3.70 (2H, s, C*H*$_2$COO); $\delta_C$ (75 MHz, $CDCl_3$) 169.4 (*C*), 143.9 (*C*), 132.8 (*C*), 130.3 (*C*H), 128.3 (*C*H), 73.5 (*C*), 54.6 (*C*), 52.8 (*C*H$_2$), 47.3 (*C*), 45.7 (*C*H$_2$); HRMS (ESI) $[M+H]^+$ calcd for $C_{24}H_{17}{}^{79}Br^{35}Cl_3O_2$ 520.9472, found 520.9479.

*4.1.20. 3-Hydroxypropyl 3,3,3-tris(4-chlorophenyl)propanoate (**37**).* 3,3,3-Tris(4-chlorophenyl)propanoic acid (4.08 g, 12.3 mmol), DMAP (14.3 mg, 1.17 mmol) and EDCI (2.35 g, 12.3 mmol) were added sequentially to a stirring solution of propane-1,3-diol (0.810 mL, 11.2 mmol) in DCM (180 mL). The resulting mixture was stirred at RT for 22 h. The reaction was quenched with water (100 mL) and the aqueous layer extracted with DCM. The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The resulting residue was purified by column chromatography (9:1 petrol ether/ethyl acetate to 1:1 petrol ether/ethyl acetate) to yield the title compound **37** (3.48 g, 67%) as a white solid. Mp 89–90 °C; $R_f$ 0.05 (4:1 petrol ether/ethyl acetate); $\nu_{max}/cm^{-1}$ 3401 br (OH), 3067 (Ar CH), 3032 (Ar CH), 2961 (CH), 2888 (CH), 1731 (C=O), 1590 (Ar C=C), 1574 (Ar C=C), 1491 (Ar C=C), 1150 (C–O–C), 1096 (Ar C–Cl), 1053 (C–OH), 1013 (C–O–C), 811 (Ar CH), 733 (C–Cl); $\delta_H$ (300 MHz, $CDCl_3$) 7.21–7.15 (6H, m, Ar–*H*), 7.12–7.00 (6H, m, Ar–*H*), 3.90 (2H, t, *J* 6.1, OC*H*$_2$), 3.56 (2H, s, C*H*$_2$COO), 3.35 (2H, t, *J* 6.1, C*H*$_2$OH), 1.54 (3H, quin., *J* 6.1, $CH_2CH_2CH_2$); $\delta_C$ (75 MHz, $CDCl_3$) 170.6 (*C*), 144.1 (*C*), 132.7 (*C*), 130.3 (*C*H), 128.3 (*C*H), 61.6 (*C*H$_2$), 59.0 (*C*H$_2$), 54.7 (*C*), 46.1 (*C*H$_2$), 31.4 (*C*H$_2$); HRMS (ESI) $[M+NH_4]^+$ calcd for $C_{24}H_{25}{}^{35}Cl_3NO_3$ 480.0895, found 480.0885.

*4.1.21. 3-(3,3,3-Tris(4-Chlorophenyl)propanoyloxy)propyl acrylate (**25**).* $Et_3N$ (3.80 mL, 27.3 mmol) was added to a stirring solution of 3-hydroxypropyl 3,3,3-tris(4-chlorophenyl)propanoate **37** (2.73 g, 5.89 mmol) in DCM (75 mL) under an argon atmosphere. The resulting mixture was cooled to 0 °C and DMAP (70.0 mg, 0.590 mmol) and acrylolyl chloride (1.10 mL, 14.0 mmol) were added. The resulting mixture was stirred for 2 h. The reaction was quenched with water (75 mL) and the aqueous layer extracted with DCM. The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The resulting residue was purified by column chromatography (9:1 petrol ether/ethyl acetate) to yield the title compound **25** (1.77 g, 63%) as a colourless oil. $R_f$ 0.43 (9:1 petrol ether/ethyl acetate); $\nu_{max}/cm^{-1}$ 3070 (Ar CH), 3036 (=CH), 2966 (CH), 2901 (CH), 1721 (C=O), 1636 (C=C), 1619 (Ar C=C), 1590 (Ar C=C), 1490 (Ar C=C), 1185 (C–O–C), 1147 (C–O–C), 1094 (Ar C–Cl), 985 (=CH), 907 (=CH), 811 (=CH), 730 (Ar CH); $\delta_H$ (300 MHz, $CDCl_3$) 7.23–7.12 (6H, m, Ar–*H*), 7.11–6.98 (6H, m, Ar–*H*), 6.31 (1H, dd, *J* 17.6, 1.5, =C*H*H), 6.01 (1H, dd, *J* 17.6, 10.3, C*H*=CH$_2$), 5.74 (1H, dd, *J* 10.3, 1.5, CH*H*), 3.95 (2H, t, *J* 6.3, C*H*$_2$OCO), 3.83 (2H, t, *J* 6.3, C*H*$_2$OCO′), 3.56 (2H, s, C*H*$_2$COO), 1.67 (2H, quin., *J* 6.3, $CH_2CH_2CH_2$); $\delta_C$ (75 MHz, $CDCl_3$) 170.1 (*C*), 165.9 (*C*), 144.1 (*C*), 132.6 (*C*), 130.9 (*C*H$_2$), 130.3 (*C*H), 128.2 (*C*H), 128.1 (*C*H), 61.1 (*C*H$_2$), 60.7 (*C*H$_2$), 54.6 (*C*), 46.0 (*C*H$_2$), 27.6 (*C*H$_2$); HRMS (ESI): $[M+NH_4]^+$ calcd for $C_{27}H_{27}{}^{35}Cl_3NO_4$ 534.1000, found 534.1002.

### 4.2. General procedure for the Cadiot–Chodkiewicz reaction

*n*-Butyl lithium (1 equiv) was added dropwise to a stirring solution of 4,4′,4″-((4-(pent-4-ynyloxy)phenyl)methanetriyl) tris(-*tert*-butylbenzene) **21** (1 equiv) in THF (0.09 M) at −78 °C. The resulting mixture was warmed to 0 °C and stirred for 40 min. Copper iodide/chloride (1.3 equiv) was added and the resulting mixture warmed to RT and stirred for 1 h. The reaction mixture was cooled to −78 °C and a solution of Box ligand (1 equiv) and 3-bromoprop-2-ynyl 3,3,3-tris(4-chlorophenyl)propanoate **22** (1 equiv) in THF (0.05 M) was added. The resulting mixture was warmed to RT and stirred until the reaction was complete. The reaction was quenched with 17.5% aq ammonia solution satd with ethylenediaminetetraacetic acid (EDTA) and stirred under air for 40 min. The aqueous layer was extracted with DCM and the combined organic layers washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The mixture was analyzed by $^1H$ NMR spectroscopic analysis (Table 1). For characterization, a sample was purified by column chromatography (hexane to 9:1 hexane/ethyl acetate) to yield thread **23** as a white solid. Mp 90–94 °C; $R_f$ 0.38 (9:1 hexane/ethyl acetate); $\nu_{max}/cm^{-1}$ 2962 (Ar CH), 2903 (CH), 2868 (CH), 2258 (C≡C), 1749 (C=O), 1606 (Ar C=C), 1505 (Ar C=C), 1492 (Ar C=C), 1248 (C–O–C), 1141 (C–O), 1096 (Ar C–Cl), 1054 (C–O–C), 824 (Ar CH); $\delta_H$ (400 MHz, $CDCl_3$) 7.28–7.23 (10H, m, Ar–*H*), 7.17–7.07 (16H, m, Ar–*H*), 6.82–6.75 (2H, m, Ar–*H*), 4.51 (2H, s, OC*H*$_2$C≡C), 4.05 (2H, t, *J* 6.6, OC*H*$_2$CH$_2$), 3.68 (2H, s, C*H*$_2$COO), 2.56 (2H, t, *J* 6.6, C*H*$_2$C≡C), 2.04 (2H, quin., *J* 6.6, $CH_2CH_2CH_2$), 1.32 (27H, s, C*H*$_3$); $\delta_C$ (101 MHz, $CDCl_3$) 169.4 (*C*), 156.5 (*C*), 148.3 (*C*), 144.1 (*C*), 143.9 (*C*), 139.8 (*C*), 132.8 (*C*), 132.3 (*C*H), 130.7 (*C*H), 130.3 (*C*H), 128.3 (*C*H), 124.0 (*C*H), 113.0 (*C*H), 81.2 (*C*), 71.7 (*C*), 68.8 (*C*), 65.8 (*C*H$_2$), 64.7 (*C*), 63.1 (*C*), 54.6 (*C*), 52.6 (*C*H$_2$), 45.8 (*C*H$_2$), 34.3 (*C*), 31.6 (*C*H$_3$), 22.7 (*C*H$_2$), 14.1 (*C*H$_2$); HRMS (ESI) $[M+NH_4]^+$ calcd for $C_{66}H_{69}{}^{35}Cl_3NO_3$ 1028.4338, found 1028.4340.

Thread **24** was also isolated from the reaction as a white solid. Mp 84–88 °C; $R_f$ 0.14 (9:1 petrol ether/ethyl acetate); $\nu_{max}/cm^{-1}$ 3075 (Ar CH), 3040 (Ar CH), 2932 (CH), 2254 (C≡C), 1747 (C=O), 1590 (Ar C=C), 1574 (Ar C=C), 1490 (Ar C=C), 1369 (CH), 1193 (Ar CH), 1138 (C–O), 1094 (Ar C–Cl), 808 (Ar CH); $\delta_H$ (300 MHz, $CDCl_3$) 7.34–7.22 (12H, m, Ar–*H*), 7.20–7.09 (12H, m, Ar–*H*), 4.54 (4H, s, C*H*$_2$C≡C), 3.71 (4H, s, C*H*$_2$COO); $\delta_C$ (75 MHz, $CDCl_3$) 169.3 (*C*), 143.9 (*C*), 132.8 (*C*), 130.3 (*C*H), 128.4 (*C*H), 73.2 (*C*), 70.3 (*C*), 54.6 (*C*), 52.3 (*C*H$_2$), 45.7 (*C*H$_2$); HRMS (ESI) $[M+NH_4]^+$ calcd for $C_{48}H_{36}{}^{35}Cl_6NO_4$ 900.0770, found 900.0773.

### 4.3. General procedure for the oxidative Heck reaction

A solution of palladium(II) acetate (20 mol%) and Box ligand (1 equiv) in DMF (0.05 M) was stirred at RT for 2.5 h. A solution of 3-(3,3,3-tris(4-chlorophenyl)propanoyloxy)propyl acrylate **25** (1 equiv), 4-(3-(4-(tris(4-*tert*-butyl-phenyl)methyl)phenoxy) propoxy)phenylboronic acid **26** (3 equiv) and benzoquinone (1 equiv) in $CHCl_3$ (0.05 M) was added. The resulting mixture was placed under an oxygen atmosphere and heated to 25 °C for 48 h. The reaction was diluted with DCM, washed with water, dried ($MgSO_4$) and concentrated under reduced pressure. The mixture was analyzed by $^1H$ NMR analysis (Table 2). For characterization, a sample was purified by column chromatography (19:1 petrol ether/ethyl acetate to 9:1 petrol ether/ethyl acetate) to yield thread **27** as a white solid. Mp 164–166 °C; $R_f$ 0.16 (9:1 petrol ether/ethyl acetate); $\nu_{max}/cm^{-1}$ 2961 (Ar CH), 2905 (CH), 2868 (CH), 1738 (C=O), 1713 (C=O), 1634 (C=C), 1604 (Ar C=C), 1506 (Ar C=C), 1492 (Ar C=C), 1473 (Ar C=C), 1246 (C–O–C), 1165 (C–O), 1096 (Ar C–Cl), 1055 (C–O–C), 826 (Ar CH); $\delta_H$ (400 MHz, $CDCl_3$) 7.66 (1H, d, *J* 15.6, C*H*=CH), 7.47 (2H, s, Ar–*H*), 7.31–7.23 (13H, m, Ar–*H*), 7.17–7.09 (13H, m, Ar–*H*), 6.97–6.91 (2H, m, Ar–*H*), 6.84–6.78 (2H, m, Ar–*H*), 6.31 (1H, d, *J* 15.6, OCOC*H*=CH), 4.23 (2H, t, *J* 6.2, C*H*$_2$O), 4.20–4.09 (4H, m, C*H*$_2$OCO, C*H*$_2$O′), 3.99 (2H, t, *J* 6.2, C*H*$_2$OCO′), 3.67 (2H, s, C*H*$_2$COO), 2.30 (2H, quin., *J* 6.2, $CH_2CH_2CH_2$), 1.82 (2H, quin., *J* 6.2, $CH_2CH_2CH_2'$), 1.33 (27H, s, C*H*$_3$); $\delta_C$ (101 MHz, $CDCl_3$) 170.2 (*C*), 167.1 (*C*), 160.8 (*C*), 156.6 (*C*), 148.3 (*C*), 144.8 (*C*), 144.2 (*C*H), 139.8 (*C*), 132.7 (*C*), 132.3 (*C*H), 130.7 (*C*H), 130.3 (*C*H), 129.8 (*C*H), 128.3 (*C*H), 127.0 (*C*), 124.1 (*C*H), 115.2 (*C*H), 114.9 (*C*H), 113.0 (*C*H), 64.7 (*C*H$_2$), 64.0 (*C*H$_2$), 63.1 (*C*), 61.4 (*C*H$_2$), 60.7 (*C*H$_2$), 54.6 (*C*), 46.1 (*C*H$_2$), 34.3 (*C*), 31.4 (*C*H$_3$), 29.3 (*C*H$_2$), 27.8 (*C*H$_2$); HRMS (ESI) $[M+NH_4]^+$ calcd for $C_{73}H_{79}{}^{35}Cl_3NO_6$ 1170.4967, found 1170.4984.

### 4.4. General procedure for the CuAAC click reaction

A solution of tetrakis(acetonitrile)copper(I) hexafluorophosphate (1 equiv) and Box ligand (1 equiv) in DCM (1 mL) was stirred for 2.5 h. A solution of prop-2-ynyl 3,3,3-tris(4-chlorophenyl)propanoate **29** (1 equiv) and 4,4′,4″-((4-(3-azido-propoxy) phenyl) methanetriyl)tris(*tert*-butylbenzene) **30** (1 equiv) in DCM (1.5 mL) was added. The resulting mixture was concentrated under reduced pressure to the required concentration and the reaction mixture heated to 25 °C until the reaction was complete. The resulting mixture was diluted with DCM, washed with 17.5% aq $NH_3$ satd with EDTA, dried ($MgSO_4$) and concentrated under reduced pressure. The mixture was analyzed by $^1$H NMR analysis (Table 3). For characterization, a sample was purified by column chromatography (4:1 petrol ether/ethyl acetate to ethyl acetate) to yield thread **31** as a white solid. Mp 129–131 °C; $R_f$ 0.14 (4:1 petrol ether/ethyl acetate); $\nu_{max}$/cm$^{-1}$ 2961 (Ar CH), 2903 (CH), 2868 (CH), 1739 (C=O), 1505 (Ar C=C), 1492 (Ar C=C), 1401 (N=N), 1363 (N=N), 1245 (C–O–C), 1185 (C–O–C), 1146 (C–O–C), 1110 (C–N), 1096 (Ar C–Cl), 1055 (C–O–C), 822 (Ar CH); $\delta_H$ (300 MHz, $CDCl_3$) 7.28–7.19 (14H, m, Ar–*H*), 7.15–7.06 (15H, m, Ar–*H*, C=C*H*N), 6.81–6.72 (2H, m, Ar–*H*), 5.00 (2H, s, O$CH_2$C=C), 4.58 (2H, t, *J* 6.3, N$CH_2$), 3.96 (2H, t, *J* 6.3, O$CH_2CH_2$), 3.68 (2H, s, C$H_2$COO), 2.38 (2H, quin., *J* 6.3, $CH_2CH_2CH_2$), 1.33 (27H, s, C$H_3$); $\delta_C$ (75 MHz, $CDCl_3$) 170.2 (*C*), 156.2 (*C*), 148.4 (*C*), 144.1 (*C*), 144.0 (*C*), 142.1 (*C*), 140.2 (*C*), 132.6 (CH), 132.4 (*C*), 130.7 (CH), 130.3 (CH), 128.2 (CH), 124.1 (CH), 112.9 (CH), 63.8 (*C*), 63.1 ($CH_2$), 57.8 ($CH_2$), 54.5 (*C*), 47.3 ($CH_2$), 46.0 ($CH_2$), 34.3 (*C*), 31.4 ($CH_3$), 30.0 ($CH_2$); HRMS (ESI) $[M+H]^+$ calcd for $C_{64}H_{67}{}^{35}Cl_3N_3O_3$ 1030.4243, found 1030.4244.


### Acknowledgements

We would like to thank EPSRC (EP/G006695/1) funding and the EPSRC Mass Spectrometry services at Swansea for analytical support.


### Supplementary data

Supplementary data available: copies of $^1$H NMR and $^{13}$C NMR spectra. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2012.10.069.

### References and notes


1. For reviews of molecular machines see: (a) Special issue on molecular machinesAcc. Chem. Res. **2001**, *34*; (b) *Molecular Switches*; Feringa, B. L., Ed.; Wiley-VCH: Weinheim, 2001; (c) Balzani, V.; Credi, A.; Venturi, M. *Molecular Devices and Machines*; Wiley-VCH: Weinheim, 2003; (d) Collin, J. P.; Sauvage, J. P. *Chem. Lett.* **2005**, *34*, 742–747; (e) Kay, E. R.; Leigh, D. A.; Zerbetto, F. *Angew. Chem., Int. Ed.* **2007**, *46*, 72–191; (f) Durot, S.; Reviriego, F.; Sauvage, J. P. *Dalton Trans.* **2010**, *39*, 10557–10579; (g) Sauvage, J. P.; Collin, J. P.; Durot, S.; Frey, J.; Heitz, V.; Sour, A.; Tock, C. *C. R. Chimie* **2010**, *13*, 315–328; (h) Silvi, S.; Venturi, M.; Credi, A. *Chem. Commun.* **2011**, 2483–2489.
2. Rosengren, K. J.; Clark, R. J.; Daly, N. L.; Göransson, U.; Jones, A.; Craik, D. J. *J. Am. Chem. Soc.* **2003**, *125*, 12464–12474.
3. Reuter, C.; Schmieder, R.; Vögtle, F. *Pure Appl. Chem.* **2000**, *72*, 2233–2241.
4. (a) Yamamoto, C.; Okamoto, Y.; Schmidt, T.; Jäger, R.; Vögtle, F. *J. Am. Chem. Soc.* **1997**, *119*, 10547–10548; (b) Kameta, N.; Hiratani, K.; Nagawa, Y. *Chem. Commun.* **2004**, 466–467; (c) Kameta, N.; Nagawa, Y.; Karikomi, M.; Hiratani, K. *Chem. Commun.* **2006**, 3714–3716; (d) Schmieder, R.; Hübner, G.; Seel, C.; Vögtle, F. *Angew. Chem., Int. Ed.* **1999**, *38*, 3528–3530; (e) Kishan, M. R.; Parham, A.; Schelhase, F.; Yoneva, A.; Silva, G.; Chen, X.; Okamoto, Y.; Vögtle, F. *Angew. Chem., Int. Ed.* **2006**, *45*, 7296–7299.
5. (a) Tachibana, Y.; Kihara, N.; Takata, T. *J. Am. Chem. Soc.* **2004**, *126*, 3438–3439; (b) Hattori, G.; Hori, T.; Miyake, Y.; Nishibayashi, Y. *J. Am. Chem. Soc.* **2007**, *129*, 12930–12931; (c) Li, Y.; Feng, Y.; He, Y.-M.; Chen, F.; Pan, J.; Fan, Q.-H. *Tetrahedron Lett.* **2008**, *49*, 2878–2881; (d) Suzaki, Y.; Shimada, K.; Chihara, E.; Saito, T.; Tsuchido, Y.; Osakada, K. *Org. Lett.* **2011**, *13*, 3774–3777.
6. Makita, Y.; Kihara, N.; Nakakoji, N.; Takata, T.; Inagaki, S.; Yamamoto, C.; Okamoto, Y. *Chem. Lett.* **2007**, *36*, 162–163.
7. Mobian, P.; Banerji, N.; Bernardinelli, G.; Lacour, J. *Org. Biomol. Chem.* **2006**, *4*, 224–231.
8. For reviews of active metal template synthesis of molecular architectures see: (a) Crowley, J. D.; Goldup, S. M.; Lee, A. L.; Leigh, D. A.; McBurney, R. T. *Chem. Soc. Rev.* **2009**, *38*, 1530–1541; (b) Beves, J. E.; Blight, B. A.; Campbell, C. J.; Leigh, D. A.; McBurney, R. T. *Angew. Chem., Int. Ed.* **2011**, *50*, 9260–9327.
9. For recent reviews on bis-oxazoline ligands, see: (a) Desimoni, G.; Faita, G.; Jørgensen, K. A. *Chem. Rev.* **2006**, *106*, 3561–3651; (b) Rasappan, R.; Laventine, D.; Reiser, O. *Coord. Chem. Rev.* **2008**, *252*, 702–714; (c) Hargaden, G. C.; Guiry, P. J. *Chem. Rev.* **2009**, *109*, 2505–2550.
10. Portada, T.; Roje, M.; Raza, Z.; Čaplar, V.; Žinić, M.; Šunjić, V. *Eur. J. Org. Chem.* **2007**, 838–856.
11. As far as we are aware, there are only a few examples of $C_1$-symmetric Box ligands with different pendant groups (non-macrocyclic), see: (a) Sibi, M. P.; Venkatraman, L.; Liu, M.; Jasperse, C. P. *J. Am. Chem. Soc.* **2001**, *123*, 8444–8445; (b) García, J. I.; Mayoral, J. A.; Pires, E.; Villalba, I. *Tetrahedron: Asymmetry* **2006**, *17*, 2270–2275; (c) Fraile, J. M.; García, J. I.; Gissibl, A.; Mayoral, J. A.; Pires, E.; Reiser, O.; Roldán, M.; Villalba, I. *Chem.—Eur. J.* **2007**, *13*, 8830–8839; (d) Orlandi, S.; Benaglia, M.; Dell'Anna, G.; Celentano, G. *J. Organomet. Chem.* **2007**, *692*, 2120–2124; (e) García, J. I.; López-Sánchez, B.; Mayoral, J. A.; Pires, E.; Villalba, I. *J. Catal.* **2008**, *258*, 378–385.
12. For $C_1$-symmetric Azabox (non-macrocyclic), see: (a) Werner, H.; Vicha, R.; Gissibl, A.; Reiser, O. *J. Org. Chem.* **2003**, *68*, 10166–10168; (b) Lang, K.; Park, J.; Hong, S. *J. Org. Chem.* **2010**, *75*, 6424–6435.
13. For $C_1$-symmetric Pybox (non-macrocyclic), see: (a) Nishiyama, H.; Soeda, N.; Naito, T.; Motoyama, Y. *Tetrahedron: Asymmetry* **1998**, *9*, 2865–2869; (b) Sada, K.; Tateishi, Y.; Shinkai, S. *Chem. Lett.* **2004**, *33*, 582–583; (c) Cornejo, A.; Fraile, J. M.; García, J. I.; Gil, M. J.; Martínez-Merino, V.; Mayoral, J. A.; Salvatella, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 458–461.
14. For $C_1$-symmetric Phebox (non-macrocyclic), see: Ohshima, T.; Kawabata, T.; Takeuchi, Y.; Kakinuma, T.; Iwasaki, T.; Yonezawa, T.; Murakami, H.; Nishiyama, H.; Mashima, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 6296–6300.
15. For recent examples of $C_1$-symmetric Box ligands with different bridging groups (non-macrocyclic), see: (a) McManus, H. A.; Cozzi, P. G.; Guiry, P. J. *Adv. Synth. Catal.* **2006**, *348*, 551–558; (b) Atodiresei, I.; Schiffers, I.; Bolm, C. *Tetrahedron: Asymmetry* **2006**, *17*, 620–633; (c) McManus, H. A.; Cozzi, P. G.; Guiry, P. *J. Org. Biomol. Chem.* **2007**, *5*, 763–766; (d) Hargaden, G. C.; O'Sullivan, T. P.; Guiry, P. J. *Org. Biomol. Chem.* **2008**, *6*, 562–566; (e) Coeffard, V.; Aylward, M.; Guiry, P. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 9152–9155; (f) Liu, L.; Zhao, Q.; Du, F.; Chen, H.; Qin, Z.; Fu, B. *Tetrahedron: Asymmetry* **2011**, *22*, 1874–1878; (g) Castillo, M. R.; Castillón, S.; Claver, C.; Fraile, J. M.; Gual, A.; Martín, M.; Mayoral, J. A.; Sola, E. *Tetrahedron* **2011**, *67*, 5402–5408; (h) Liu, L.; Ma, H.; Fu, B. *Molecules* **2012**, *17*, 1992–1999; (i) Qu, J. P.; Liang, Y.; Xu, H.; Sun, X.-L.; Yu, Z.-X.; Tang, Y. *Chem.—Eur. J.* **2012**, *18*, 2196–2201.
16. Goldup, S. M.; Leigh, D. A.; McBurney, R. T.; McGonigal, P. R.; Plant, A. *Chem. Sci.* **2010**, *1*, 383–386.
17. For general Cadiot–Chodkiewicz reaction see: (a) Cadiot, P.; Chodkiewicz, W. In *Chemistry of Acetylenes*; Viehe, H. G., Ed.; Dekker: New York, NY, 1969; pp 597–647; (b) Siemsen, P.; Livingston, R. C.; Diederich, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 2632–2657.
18. For general oxidative Heck reaction see: (a) Du, X.; Suguro, M.; Hirabayashi, K.; Mori, A. *Org. Lett.* **2001**, *3*, 3313–3316; (b) McDonald, R. I.; Liu, G.; Stahl, S. S. *Chem. Rev.* **2011**, *111*, 2981–3019.
19. For general CuAAC 'click' reaction see: (a) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004–2021; (b) Meldal, M.; Tornøe, C. W. *Chem. Rev.* **2008**, *108*, 2952–3015; (c) Liang, L.; Astruc, D. *Coord. Chem. Rev.* **2011**, *255*, 2933–2945.
20. For application of the Cadiot–Chodkiewicz reaction in rotaxane and catenane synthesis, see: (a) Berná, J.; Goldup, S. M.; Lee, A. L.; Leigh, D. A.; Symes, M. D.; Teobaldi, G.; Zerbetto, F. *Angew. Chem., Int. Ed.* **2008**, *47*, 4392–4396; (b) Goldup, S. M.; Leigh, D. A.; Long, T.; McGonigal, P. R.; Symes, M. D.; Wu, J. *J. Am. Chem. Soc.* **2009**, *131*, 15924–15929; (c) Sato, Y.; Yamasaki, R.; Saito, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 504–507.
21. For application of the oxidative Heck reaction in rotaxane synthesis, see: Crowley, J. D.; Hänni, K. D.; Lee, A. L.; Leigh, D. A. *J. Am. Chem. Soc.* **2007**, *129*, 12092–12093.
22. For application of the CuAAC 'click' reaction in the active metal synthesis of rotaxanes and catenanes, see: (a) Aucagne, V.; Hänni, K. D.; Leigh, D. A.; Lusby, P. J.; Walker, D. B. *J. Am. Chem. Soc.* **2006**, *128*, 2186–2187; (b) Aucagne, V.; Berná, J.; Crowley, J. D.; Goldup, S. M.; Hänni, K. D.; Leigh, D. A.; Lusby, P. J.; Ronaldson, V. E.; Slawin, A. M. Z.; Viterisi, A.; Walker, D. B. *J. Am. Chem. Soc.* **2007**, *129*, 11950–11963; (c) Goldup, S. M.; Leigh, D. A.; McGonigal, P. R.; Ronaldson, V. E.; Slawin, A. M. Z. *J. Am. Chem. Soc.* **2010**, *132*, 315–320; (d) Lahlali, H.; Jobe, K.; Watkinson, M.; Goldup, S. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 4151–4155; and ref. 20b.
23. For application of the CuAAC 'click' reaction in the non-active metal synthesis of rotaxanes and catenanes, see: (a) Miljanić, O. Š.; Dichtel, W. R.; Mortezaei, S.; Stoddart, J. F. *Org. Lett.* **2006**, *8*, 4835–4838; (b) Dichtel, W. R.; Miljanić, O. Š.; Spruell, J. M.; Heath, J. R.; Stoddart, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 10388–10390; (c) Mobian, P.; Collin, J. P.; Sauvage, J. P. *Tetrahedron Lett.* **2006**, *47*, 4907–4909; (d) Loethen, S.; Ooya, T.; Choi, H. S.; Yui, N.; Thompson, D. H. *Biomacromolecules* **2006**, *7*, 2501–2506; (e) Kumar, R.; El-Sagheer, A.; Tumpane, J.; Lincoln, P.; Wilhelmsson, L. M.; Brown, T. *J. Am. Chem. Soc.* **2007**, *129*, 6859–6864; (f) Miljanić, O. Š.; Dichtel, W. R.; Khan, S. I.; Mortezaei, S.; Heath, J. R.; Stoddart, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 8236–8246; (g) Aprahamian, I.; Dichtel, W. R.; Ikeda, T.; Heath, J. R.; Stoddart, J. F. *Org. Lett.* **2007**, *9*, 1287–1290; (h) Aprahamian, I.; Yasuda, T.; Ikeda, T.; Saha, S.; Dichtel, W. R.; Isoda, K.; Kato,

T.; Stoddart, J. F. *Angew. Chem., Int. Ed.* **2007**, *46*, 4675–4679; (i) Frey, J.; Tock, C.; Collin, J. P.; Heitz, V.; Sauvage, J. P. *J. Am. Chem. Soc.* **2008**, *130*, 4529–4593; (j) Zhao, Y.-L.; Dichtel, W. R.; Trabolsi, A.; Saha, S.; Aprahamian, I.; Stoddart, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 11294–11296; (k) Megiatto, J. D., Jr.; Schuster, D. I. *J. Am. Chem. Soc.* **2008**, *130*, 12872–12873; (l) Gassensmith, J. J.; Barr, L.; Baumes, J. M.; Paek, A.; Nguyen, A.; Smith, B. D. *Org. Lett.* **2008**, *10*, 3343–3346; (m) Durot, S.; Mobian, P.; Collin, J. P.; Sauvage, J. P. *Tetrahedron* **2008**, *64*, 8496–8503; (n) Mullen, K. M.; Gunter, M. J. *J. Org. Chem.* **2008**, *73*, 3336–3350; (o) Aprahamian, I.; Olsen, J. C.; Trabolsi, A.; Stoddart, J. F. *Chem.—Eur. J.* **2008**, *14*, 3889–3895; (p) Spruell, J. M.; Dichtel, W. R.; Heath, J. R.; Stoddart, J. F. *Chem.—Eur. J.* **2008**, *14*, 4168–4177; (q) Barrell, M. J.; Leigh, D. A.; Lusby, P. J.; Slawin, A. M. Z. *Angew. Chem., Int. Ed.* **2008**, *47*, 8036–8039; (r) Bria, M.; Bigot, J.; Cooke, G.; Lyskawa, J.; Rabani, G.; Rotello, V. M.; Woisel, P. *Tetrahedron* **2009**, *65*, 400–407; (s) Collin, J.-P.; Frey, J.; Heitz, V.; Sauvage, J.-P.; Tock, C.; Allouche, L. *J. Am. Chem. Soc.* **2009**, *131*, 5609–5620; (t) Collin, J. P.; Sauvage, J. P.; Trolez, Y.; Rissanen, K. *New J. Chem.* **2009**, *33*, 2148–2154; (u) Megiatto, J. D., Jr.; Schuster, D. I. *Chem.—Eur. J.* **2009**, *15*, 5444–5448; (v) Megiatto, J. D., Jr.; Schuster, D. I.; Abwandner, S.; de Miguel, G.; Guldi, D. M. *J. Am. Chem. Soc.* **2010**, *132*, 3847–3861; (x) Collin, J.-P.; Durola, F.; Frey, J.; Heitz, V.; Reviriego, F.; Sauvage, J.-P.; Trolez, Y.; Rissanen, K. *J. Am. Chem. Soc.* **2010**, *132*, 6840–6850; (y) Megiatto, J. D., Jr.; Schuster, D. I. *New J. Chem.* **2010**, *34*, 276–286; (z) Megiatto, J. D., Jr.; Schuster, D. I. *Org. Lett.* **2011**, *13*, 1808–1811; (aa) Hancock, L. M.; Beer, P. D. *Chem. Commun.* **2011**, 6012–6014; (ab) Collin, J. P.; Durot, S.; Sauvage, J. P.; Trolez, Y. *New J. Chem.* **2011**, *35*, 2009–2012; (ac) Collin, J. P.; Durot, S.; Keller, M.; Sauvage, J. P.; Trolez, Y.; Cetina, M.; Rissanen, K. *Chem.—Eur. J.* **2011**, *17*, 947–957; (ad) Li, H.; Fahrenbach, A. C.; Coskun, A.; Zhu, Z.; Barin, G.; Zhao, Y. L.; Botros, Y. Y.; Sauvage, J. P.; Stoddart, J. F. *Angew. Chem., Int. Ed.* **2011**, *50*, 6782–6788.

24. (a) Akiyama, K.; Wakabayashi, K.; Mikami, K. *Adv. Synth. Catal.* **2005**, *347*, 1569–1575; (b) Yoo, K. S.; Park, C. P.; Yoon, C. H.; Sakaguchi, S.; O'Neill, J.; Jung, K. W. *Org. Lett.* **2007**, *9*, 3933–3935.
25. Díaz-Torres, R.; Alvarez, S. *Dalton Trans.* **2011**, *40*, 10742–10750.
26. Holmes, R. R.; Day, R. O.; Setzer, W. N.; Sopchik, A. E.; Bentrude, W. G. *J. Am. Chem. Soc.* **1984**, *106*, 2353–2358.
27. Berná, J.; Crowley, J. D.; Goldup, S. M.; Hänni, K. D.; Lee, A. L.; Leigh, D. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 5709–5713.
28. Chavda, S.; Coulbeck, E.; Dingjan, M.; Eames, J.; Flinn, A.; Northen, J. *Tetrahedron: Asymmetry* **2008**, *19*, 1536–1548.