A Mechanically Planar Chiral Rotaxane Ligand for Enantioselective Catalysis

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SUMMARY
Rotaxanes are interlocked molecules in which a molecular ring is trapped on a dumbbell-shaped axle due to its inability to escape over the bulky end groups, resulting in a so-called mechanical bond. Interlocked molecules have mainly been studied as components of molecular machines, but the crowded, flexible environment created by threading one molecule through another, reminiscent of the active site of an enzyme, has also been explored in catalysis and sensing. However, so far the applications of one of the most intriguing properties of interlocked molecules, their ability to display stereogenic units that do not rely on the stereochemistry of their covalent subunits, termed "mechanical chirality", have yet to be properly explored and prototypical demonstration of the applications of mechanically chiral rotaxanes remain scarce. Here we describe a mechanically planar chiral rotaxane-based Au complex that mediates a cyclopropanation reaction with stereoselectivities that are comparable with conventional covalent catalyst reported for this reaction.

INTRODUCTION
Interlocked molecules such as rotaxanes, in which a dumbbell shaped axle is threaded through a macrocycle, and catenanes, in which two or more macrocycles are held together in a manner akin to links in a chain,1 are most commonly investigated as components of molecular machines,2 building on the pioneering work of Stoddart and Sauvage who were awarded the Nobel Prize for their efforts in 2016.3,4,5 In contrast, one of the most intriguing structural properties of interlocked molecules, their ability to display enantiotopic stereogenic elements that do not rely on covalent stereochemistry,6 has received much less attention, despite the possibility of such enantiomerism being discussed early in the development of the field.7,8 Such "mechanical" stereogenic units can arise due to desymmetrisation of one of the covalent sub-units by the relative position of the other (co-conformational chirality), the combination of sub-units with appropriate symmetry properties (conditional mechanical chirality) or due to the unconditional topology of the mechanical bond itself (Figure 1a).6

Figure 1. Different forms of chirality in mechanically and covalently bonded molecules
(A) Examples of i. co-conformational, ii. conditional mechanical and iii. unconditional topological stereogenic units.
(B) Examples of covalently bonded chiral acyl transfer catalysts based on i. point,9 ii. axial,10 iii. planar11 and iv. helical12 stereogenic units.

The relative paucity of even prototypical applications of mechanically chiral molecules is at least in part because enantiopure samples were historically hard to synthesize, with the pioneering work, carried out by Vogtle, Okamoto and Sauvage,11-14 requiring the use of chiral stationary phase HPLC to separate the enantiomeric products from a racemic mixture. Using this approach, Vogtle and co-workers showed that mechanically planar chiral rotaxanes and topologically chiral catenanes displayed strong electronic circular dichroism (CD),15 Hirose and co-workers disclosed a mechanically planar chiral rotaxane that selectively binds and senses the enantiomers of small chiral molecules,15 and Takata and co-workers demonstrated that the mechanically planar chiral stereogenic unit can direct the helical twist of a poly-diacylene material.16 More recently, Saito and co-workers demonstrated the separation of co-conformationally mechanically planar chiral rotaxanes and used the link between the rate of racemisation and co-conformational motion to determine the energy barrier for shuttling.17 and Credi and co-workers demonstrated a co-conformationally mechanically planar chiral molecule that shuttles between achiral and chiral states, the latter of which could be biased by the binding of a small chiral guest.18

However, of these unusual forms of stereochemistry, only co-conformational point chirality has been exploited in catalysis; in 2015 Leigh and co-workers demonstrated an enantioselective co-conformationally covalent point chiral organocatalyst (Figure 1A) that mediated enamine and iminium activation.19,20,21 In contrast, the full complement of covalent stereogenic units,22 including point,23 axial,24 planar25 and helical26 chiriotropic elements,27 have been applied in the development of new scaffolds to mediate enantioselective processes (Figure 1a) since the Nobel Prize was awarded in 2001 to Noyori, Knowles and Sharpless for their contributions to the development of enantioselective catalysis.28, 29, 30 Indeed, recent work has aimed at expanding the mechanisms by which stereochemical information is transferred to the reaction space including the use of chiral counterions,31 chiral-at-metal systems,32 helical artificial33 and natural34 polymers, chiral solvents,35 and chiral capsules.36

Building on our recent effort to improve access to mechanically chiral molecules through the use of chiral derivatizing units37,38 and auxiliaries,39 here we demonstrate the first example of enantioselective catalysis with a mechanically planar chiral rotaxane, one of the simplest conditional mechanical stereogenic units, which arises when an achiral C8 macrocycle encircles an achiral C4 axle.6 Our rotaxane catalyst displays enantioselectivities in an Au+ mediated cyclopropanation reaction comparable to previously reported covalent catalysts.40 Our results suggest that mechanical stereochemistry has untapped potential in the development of new enantioselective catalytic systems.
RESULTS AND DISCUSSION

Synthesis and Characterisation of Mechanically Planar Chiral Complex [Au6(Cl)]

To demonstrate the potential of mechanical stereochemistry in catalysis we selected a Au-mediated reaction for our study; Au-mediated reactions are inherently difficult to render enantioselective as a result of the linear coordination chemistry of the metal ion. These challenges are typically overcome through the use of large, monodentate ligands that project substituents into the reaction space, or the use of di-Au complexes in which aurophilic interactions pre-organise the complex with one metal ion playing the role of catalyst and the other of a structural unit. Given that we have previously shown that the mechanical bond can be used to project steric bulk around an Au centre, leading to highly diastereoselective catalysis, we proposed that similar effects might be observed in the case of a mechanically chiral derivative, leading to enantioselective catalysis.

Rotaxane Au complex [Au6(Cl)] was synthesised using our small macrocycle modification4 of Leigh’s active template4 Cu-mediated alkyne-azole cycloaddition reaction (AT-CuAAC), employing amino-acid derived azide 1 as a stereo-differentiating unit,46 borane protected propargylphosphine 2 as the alkyne coupling partner, and readily available C14(C1) symmetric macrocycle 3,47 as the key mechanical bond forming step. We typically carry out the AT-CuAAC reaction in the presence of excess NPr2Et, which accelerates the reaction by favouring the formation of the key macrocyclic-CuI-acetylide complex intermediate. However, in this case, NPr2Et was found to cause epimerisation of the azide stereocentre, resulting in a mixture of all four possible stereoisomeric products. Replacing NPr2Et with Potron Sponge® drastically reduced the epimerisation side reaction, allowing the mixture of diastereomeric phosphine oxides 4 to be separated with excellent stereochemical purity after demetallation and oxidative work-up. Using this sequence we were able to isolate rotaxanes (S,Rmp)-4 (e.r. = 99 : 1, d.r. > 99 : 1) and (S,Smp)-4 ((S,Smp)-4) (R,Smp)-4 = 98.4 : 1.0 : 0.6) in an acceptable combined yield of 54%. Alkylation of diastereomer (S,Rmp)-4 with BnI erased the covalent stereogenic unit to produce rotaxane (Rmp)-5 for which the mechanical bond provides the sole stereochemical unit in excellent yield and enantiopurity (81%, e.r. = 99 : 1). Subsequent reduction of the phosphine oxide moiety and coordination of AuCl produced AuI precatayst [Au{([Rmp]-6)(Cl)}], the enantiopurity of which was assumed to be the same as that of (Rmp)-5 (99 : 1 e.r.) as the mechanical bond is configurationally stable. The same procedures starting from (S,Smp)-4 produced [Au{([Smp]-6)(Cl)}] [1 : 99 e.r.].

![Scheme 1. Synthesis of Mechanically Planar Chiral Rotaxane Pre-Catalysts](image)

Reagents and conditions: 1. (i) [Cu(MeCN)]2PF6, 4H-sponge®, CH2Cl2, rt, 8 h; (ii) KCN, MeOH-CH2Cl2, [1 : 1], rt, 30 min; (iii) H2O2 (35%, w/v in H2O), CH2Cl2, rt, 5 min. 72% combined yield over 3 steps prior to separation of diastereomers. (S,Rmp)-4 30%, e.r. = 99 : 1, d.r. > 99 : 1; (S,Smp)-4 24%; (S,Smp)-4 (R,Smp)-4 = 98.4 : 1.0 : 0.6. 2. LiHMDS, THF, –78 ºC then, BnI, –78 to rt, 18 h. (Rmp)-5: 81% (99 : 1 e.r.); (Smp)-6 63% (1 : 99 e.r.; not shown; see ESI). 3. HSCl, N2H4, PhMe, CH2Cl2, 100 C, 3 d. 4. (Me)2AuCl, CH2Cl2, rt, 1 h. (Rmp)-5: 64% yield over two steps (e.r. = 99 : 1). (Smp)-6: 62% (e.r. = 1 : 99; not shown; see ESI).

Rotaxanes 4, 5 and 6 were isolated and characterised in full by NMR, MS, HPLC and CD (see ESI for full details). The absolute stereochemistries of phosphine oxides (S,Rmp)-4 and (S,Smp)-4 were assigned by single crystal x-ray diffraction (Figure 2A and 2B); the internal stereochemical reference provided by the azide-derived unit allowed the orientation of the macrocycle to be determined unambiguously and the stereochemical labels were assigned using our established approach.5 The absolute stereochemistry of rotaxanes 5 and 6 were inferred by noting that the mechanical stereochemistry of the corresponding diastereomeric starting materials cannot be altered in subsequent reactions.

The 1H NMR spectra of diastereomers (S,Rmp)-4 and (S,Smp)-4 (Figure 2Cii and 2Ciii respectively) display the typical features of such interlocked molecules,44 many of the signals corresponding to the axle and macrocycle components, including H2, H6, H8a, and H8b are shifted relative to the non-interlocked macrocycle (Figure 2Cii), and triazole proton H6 appears at high chemical shift due to the formation of an intercomponent C–H•••N hydrogen bond with the bipyrindine, as observed in the solid state structures (Figures 2A and 2B). However, their 1H NMR spectra are clearly distinct, in keeping with the diastereomeric relationship between the two products, as are their CD spectra (see ESI). Alkylation of rotaxanes 4 to give rotaxanes 5, produced materials with identical 1H NMR spectra (Figure 2Biv) but mirror image CD spectra (Figure 2D), in keeping with the enantiomeric relationship between these products. Strikingly, in addition to the expected shielding/deshielding of signals, the aromatic protons corresponding to the diastereotopic benzylic units of the axle in rotaxanes 5 are clearly distinct (e.g. benzyl methylene protons H7 and H8), suggesting that the stereochemistry of the mechanical bond is well expressed onto the axle.
Enantioselective Cyclopropanation Reactions Mediated by Rotaxane \([\text{Au}((R)\text{-SEGPHOS})\text{(AuCl)}]\)

With precatalyst \([\text{Au}((R)\text{-SEGPHOS})\text{(AuCl)}]\) in hand, we investigated its behaviour in the enantioselective Au\(^{+}\)-mediated variant of the Ohe-Uemura cyclopropanation of alkenes by propargylic esters originally reported by Toste and co-workers using \((R)\)-DTBM-SEGPHOS\(^{\circ}\)[AuCl] \(_2\) and resulting in stereoselectivities from 80 : 20 to 97 : 3 \(e.r.\). More recently, Fuerstner and co-workers reported a mono-dentate binol-derived phosphoramite ligand for the same reaction,\(^{40}\) and Toste and co-workers reported a reaction system that employs Au nanoclusters embedded in a chiral self-assembled monolayer.\(^{41}\)

Under conditions previously optimised for an analogous achiral rotaxane-based catalyst,\(^{43}\) \([\text{Au}((R)\text{-SEGPHOS})\text{(AuCl)}]\) mediated the reaction of benzoyl ester 7 with styrene 8 to produce cyclopropanes 9 in excellent selectivity for the \(cis\) diastereomer (Table 1, entry 1). The role of Cu\(^{+}\) additive is to bind to the bipyridine moiety, preventing the Lewis base inhibition of the Au\(^{+}\) centre; reactions mediated by \([\text{Au}((4)\text{-Cl})]\) in the absence of Cu\(^{+}\) were unsuccessful (entry 2) and other cationic additives failed to activate the catalyst (see ESI). Analysis of the purified major diastereomer by chiral stationary phase HPLC revealed reasonable enantioselectivity for \((15,28)\) 9 \(e.r. = 72 : 28\). As expected, replacing \([\text{Au}((R)\text{-SEGPHOS})\text{(AuCl)}]\) with \([\text{Au}((S)\text{-SEGPHOS})\text{(AuCl)}]\) produced 9 with opposite enantioselectivity (entry 3). Variation of the solvent led to changes in the observed \(e.r.\) of \(cis\)-9, but no significant improvement (entries 4-7). Cooling the reaction to 0 °C improved the \(e.r.\) of the major diastereomer to 78 : 22 (entry 8). Cooling the reaction mixture further led to no significant improvement and slowed the process considerably (entry 9). For comparison, the same reaction mediated by \((R)\)-DTBM-SEGPHOS\(^{\circ}\)[AuCl] reported by Toste and co-workers produces cyclopropanes 9 in moderately higher and opposite stereoselectivity (entry 10).\(^{40}\)

\((R)\)-DTBM-SEGPHOS\(^{\circ}\)[AuCl] was reported to deliver higher stereoselectivity with the pivaloyl derivative of propargyl ester 7.\(^{40}\) However, in the case of \([\text{Au}((R)\text{-SEGPHOS})\text{(AuCl)}]\), cyclopropane 10 was produced in lower stereoselectivity than 9 (Figure 3). This raised the question as to whether the reduced stereoselectivity was inherent to \(\alpha\)-alkyl esters or if \(\pi\)-interactions between the ester component and the ligand play a role in the stereoselectivity. Phenylacetic ester-derived cyclopropane 11 was produced in comparable selectivity to 9, suggesting that \(\alpha\)-alkyl esters are tolerated by \([\text{Au}((4)\text{-Cl})]\) and that \(\pi\)-interactions play a role in the stereoselectivity. Variation of the benzoyl moiety to introduce strongly electron withdrawing or donating groups (cyclopropanes 12 and 13 respectively) led to a slight reduction in reaction stereoselectivity. In contrast, bulky alkyl groups on the benzoate moiety increased the reaction stereoselectivity; \(\rho\)-Bu benzyl cyclopropane 14 and 3,5-di-\(\text{Bu}\) substituted cyclopropane 15 were produced in good yield and stereoselectivity. Finally, replacing styrene with an alkyl ester resulted in a drop in diastereoselectivity, as is typically observed,\(^{40}\) but cyclopropane \(cis\)-16 was still produced in reasonable enantioselectivity.
In brief (for full details see ESI), we began by locating the lowest energy transition state (Gaussian '09, CAM-B3LYP, 6-31G*/SDD(Au)) for the reaction of 7 with 8 mediated by [Au(ppy)2]Cl], building on previous work by Echavarren and co-workers in a similar reaction.53 In keeping with this previous report, the reaction of the carbene derived from 7 with styrene (8) was found to be a two-step process and we thus assumed a similar pathway for the reaction mediated by [Au(6)Cl]) (Figure 4A); coordination of Cu and abstraction of the Cl ligand gives rise to proposed active catalyst [AuCu(6)]54 which coordinates to alkyne 7 to give complex I that undergoes a rearrangement to produce key...
carbene intermediate II. Addition of styrene to II produces carbocation III via key transition state TS1, in the process setting the stereochemistry of C1 of the cyclopropane product. Subsequent rapid ring closure gives rise to cyclopropane 9 and regenerates the catalyst.

Figure 4. Reaction Pathway and Modelled Transition State Structures
(A) Reaction pathway determined by computational analysis (CAM-B3LYP, 6-31G*/SDD(Au)), for the reaction of 7 and 8 mediated by [Au(PPh3)3(Cl)] and presumed for the reaction of [Au(6)(Cl)] (shown). R = C(Bn)2CO:Pr;
(B) Modelled (CHCl3, CAM-B3LYP, 6-31G/SDD) structure of TS1 leading to (1R,2S)-9 for the reaction of 7 with 8 mediated by the Cu(I) complex of [Au((R)3]-6)1+ with selected intercomponent interactions highlighted (see ESI for more detail).
(C) Modelled (CHCl3, CAM-B3LYP, 6-31G/SDD) structure of TS1 leading to (1S,2R)-9 for the reaction of 7 with 8 mediated by the Cu(I) complex of [Au((R)3]-6)1+ with selected intercomponent interactions highlighted (see ESI for more detail).

In order to investigate the reaction mediated by rotaxane [Au(6)(Cl)], the transition state model found for the reaction mediated by [Au(PPh3)3(Cl)] was modified by attachment to the Cu(I)-coordinated rotaxane framework. A conformational search (Spartan '10, MMFF+) with the transition state fragment frozen yielded low energy conformers for each diastereomeric complex which were optimised using DFT (CAM-B3LYP, 6-31G/SDD(Cu,Au)), again with the transition state fragment frozen, to identify the lowest energy conformation. An Onioma calculation (CAM-B3LYP:UFF, 6-31G/SDD(Au)), followed by a full DFT optimisation of the whole unfrozen molecule (CAM-B3LYP, 631G/SDD(Cu,Au)) first in the gas phase then in solvent (CHCl3, polarizable continuum model) yielded transition state models (R<sub>max</sub>Re)-TS1 and (R<sub>max</sub>Si)-TS1 (Figures 4B and 4C respectively) that were determined to be first order saddle points with a single imaginary frequency.

Examining the models of (R<sub>max</sub>Re)-TS1 and (R<sub>max</sub>Si)-TS1 reveals that, in spite of its size and large number of rotatable bonds, the rotaxane framework is actually relatively rigid due to steric crowding combined with the coordination of the Cu(I). A complex network of short intra- and inter-component contacts, including CH hydrogen bonds, CHπ interactions and a cation–π interaction between the Cu(I) ion and one of the Ph rings of the phosphine ligand stabilises the system further and projects the Au(I) centre bearing the reactive carbene moiety towards the macrocycle, into the space around one of the phenoxyl ether moieties. It is perhaps noteworthy that the optimised structures are similar to the solid-state structures of rotaxanes 4 determined by x-ray diffraction in which the phosphine substituent (O) is also projected towards the Ar rings of the phosphine ligand, thus providing a sterically crowded environment that shields one face of the carbene unit, restricts the rotation of the substrate around the Au-P axis and pre-organises the substrates through non-covalent interactions, thus providing a well expressed chiral environment for the catalysis to take place within.
Finally, comparison of the calculated relative energies of \((R_{\text{exp}})-\text{TS1}\) and \((R_{\text{exp}})-\text{TS1}\) revealed remarkable agreement, given the size of the system, between experiment and theory; \((R_{\text{exp}})-\text{TS1}\) was found to be favoured by ~2.3 kJmol\(^{-1}\), corresponding to a stereoselectivity of 74 : 26 in favour of the major observed product \((S,2R)-9\). However, caution should be taken when interpreting this level of agreement; the equivalent gas phase models (6-31G(SD)) of \((R_{\text{exp}})-\text{TS1}\) and \((R_{\text{exp}})-\text{TS1}\) predicted the opposite stereoselectivity \((|R_{\text{exp}}|-\text{TS1})\) favoured by ~1.7 kJmol\(^{-1}\). Conversely re-optimisation in the gas or solution phase\(^{31}\) with a larger 6-31G* basis set resulted in a higher predicted selectivity for the correct diastereomer, demonstrating the uncertainty in the absolute values generated in such complex systems. Thus, the molecular models of \((R_{\text{exp}})-\text{TS1}\) and \((R_{\text{exp}})-\text{TS1}\) should be considered qualitative, providing some insight into the potential interactions and the chiral environment created by the mechanical bond around the reacting Au\(^+\) carbene. A more detailed study, combined with many more comparisons between experiment and theory, would be required to determine the details of the key intermolecular interactions that lead to the observed stereoselectivity.

CONCLUSIONS

Although the first enantiopure mechanically planar chiral rotaxane was reported over two decades ago\(^{32}\), this is, to our knowledge the first time that this stereogenic unit has been applied in catalysis. The results presented clearly demonstrate that the mechanically planar chiral stereogenic unit can direct enantioselective catalysis and further suggest that other mechanical stereogenic units\(^{33}\) such as the axial and topological chiral units in catenanes have potential catalytic applications. However, although the stereoselectivities observed in the cyclopropanation reaction studied are within striking distance of those reported previously using covalent catalysts,\(^{40}\) challenges obviously remain to be overcome if mechanically planar chiral rotaxanes are to become useful tools in organic synthesis. Most obviously, despite recent progress in the area,\(^{37,38,39}\) the synthesis of mechanically chiral interlocked molecules is still challenging, in this case specifically due to the low stereoselectivity observed in the mechanical bond forming step and the epimerisation of the unit derived from the \(\alpha\)-chiral azide, which although it allows the separation of the diastereomers, complicates the purification. Secondly, in order to allow new candidate structures to be designed, a clear understanding of the interactions leading to stereoselectivity would be extremely helpful. Based on the preliminary molecular modelling presented, it seems that modern computational chemistry may well be able to aid this process.

In the long term, we see a place for mechanical chirality in catalysis, particularly where it is otherwise challenging to project chiral information into the reaction space, as in the Au\(^+\)-mediated reaction presented here; it is clear that the crowded, three-dimensional nature of the mechanical bond is well suited to generating a chiral pocket for catalysis to take place within.\(^{54}\) Furthermore, combining chiral mechanical stereogenic units with the well-developed chemistry of interlocked molecular shuttles\(^{55,57}\) should allow the influence of the stereogenic mechanical bond to be modulated\(^{56}\) in a stimuli responsive manner in order to develop switchable chiral catalysts, for instance to produce both hands of a given chiral product.\(^{57}\) The same principles may also hold in the development of enantioselective sensors for chiral molecules.

What is clear, based on these results, is that the chemical applications\(^{60}\) of mechanically chiral interlocked molecules deserve further investigation.

SUPPLEMENTAL INFORMATION

Supplemental Information includes procedures and characterization data for rotaxanes 4, 5 and 6, cyclopropanes 9-16 and their precursors, as we as full details of the computational modelling carried out.

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AUTHOR CONTRIBUTIONS

S.M.G. conceived the project and secured project funding. A.W.H contributed to the design of experiments and methodology, and their execution. S.M.G. carried out the computational modelling. S.M.G. wrote the manuscript with input from A.W.H. and both authors contributed to the reviewing and editing of the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

REFERENCES AND NOTES

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