



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.

© 2012 Elsevier Ltd. All rights reserved.

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.

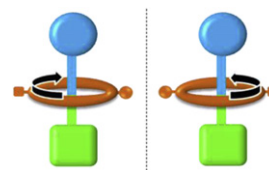
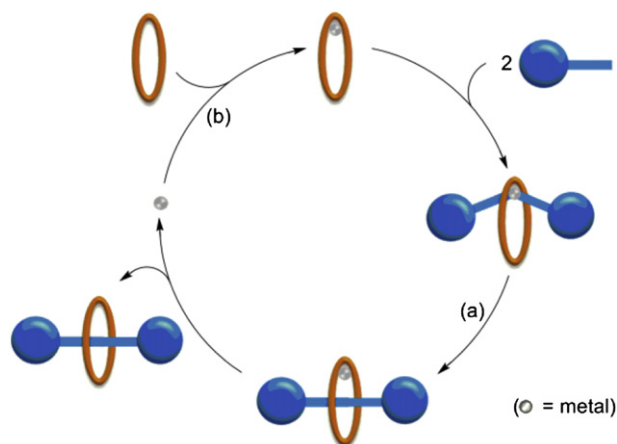


Fig. 1. Mechanical planar chirality in rotaxanes.

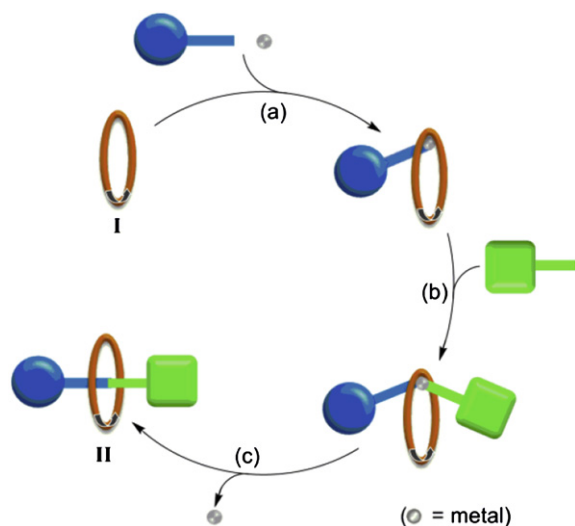
Recently, Leigh and co-workers pioneered the use of the active-template metal strategy as an efficient way of synthesizing interlocked molecules.⁸ The active-metal template strategy utilises the metal to play a dual role of template for entwining or threading the components and as a catalyst for covalent 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).



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.



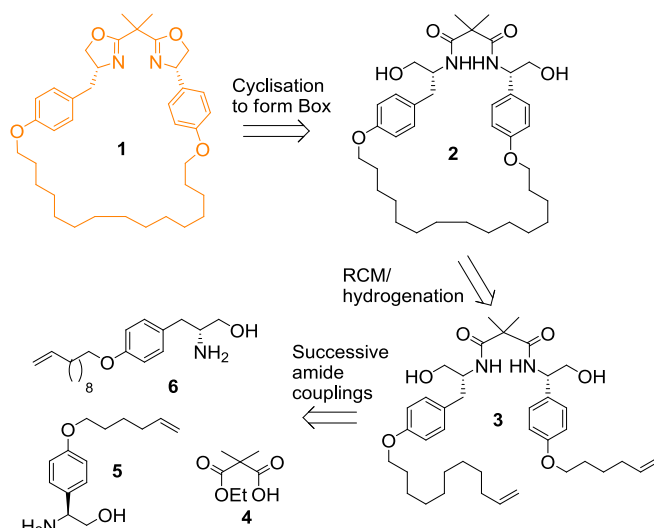
Scheme 2. Proposed asymmetric active-metal template for rotaxane formation. (a) Approach of first fragment to less sterically hindered face of asymmetric macrocycle I. (b) Approach of second fragment to opposite face. (c) Covalent bond-forming reaction and demetallation to furnish chiral rotaxane II.

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 Cadot–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

Download English Version:

<https://daneshyari.com/en/article/5218578>

Download Persian Version:

<https://daneshyari.com/article/5218578>

[Daneshyari.com](https://daneshyari.com)