Communication

Asymmetric Catalysis with a Mechanically Point-Chiral Rotaxane

Yusuf Cakmak, Sundus Erbas-Cakmak, and David A. Leigh

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Asymmetric Catalysis with a Mechanically Point-Chiral Rotaxane

Yusuf Cakmak,‡ Sundus Erbas-Cakmak,‡ David A. Leigh*

School of Chemistry, University of Manchester, Oxford Road, Manchester, M13 9PL, United Kingdom

Supporting Information Placeholder

ABSTRACT: Mechanical point-chirality in a [2]rotaxane is utilized for asymmetric catalysis. Stable enantiomers of the rotaxane result from a bulky group in the middle of the thread preventing a benzylic amide macrocycle shuttling between different sides of a prochiral center, creating point chirality in the vicinity of a secondary amine group. The resulting mechanochirogenesis delivers enantioselective organocatalysis via both enamine (up to 71:29 er) and iminium (up to 68:32 er) activation modes.

Distinctive features imparted by the mechanical bonding in rotaxanes[1] (such as their dynamic properties and the ability of the ring to mask regions of the thread) are beginning to be investigated in various aspects of catalysis.[2-7] The position of the macrocycle on rotaxane threads has been used to conceal or expose amine groups that can promote different aminocatalysis activation modes[3] and threaded molecular structures have been exploited in processive[4] and sequence-specific[5] catalysis. A rotaxane has been demonstrated to be an effective chiral ligand in nickel-catalyzed Michael addition reactions[6] and a rotaxane complex was recently employed[7] in a gold-mediated cyclopropanation. In both of the latter two cases embedding the coordinated metal ion within the well-defined binding pocket of the rotaxane resulted in higher stereoselectivity of the products than when using the non-interlocked components as ligands (enantioselectivity in the case of the chiral rotaxane-nickel catalyst;[6] diastereoselectivity with the achiral rotaxane-gold catalyst[7]). However, to date asymmetric catalysis with rotaxanes has only utilized conventional chiral elements.[2b,2f,3b,6,7] Here we report on the use of a previously unexplored feature of rotaxane architectures in catalysis, that of chirality induced by the mechanical bond.[8,9]

The chemical structures of the rotaxane, (*S*)-**1**, and its parent thread, **T1**, are shown in Figure 1. Thread **T1** is achiral, possessing a mirror place through the prochiral center labeled C_{11}. In the rotaxane, however, the bulky 4-tolylamine group (shown in red, Figure 1) prevents macrocycle shuttling between the two succinamide stations (shown in green) resulting in a loss of symmetry. Accordingly, rotaxane (*S*)-**1** has a center of point chirality (C_{11}) with the two succinamide groups of the thread in different chemical environments, one accessible to the macrocycle and one not. Establishing point chiral centers through mechanical bonding is rare[10] and chiral systems of this type have not previously been investigated for potential applications.

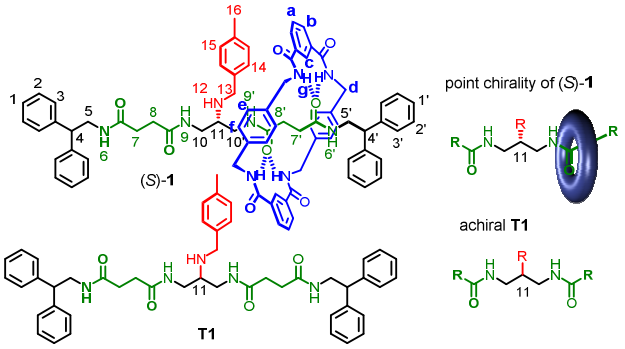
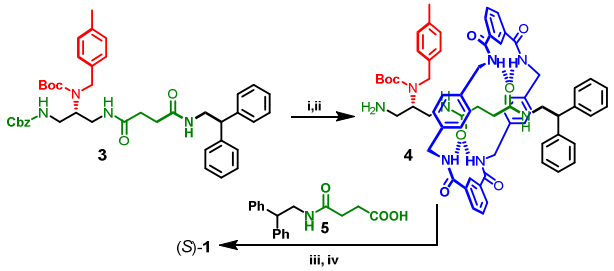


Figure 1. Chemical structures of rotaxane (*S*)-**1** and thread **T1**, showing the mechanically induced chirality of the rotaxane. The carbon labelled C_{11} is a prochiral center in the non-interlocked thread (**T1**) but a chiral center in the rotaxane ((*S*)-**1**) as the 4-tolylamine group blocks shuttling of the macrocycle to the other side of the thread.

Two rotaxanes, (*S*)-**1** with the 4-tolylamine group and (*S*)-**2** bearing an analogous 3,5-bis(trifluoromethyl)benzylamine barrier, were prepared in enantioenriched form (84 % *ee* in each case, as indicated by chiral HPLC, see Supporting Information) by unambiguous synthetic routes (see Supporting Information). In each rotaxane synthesis the key steps involve the five-component macrocyclization about a chiral succinamide thread (e.g. **3**) to form a [2]rotaxane intermediate (e.g. **4**), followed by extension of the stopper (with **5**) to form the second, inaccessible, succinamide group of the axle, shown in Scheme 1 for the synthesis of (*S*)-**1**.

Scheme 1. Synthesis of mechanically point-chiral rotaxane (*S*)-1.[a]



[a]Reagents and conditions: (i) Isophthaloyl chloride, *p*-xylylenediamine, NEt_3, $CHCl_3$, RT, 20 h, 33 %; (ii) Pd/C, H_2, CH_2Cl_2, MeOH, RT, 16 h, 91 %; (iii) **5**, *N*,*N*′-dicyclohexylcarbodiimide, dimethylaminopyridine, THF:CH_2Cl_2, RT, 16 h, 81 %; (iv) CF_3CO_2H, CH_2Cl_2, RT, 12 h, 73 %.

Comparison of the ^{1}H NMR spectrum of rotaxane (*S*)-**1** with that of the component thread, **T1,** in CD_2Cl_2 shows an upfield shift of one set of succinamide CH_2CH_2 protons ($\Delta\delta$H = –1.25 ppm) in the rotaxane due to shielding by the aromatic rings of the encapsulating macrocycle (Figure 2, $H_{7,8}$ in the thread splits into two sets of protons, $H_{7,8}$ and $H_{7',8'}$, in the rotaxane). This is a result of the amine group being too bulky for the macrocycle to pass.

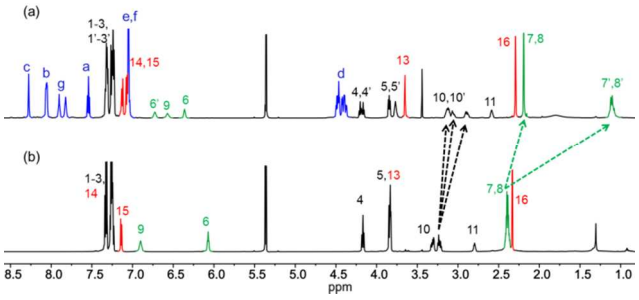
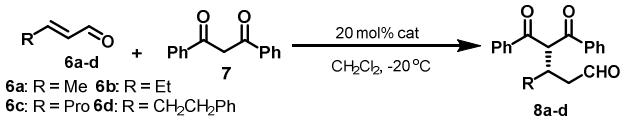


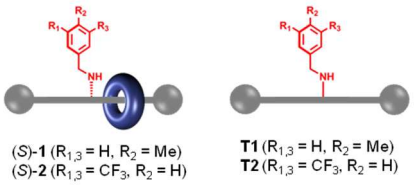
Figure 2. ^{1}H NMR Spectra (600 MHz, CD2Cl2, 298 K) of (a) rotaxane (*S*)-**1** and (b) thread **T1**. The letter, number and color assignments correspond to those shown in Figure 1.

Desymmetrization of the rotaxane axle through the mechanically locked location of the macrocycle creates point chirality at carbon C_{11}. The circular dichroism (CD) spectrum of (*S*)-**1** in $CHCl_3$ confirms this mechanical chirogenesis (Figure S3). In contrast, the achiral thread, **T1**, does not display a CD response.

Space-filling models of rotaxane (*S*)-**1** suggest that the presence of the macrocycle on one side of the axle should create a well-expressed chiral environment around the amine group (Figure S4). We therefore investigated the efficacy of the chiral rotaxane in asymmetric organocatalysis, firstly through iminium activation with the Michael addition of 1,3-diphenyl-1,3-propanedione to α,β-unsaturated aldehydes (Table 1). At -20 °C in CH_2Cl_2 using 20 mol% of the achiral threads as catalyst (**T1** and **T2**), we obtained a racemic mixture of products (entries 1 and 6, Table 1). In contrast, using (*S*)-**1** as catalyst, we obtained an excess of the (*S*)-Michael adducts (entries 2-5, Table 1). Aldehydes with smaller alkyl substituents (e.g. **6**) gave the best enantiomeric ratios, the best being 68:32 (R = Me) in favor of (*S*)-product (entry 2, Table 1). Rotaxane (*S*)-**2**, which possesses a different aryl substituent, gave similar enantioselectivities (entry 7, Table 1). Decreasing the polarity of the reaction solvent (CH_2Cl_2) by adding less polar solvents (CCl_4, Et_2O, $PhCH_3$) had no significant effect on the enantiomeric ratio of the products (Table S1). Decreasing the reaction temperature below -20 °C led to modest increases in enantioselectivity (69:31 *er* for **8a**), whereas at room temperature racemic mixtures of products were obtained (Table S2).

Table 1. Enantioselective Michael addition of 1,3-diphenyl-1,3-propanedione to α,β-unsaturated aldehydes via iminium catalysis using rotaxanes (*S*)-1, (*S*)-2, and the parent threads T1 or T2 as catalysts.

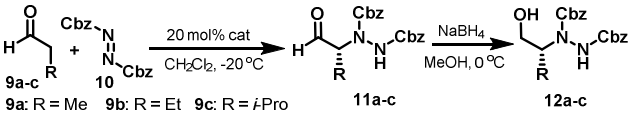


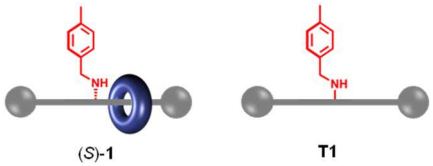


entry[a]	cat.	R (**6**)	conv. (%) (24/48 h)[b]	*er* of **8** (*S*:*R*)[c]
1	**T1**	Me	63/95	50:50
2	(*S*)-**1**[d]	Me	50/77	68:32
3	(*S*)-**1**[d]	Et	-/58	58:42
4	(*S*)-**1**[d]	Pr	-/36	55:45
5	(*S*)-**1**[d]	CH_2CH_2Ph	90/-	57:43
6	**T2**	Me	29/44[e]	50:50
7	(*S*)-**2**[d]	Me	70/95	67:33

[a]Reactions were run with 12.5 μmol **7**, 25.0 μmol unsaturated aldehyde (**6a-d**) in 50 μl of CH_2Cl_2 at -20 °C with 20 % catalyst loading. [b]Conversions estimated by ^{1}H NMR. [c]*er* values determined by HPLC after 24 h. [d]84 % ee. [e]Low conversions with the **T2** catalyst may be due to the poor solubility of this compound in the reaction medium.

Table 2. Enantioselective enamine catalysis by (*S*)-1 or T1: Asymmetric α-amination of aldehydes with dibenzyl azodicarboxylate.





entry[a]	cat.	R (**9**)	conv. (%)[b]	*er* of **12** (*S*:*R*)[c]
1	**T1**	Me	>95	50:50
2	(*S*)-**1**[d]	Me	>95	70:30
3	(*S*)-**1**[d]	Et	>95	71:29
4	(*S*)-**1**[d]	*i*-Pr	>95	67:33

[a]Reactions were run with 12.5 μmol **10**, 25.0 μmol unsaturated aldehyde (**9a-c**) in 50 μl of CH_2Cl_2 at -20 °C with 20% catalyst loading. After 24 h, reactions were quenched with MeOH and excess $NaBH_4$

at o °C. [b]Conversions are for compound **11**, estimated by ^{1}H NMR. [c]*er* values determined by HPLC after 24 h. [d]84 % *ee*.

To investigate the effectiveness of these mechanically point-chiral catalysts using a different activation mode, we examined the efficacy of (*S*)-**1** in an enamine-mediated α-amination reaction (Table 2). Dibenzyl azodicarboxylate (**10**) was employed as a nitrogen electrophile and reacted with aldehydes possessing various substituents (**9a-c**, Table 2). Due to the configurational instability of the α-aminated products (**11a-c**), the enantioselectivity of the rotaxane-catalyzed reaction was assessed after reduction to the corresponding alcohol (**12a-c**).[11] The result was enantiomeric ratios of up to 71:29 *er* (entry 3, Table 2), similar to those obtained in the iminium activation mode catalyzed reaction (Table 1).

The point chirality previously exploited in asymmetric catalysis has invariably arisen from four different covalent groups attached to the tetrahedral center. Our results show that point chirality induced by mechanical bonding between an achiral macrocycle and an achiral thread can also be used to generate a chiral space suitable for asymmetric catalysis. We anticipate that the expression of mechanically generated chirality for asymmetric catalysis, either by ligated metals or through organocatalysis, may be further enhanced through the structural optimization of the rotaxane components.

ASSOCIATED CONTENT

Supporting Information

Additional figures and tables, experimental details, synthetic procedures and characterization data are available in The Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

david.leigh@manchester.ac.uk

Author Contributions

‡These authors contributed equally.

Notes

The authors declare no competing financial interests.

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Table of Contents entry