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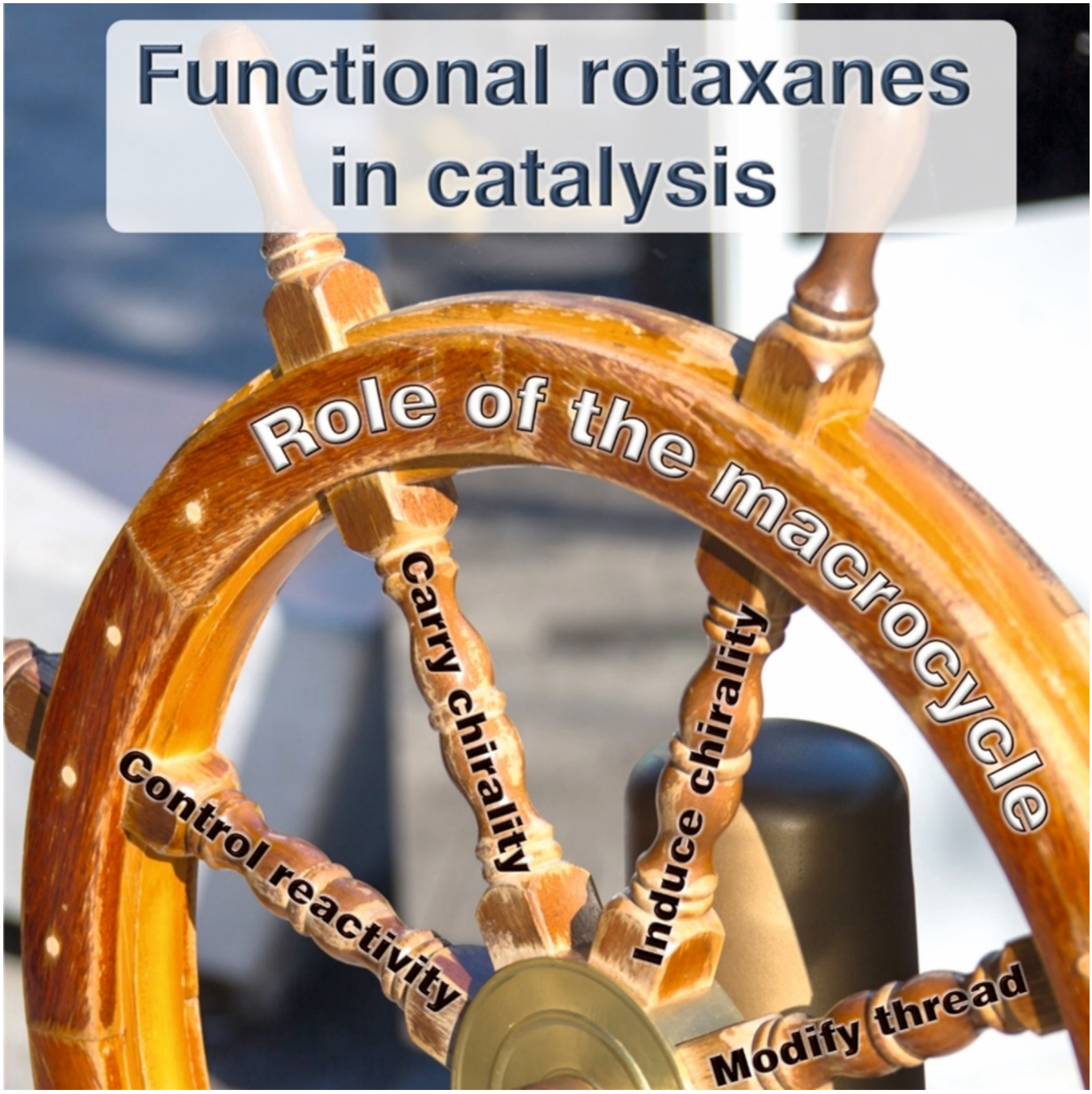
Macrocycles |*Reviews Showcase*|

Functional Rotaxanes in Catalysis

Carel Kwamen and Jochen Niemeyer*[a]

In memory of Prof. Carsten Schmuck.



Abstract: Mechanically interlocked molecules (MIMs) have gained attention in the field of catalysis due to their unique molecular properties. Central to MIMs, rotaxanes are highly promising and attractive supramolecular catalysts due to their unique three-dimensional structures and the flexibility of their subcomponents. This Minireview discusses the use of rotaxanes in organocatalysis and transition-metal catalysis.

1. Introduction

Next to catenanes[1] and molecular knots,[2] rotaxanes are a subclass of mechanically interlocked molecules (MIMs).[3] Rotaxanes consist of a macrocycle, which is threaded on a linear molecular component (thread or axle), where the dissociation of both components is prohibited by large stoppers at the termini of the thread. While higher [*n*]rotaxanes may contain several macrocycles and/or threads, [2]rotaxanes with one macrocycle and one thread are the most commonly employed version (and probably the most commonly employed type of MIMs in general). Rotaxanes have several advantages that make them highly attractive. Since the pioneering synthesis of Harrison in the late 1960's,[4] the amazing properties of these molecules have contributed immensely to the growing interest of the scientific community to explore and develop potential applications.[5–11] Nowadays, rotaxanes have been used for the design of nanoscale devices and functional molecular systems (drug delivery systems,[5] sensors[6] and responsive materials[7]) and molecular machines (muscles,[8] shuttles,[9] rotors[10] and switches[11]) among many others. The importance of this captivating area was acknowledged by the award of the 2016 Nobel Prize in Chemistry to Jean-Pierre Sauvage, Sir J. Fraser Stoddart and Bernard L. Feringa for their work on molecular machines.[12] Another promising application for rotaxanes, which has found growing attention in the last years, is the field of catalysis. Rotaxanes are particularly attractive for an application in catalysis for several reasons: They possess unique three-dimensional structures that can be used to create confined spaces for catalysis.[13] Their subcomponents are flexible with regard to their co-conformations, which allows the design of switchable systems.[14] The mechanical linking of subcomponents can be used to spatially arrange multiple functional groups.[15] Last but not least, rotaxanes can display a mechanical chirality[16] even in the absence of any classical element of chirality, which makes them interesting candidates for stereoselective catalysis.[17] The numerous and diverse recent research efforts in this arena led to the development of rotaxanes as organocatalysts and as ligands in metal-catalysed processes.[18] In this review, we summarise and discuss the recent advances in the application of rotaxanes in the field of catalysis. Thus, we provide a concise description based on the type of catalysis: starting with rotaxanes in organocatalysis (chapter 2) and followed by rotaxanes in transition-metal catalysis (chapter 3). We will classify the different examples based on the function of the rotaxane macrocycle in each specific case (vide infra), trying to shed light on the conceptual developments and the mechanistic details of the rotaxane-catalysts developed so far. Although highly interesting in its own right, this review will not discuss such processes where catalytic reactions are used for the synthesis of rotaxanes, such as the active-template approach and related works.[19]

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2. Rotaxane-based Organocatalysts

Known for more than a century now, the field of organocatalysis has considerably flourished over the past two decades and is now widely accepted as one of the main branches of chemical catalysis.[20] Rotaxanes have recently been established as a novel class of organocatalysts: Oftentimes they inherently feature functional groups that are suitable for organocatalysis (e.g. nucleophilic secondary amines that stem from the template synthesis), or they can easily be functionalised with suitable catalytically active groups. In this chapter, we will discuss selected examples of rotaxane-catalysts, grouped by the role of the macrocyclic component. To this end, the macrocyclic unit can have different functions, such as controlling reactivity (chapter 2.1), carrying of chiral information (chapter 2.2), introduction or modulation of chirality (chapter 2.3) and finally the use of the thread as the reaction substrate (chapter 2.4). Further examples are not fully discussed, such as examples where the macrocycle has no significant influence on the reaction outcome or where reaction products and macrocyclic catalysts form rotaxane-type structures.[21]

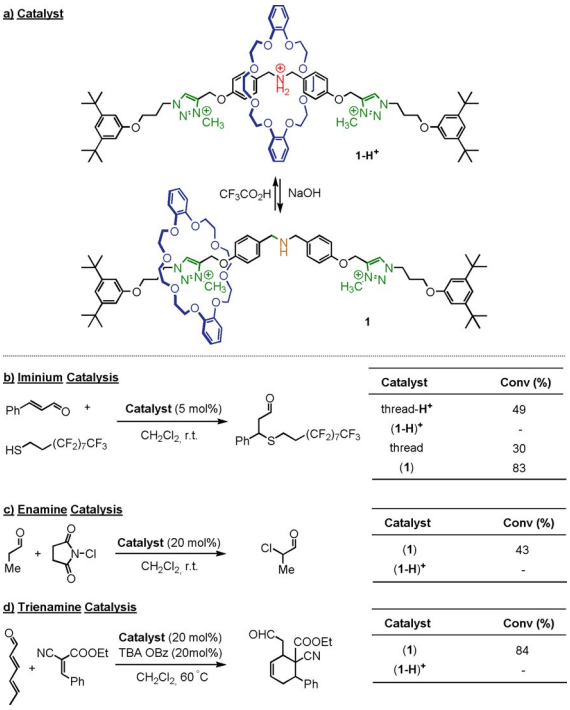
2.1. Macrocycle controls reactivity

Although [2]rotaxanes are characterised by a free movement of the macrocycle along the thread (or parts of it), many rotaxanes feature a preferred station (or recognition site) for the macrocycle. Oftentimes, this recognition site stems from their template synthesis (e.g. an ammonium-group which was used for templation of a crown-ether macrocycle), but it remains in the final rotaxane and thus thermodynamically favours one co-

conformation of the rotaxane. However, some rotaxanes may contain two (or more) stations for their macrocycle. The binding choice of the macrocycle to either of the recognition sites depends on the strength of the bonding interactions, so that the time-averaged preferred station is that with the stronger interaction (or higher association constant) to the macrocycle. In such a case, the use of a chemical or physical external stimulus can reversibly alter the association constants. Depending of the type of station, such an external stimulus can be of chemical, electrochemical, or even photochemical nature.

A switchable rotaxane-catalyst (**1**), which performs a shuttling motion in response to an external stimulus, was developed by Leigh in 2012 (Scheme 1).[22] Leigh's system consisted of a dibenzo-24-crown-8 macrocycle which could either be stationed at the central ammonium moiety (favoured for protonated thread) or at the peripheral triazolium moiety (favoured for deprotonated thread). Thus, addition of acid or base permits an *on-off* switching of the catalytic activity of the rotaxane (Scheme 1 a).

Applied for the Michael addition of an aliphatic thiol to *trans*-cinnamaldehyde (Scheme 1 b), the catalyst could be effectively switched between the *on*-state (**1**) where the catalyst site is revealed and the *off*-state (**1-H**)$^+$ in which the catalyst site is concealed. While the protonated catalyst (**1-H**)$^+$ showed no conversion after 5 days, its corresponding non-interlocked ammonium thread provided 49 % conversion. This shows that protonation alone is not sufficient for complete *off*-switching, but only the additional binding of the macrocycle completely shuts down the catalytic activity (possibly by decreasing the acidity of the ammonium-group). When deprotonated, both the secondary amine catalyst (**1**) and its non-interlocked counterpart could effectively catalyse the reaction with 83 % and 30 % conversion, respectively.



Scheme 1. a) Leigh's switchable rotaxane organocatalyst: Acid-base control over the position of the macrocycle on the axle between the protonated (*off* state) and deprotonated (*on* state). b) Michael addition of an aliphatic thiol to *trans*-cinnamaldehyde via iminium catalysis with the rotaxane and the thread as catalyst. c) Nucleophilic addition of aldehydes to *N*-chloro-succinimide via enamine catalysis. d) Diels–Alder reaction of 2,4-dienals to cyanoacetates via the trienamine activation.

Two years later, Leigh and co-workers also showed that this same catalyst could act through different activation mechanisms (Scheme 1).[23] Depending on the binding interactions and the exposure of the catalytic site, different activation modes could be identified for the organocatalyst (**1**). Apart from the Michael addition, which was performed via iminium catalysis, the organocatalyst (**1**) was shown to promote the nucleophilic addition of aldehydes to *N*-chloro-succinimide via enamine catalysis (Scheme 1 c) and the Diels-Alder reaction of 2,4-dienals to cyanoacetates via trienamine activation (Scheme 1 d). In all cases, the *off*-state protonated catalyst (**1-H**)$^+$ showed little to no reactivity whereas the *on*-state deprotonated one (**1**) showed catalytic activity with moderate to excellent yields.

Few years later, further studies on the same organocatalyst led to the discovery of its dual functionality (Scheme 2).[24] In its protonated form, organocatalyst (**1-H**)$^+$ was shown to act as an anion binding catalyst in which the exposed triazolium units in a bent conformation act as the anion binding site (Scheme 2 a). Used for both the Ritter reaction of bromodiphenylmethane and the reaction of 1-chloroisochroman with a silyl ketene acetal (Scheme 2 b), the deprotonated organocatalyst (**1**) proved inactive while the protonated rotaxane (**1-H**)$^+$

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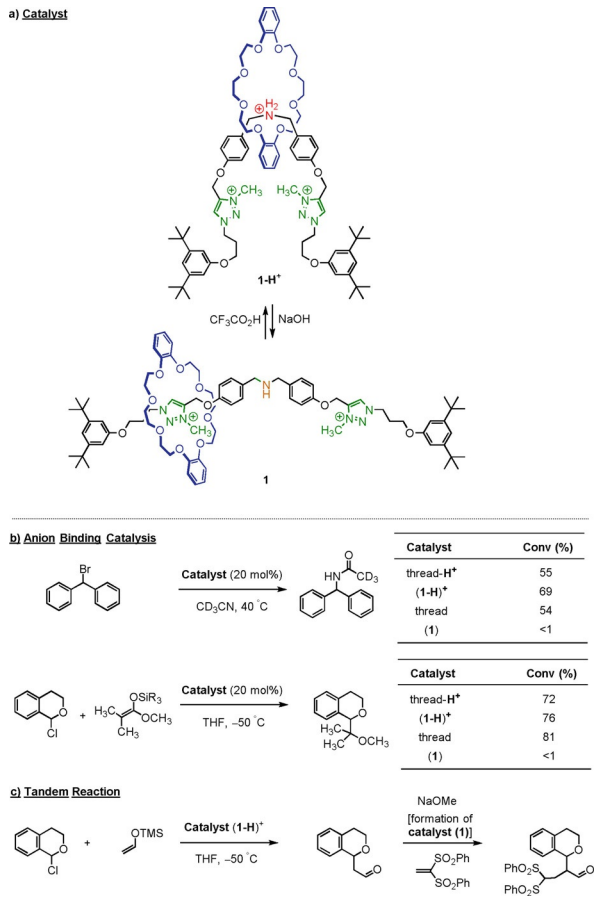
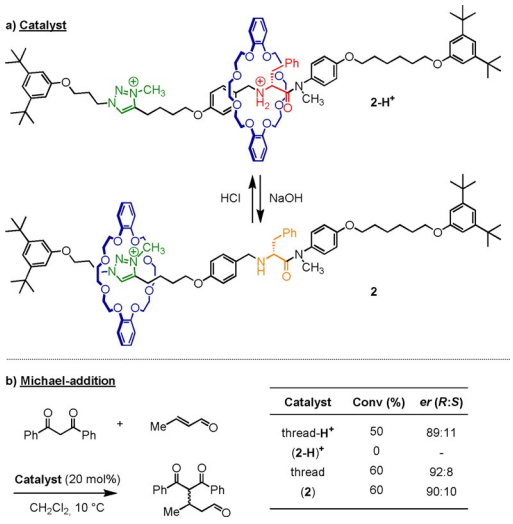
Jochen Niemeyer studied chemistry at the University of Muenster (Germany) and obtained his PhD in 2009 in the group of Prof. Gerhard Erker. After postdoctoral work with Prof. Simon Aldridge in Oxford (2010–2011), he worked in the R&D department of Evonik Industries AG. In 2014, Jochen started his independent career at the University of Duisburg-Essen (Germany) and has since been working on the development of supramolecular chemosensors and interlocked organocatalysts. His research has been awarded with the Thieme Chemistry Journal Award in 2018 and the research prize of the Dr. Otto Röhm Foundation in 2019.



Catalyst	Conv (%)
thread-H+	55
(1-H)+	69
thread	54
(1)	<1

Catalyst	Conv (%)
thread-H+	72
(1-H)+	76
thread	81
(1)	<1

Scheme 2. a) Leigh's switchable rotaxane catalyst: Acid-base control over the position of the macrocycle on the axle between the protonated and deprotonated states of the rotaxane catalyst. b) Anion binding reactions with the rotaxane and the thread as catalyst. c) Tandem reaction with the switchable rotaxane $(\mathbf{1\text{-}H})^+$.



Catalyst	Conv (%)	er (R:S)
thread-H+	50	89:11
(2-H)+	0	-
thread	60	92:8
(2)	60	90:10

Scheme 3. a) Leigh's chiral rotaxane organocatalyst: Acid-base control over the position of the macrocycle on the axle between the protonated and deprotonated states of the rotaxane catalyst. b) Michael addition of 1,3-diphenyl-1,3-propanedione to (*E*)-crotonaldehyde with either the rotaxane or the thread as catalyst.

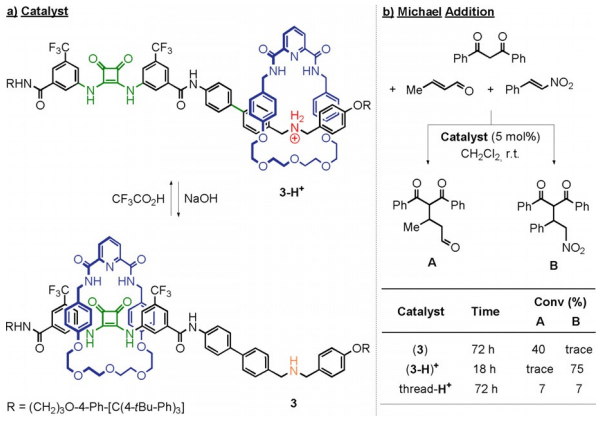
and the non-interlocked thread (in both the protonated and deprotonated forms) showed relatively high efficiency with high conversions. Applied for a one-pot, two-step tandem reaction with the ability to be switched between two catalytic states, the rotaxane organocatalyst favours different reactions depending on the revealed or concealed catalytic sites. The catalyst $(\mathbf{1\text{-}H})^+$ facilitates the reaction between 1-chloroisochroman and TMS-protected vinyl alcohol by anion-binding catalysis providing an α-substituted acetaldehyde derivative. This is then activated via enamine-catalysis by the deprotonated form of the catalyst, resulting in its reaction with vinyldisulfone to yield the α,α-disubstituted aldehyde product (Scheme 2c).

Meanwhile in 2014, the same group reported a chiral version of their switchable organocatalyst (Scheme 3). Similarly to the previous rotaxane (**1**), the rotaxane catalyst (**2**) consists of a dibenzo-24-crown-8 macrocycle which can be translocated between the triazolium ring and the chiral acyclic secondary amine contained on the axle (Scheme 3a).[25] Effectively switched between the *off*-mode $(\mathbf{2\text{-}H})^+$ where the macrocycle blocks the amine catalytic group and the *on*-mode (**2**) where the macrocycle stays on the triazolium unit, the rotaxane catalyst was applied for the asymmetric Michael addition of 1,3-diphenyl-1,3-propanedione to (*E*)-crotonaldehyde (Scheme 3b). With the protonated catalyst $(\mathbf{2\text{-}H})^+$, no conversion takes place after 24 hours of reaction while the corresponding non-interlocked thread provides 50% conversion with a 89:11 enantiomeric ratio. When deprotonated, both the *on*-state catalyst (**2**) and its corresponding non-interlocked thread give 60% conversion with similar enantioselectivities of 90:10 for (**2**) vs. 92:8 for the thread. Thus, the presence of the macrocycle does not influence the stereoselectivity of the catalyst, as might be expected due to the large distance between the two stations, but it does allow for an effective *on*/*off*-switching.

In 2015, Leigh and co-workers reported the first example of a switchable rotaxane catalyst in which the translocation of the macrocycle between two catalytically active groups permits a change in the substrate selectivity (Scheme 4).[26]

They developed a rotaxane consisting of a pyridine-dicarboxamide macrocycle and a thread featuring both an amine/ammonium- and a squaramide group (Scheme 4a). The rotaxane can be effectively switched between two states: In the protonated state $(\mathbf{3\text{-}H})^+$ the ammonium unit is the preferred station of the macrocycle leaving the revealed squaramide group to act as catalytic group through hydrogen bond activation. In the deprotonated state (**3**) the macrocycle binds the squaramide group leaving the secondary amine to act as catalyst through iminium or enamine activation.

To investigate its catalytic activity, the rotaxane was tested on the Michael addition of a mixture of 1,3-diphenyl-propane-1,3-dione, crotonaldehyde and *trans*-ß-nitrostyrene (Scheme 4b). Depending on the revealed catalytic site on the rotaxane, the 1,3-diphenylpropan-1,3-dione reacts either with the crotonaldehyde or the *trans*-β-nitrostyrene thus giving rise to different products. While the protonated form $(\mathbf{3\text{-}H})^+$ with the exposed squaramide unit promotes the reaction of *trans*-β-



Catalyst	Time	Conv (%) A	Conv (%) B
(**3**)	72 h	40	trace
(**3-H**)$^+$	18 h	trace	75
thread-**H**$^+$	72 h	7	7

Scheme 4. a) Leigh's switchable rotaxane catalyst: Acid-base control over the position of the macrocycle on the axle between the protonated and deprotonated states of the rotaxane catalyst. b) Michael addition reactions through either hydrogen-bond activation or iminium catalysis with either the rotaxane or the thread as catalyst.

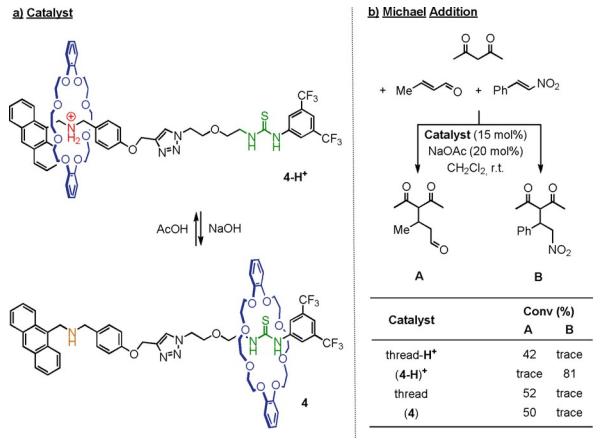
nitrostyrene via hydrogen-bond activation with a 75% conversion, the deprotonated catalyst (**3**) with the revealed secondary amine fosters the reaction of the crotonaldehyde via iminium catalysis with a 40% conversion. In each case, the rotaxane permits a complete control of selectivity as the other products are found only in traces. Meanwhile the less selective free thread promotes the reaction of both electrophiles providing a 1:1 mixture of both products with low conversion (7% each).

One year later, Leung reported a similar rotaxane (**4**) composed of an amine and a thiourea-station (Scheme 5).[27] Here also, the translocation of the macrocycle allows different activation mechanisms based on the available catalytic sites (Scheme 5a). With a similar set of reactants as in the case of Leigh, the protonated form (**4-H**)$^+$, in which the thiourea unit is exposed, promotes hydrogen bond donor catalysis of the nitroolefin with 81% conversion. The deprotonated catalyst (**4**), in which the secondary amine is revealed, promotes iminium catalysis with 50% conversion. In contrast, both the protonated and deprotonated forms of the thread favour the iminium process with moderate conversions of 52% and 42% respectively (Scheme 5b). The special feature of the Leung system is the presence of the fluorescent anthracene unit, which signals the current switching state of the catalyst. In the deprotonated form, the fluorescence is quenched by photo-electron-transfer from the secondary amine, while the fluorescence is switched on in the protonated state.

Berna and co-workers later introduced a photoswitchable rotaxane system composed of an amide-based macrocycle which can be shifted between the fumaramide station and the thiodiglycol amide station of the thread (Scheme 6).[28] In the (*E*)-form, the macrocycle preferentially binds the fumaramide station while its (*Z*) isomer, reversibly obtained by light irradiation, preferentially locates the macrocycle at the thiodiglycol amide unit.

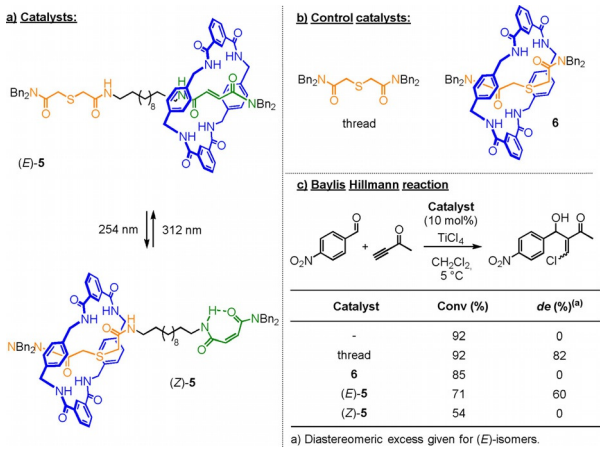
In the titanium mediated Baylis–Hillman reaction between aldehydes and alkynes, the reaction in absence of a sulfide-based co-catalyst yields the product in good yield, but without diastereoselectivity. Adding the thread gives a considerable stereoselectivity (82% *de*), with the sulfide acting as a nucleophilic organocatalyst. This reactivity is shut down in the control catalyst (**6**), where the macrocycle is permanently located around the sulfide. However, the rotaxane (**5**) allows for an efficient switching: In the (*E*)-form, the macrocycle occupies the fumaramide station, so that the sulfide can act as nucleophile, resulting in 60% *de* for the catalytic reaction. Photoswitching to the (*Z*)-form leads to complete loss of stereoselectivity, since the sulfide-station is now blocked (Scheme 6b).

Beer and co-workers investigated the use of rotaxanes for the ring-opening polymerisation (ROP) of *rac*-lactide (Scheme 7).[29] Their study was based on rotaxanes bearing a crown ether macrocycle and a thread featuring an ammonium station together with an additional thiourea or triazole moiety (Scheme 7a). In the protonated form of the rotaxane, the macrocycle binds to the ammonium unit while in the deprotonat-



Catalyst	Conv (%) A	Conv (%) B
thread-**H**$^+$	42	trace
(**4-H**)$^+$	trace	81
thread	52	trace
(**4**)	50	trace

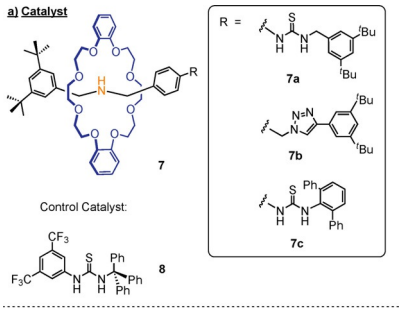
Scheme 5. a) Leung's fluorescent rotaxane: Acid-base control over the position of the macrocycle on the axle between the protonated and deprotonated states. b) Michael addition reactions through either hydrogen-bond activation or iminium catalysis with either the rotaxane or the thread as catalyst.



Catalyst	Conv (%)	*de* (%)[a]
-	92	0
thread	92	82
6	85	0
(*E*)-**5**	71	60
(*Z*)-**5**	54	0

a) Diastereomeric excess given for (*E*)-isomers.

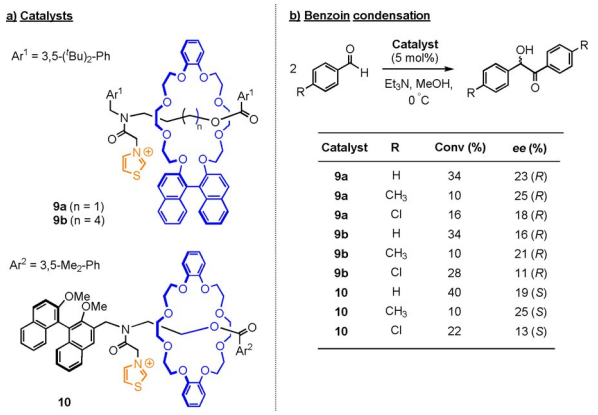
Scheme 6. a) Berna's photoswitchable rotaxane: Irradiation control over the position of the macrocycle on the axle between the olefinic diamide and the thiodiglycol amide units of the rotaxane catalyst. b) Control catalysts, c) Baylis–Hillman reaction with either the rotaxane or the thread as catalyst.



b) Polymerisation of *rac*-lactide

Catalyst	Time (h)	Conv (%)	P_i[d]
7a	96	80	0.81±0.03
7b	11	80	0.66±0.03
7c	3	90	0.73±0.02
8	5	98	0.69±0.01

Scheme 7. a) Beer's rotaxane and control catalysts for the ROP of *rac*-lactide. b) Polymerisation results with the different catalysts.



Catalyst	R	Conv (%)	ee (%)
9a	H	34	23 (*R*)
9a	CH_3	10	25 (*R*)
9a	Cl	16	18 (*R*)
9b	H	34	16 (*R*)
9b	CH_3	10	21 (*R*)
9b	Cl	28	11 (*R*)
10	H	40	19 (*S*)
10	CH_3	10	25 (*S*)
10	Cl	22	13 (*S*)

Scheme 8. a) Takata's chiral rotaxanes with thiazolium-groups. b) Asymmetric benzoin condensation with the different rotaxane-catalysts.

ed form, the macrocycle becomes weakly bound to the amine with the possibility of moving freely along the axle. This leads to an *on*-switching for catalysis. Applied for the ROP of *rac*-lactide, both the control catalyst (**8**) and the rotaxane catalyst (**7c**) gave satisfactory yields after only 3–5 h while the others (**7a**,**b**) required longer reaction times. These differences are attributed to the relative occupancies of the macrocycle at the catalytically active amine-site in the different catalysts. Interestingly, the rotaxanes with the thiourea moiety (**7a**/**c**) showed relatively higher isoselectivity (P_i) compared to the triazole-based rotaxane (**7b**) and the control catalyst (**8**) (Scheme 7b).

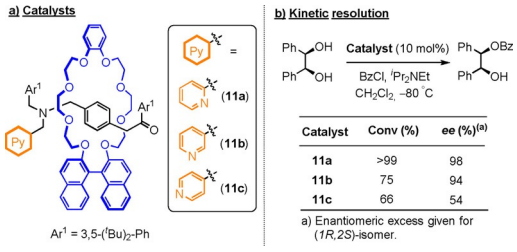
2.2. Macrocycle carries chiral information

Important for many applications, enantiomerically pure compounds are frequently obtained by asymmetric catalysis in which a chiral catalyst transmits its chiral information to the new molecules. In the case of a rotaxane catalyst, the chiral information can be present on one component (e.g. the macrocycle), while the catalytically active group can be present on the other component (e.g. the thread). Due to the spatial proximity of both components, this still allows stereoselective catalysis, with the transfer of chiral information brought about by the mechanical bond.

The first chiral catalytically active rotaxane catalyst was reported in 2004 by Takata and co-workers (Scheme 8).[30] They described the asymmetric benzoin condensation using a rotaxane with a catalytically active thiazolium unit on the thread. The chiral information was introduced via a 1,1′-binaphthyl-2,2′-diol (BINOL) unit, which was either integrated in the macrocycle (catalysts **9a**/**b**) or attached to the thread (catalyst **10**). In general, only moderate conversions and stereoselectivities were observed. Interestingly, the position of the BINOL-unit has a profound influence on the stereoselectivity: Rotaxane (**10**) featuring an achiral macrocycle and a chiral thread favours the formation of the (*S*)-products. In contrast, the rotaxanes (**9a**/**b**), which feature a chiral macrocycle, preferably gave the (*R*)-products, independent on the length of the thread (Scheme 8b).

In 2016, the same group reported on a novel rotaxane-type asymmetric catalyst based on the same design-principle (Scheme 9).[31] Rotaxanes **11a**/**b**/**c** consist of a BINOL-based crown ether macrocycle (responsible for the introduction of chirality) and a thread containing a nucleophilic pyridine group (Scheme 9a). The influence of the position of the nucleophilic nitrogen relatively to the linker connecting it to the thread was investigated in detail, based on the asymmetric *O*-benzoylation of *meso*-1,2-diphenylethane-1,2-diol with benzoyl chloride as a test reaction (Scheme 9b). While the *para*-pyridyl group (**11c**) only led to 54% *ee*, it was found that the *ortho*- and *meta*-pyridyl groups (**11a**/**b**) gave excellent stereoselectivities (94–98% *ee*). This shows that the mechanical bond between a chiral macrocycle and a catalytically active thread, despite the possibility for several co-conformations, can lead to an efficient transfer of chiral information.

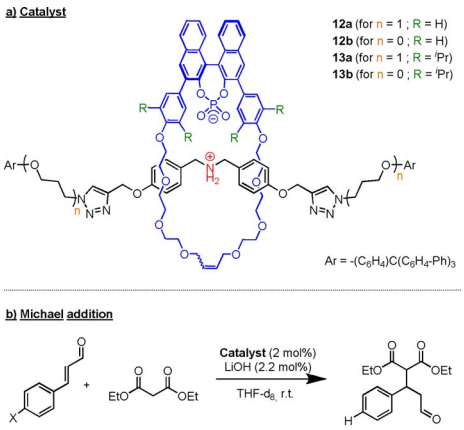
More recently, Niemeyer and co-workers investigated the first application of a chiral acid/base-functionalised rotaxane for asymmetric catalysis (Scheme 10).[32] Consisting of a Brønsted-acidic macrocycle based on a chiral 1,1′-binaphthyl-phosphoric acid and a Brønsted-basic thread featuring a central secondary amine, the rotaxanes **12a**/**b** and **13a**/**b** proved to efficiently catalyse the addition of diethyl malonate to cinnamaldehyde after activation with LiOH (Scheme 10b). No important difference was observed with a length change of the rotaxane



Catalyst	Conv (%)	ee (%)[a]
11a	>99	98
11b	75	94
11c	66	54

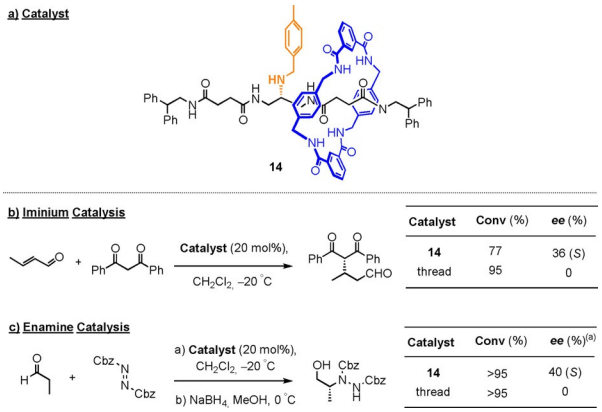
a) Enantiomeric excess given for (*1R*,*2S*)-isomer.

Scheme 9. a) Takata's chiral rotaxanes with pyridine-groups. b) Asymmetric *O*-benzoylation of *meso*-1,2-diphenylethane-1,2-diol with the different rotaxane-catalysts.



Catalyst	x	Conv (%)	ee (%)
12a	H	91	14
12b	H	92	14
13a	H	88	53
13b	H	87	37
macrocyle (R = H) + thread **a**	H	45	22
macrocyle (R = H) + thread **b**	H	35	23
macrocyle (R = ^{i}Pr) + thread **a**	H	76	9
macrocyle (R = ^{i}Pr) + thread **b**	H	78	7

Scheme 10. a) Niemeyer's bifunctional chiral rotaxane b) Asymmetric Michael addition of diethyl malonate to cinnamaldehyde with either the rotaxanes or the non-interlocked mixtures of macrocycle + thread as catalysts.



Catalyst	Conv (%)	ee (%)
14	77	36 (*S*)
thread	95	0

Catalyst	Conv (%)	ee (%)[a]
14	>95	40 (*S*)
thread	>95	0

Scheme 11. a) Leigh's mechanical point-chiral rotaxane. b) Iminium catalysis reaction with either the rotaxane or the thread as catalyst. c) Enamine catalysis reaction with either the rotaxane or the thread as catalyst.

thread (**12a** and **12b**) whereas the introduction of bulkier substituents (**13a** and **13b**) impressively increases the stereoselectivity. Compared to their non-interlocked counterparts which provided lower conversions and stereoselectivities (76/78% conversion, 9/7% *ee*), the isopropyl-substituted rotaxanes (**13a**/**13b**) showed considerably higher stereoinduction associated with high reaction rates (88/87% conversion, 53/37% *ee*). DFT-calculations showed that the reaction most likely does not proceed via iminium activation of the aldehyde substrate, but by a Lewis-acid activation of the Li-phosphate. Furthermore, it was found that the cooperative action of the Li-phosphate and the amine/ammonium-group is crucial for the reaction outcome, thus establishing the importance of the mechanical bond for the activity and selectivity.

2.3 An achiral macrocycle introduces or modulates chiral information

The chemical space created by the different components of rotaxanes can form a unique reaction environment for asymmetric reactions. This cannot only be used for the design of switchable catalysts (see chapter 2.1), but also for the generation of a mechanical chirality from achiral components or for the modulation of a chiral information that is already present on one of the components.

In 2016, Leigh and co-workers developed the first example of asymmetric catalysis with a mechanically point chiral rotaxane catalyst (**14**, Scheme 11).[33] The chirality was created by threading the macrocycle on one side of the symmetrical thread. The thread contains two succinamide stations (one of which binds the macrocycle) and a central secondary amine. Introduction of a bulky *p*-tolyl substituent on the amine prevents the macrocycle from shuttling between the two stations, so that the two mechanically point chiral enantiomers cannot interconvert and can thus be separated (Scheme 11a).

For enantioselective catalysis, an enantiomerically enriched rotaxane (84% *ee* of the (*S*)-isomer) was used. In iminium catalysis, namely the addition of 1,3-diphenyl-propane-1,3-dione to an α,β-unsaturated aldehyde (Scheme 11b), the Michael product was obtained with high conversion (77%) and stereoselectivity (36% *ee*). Enamine catalysis, namely the addition of aldehydes to dibenzyl azodicarboxylate (Scheme 11c), yielded the hydrazine product with >95% conversion and remarkable stereoselectivity of 40% *ee*.

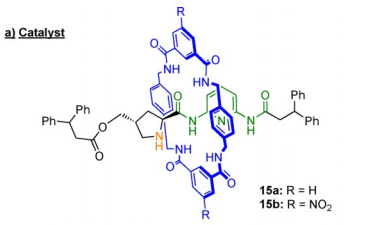
Berna and co-workers described a rotaxane organocatalyst using a chiral thread.[34] They developed two chiral prolinamide-based rotaxanes (**15a/b**) that differ in the peripheral substitution of the macrocycle (R = H or NO_2), which allows a modulation of the hydrogen-bonding ability. The rotaxanes carry a diacylaminopyridine (DAP) moiety on the thread, which is in close proximity to the catalytically active proline-unit (Scheme 12a). The DAP acts as a binding station for *N*-hexylthymine (HT), which can thus act as a cofactor for the catalysis.

The rotaxane was employed for vinylogous aldol-reaction of acetone to nitrostyrene in comparison to the thread alone. In absence of the HT-cofactor, no conversion was observed for the thread, while slight conversion (28–55%) was observed for the rotaxanes. However, the observed stereoselectivities were low (8–14%).

In presence of the HT-cofactor, however, there is a drastic increase in conversion (85–95%) and stereoselectivity (56–82%) for the rotaxane-catalysts. The same is not true for the thread in presence of HT (17% conversion, 14% *ee*), showing that the presence of the macrocycle has a profound influence on the catalytic behaviour.

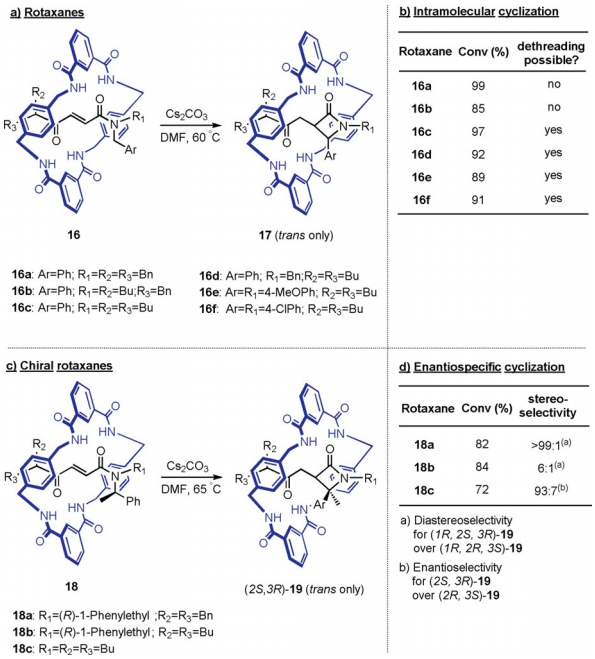
2.4 Macrocycle employs thread as substrate

When a macrocyclic catalyst performs a catalytic transformation on a substrate, this can happen in a pseudorotaxane or rotaxane-type structure. Such modification of a thread by a



Catalyst	*N*-hexylthymine (eq)	Conv (%)	*ee* (%)
15a	0	55	14
15b	0	28	8
thread	0	<5	-
15a	5	85	56
15b	5	95	82
thread	5	17	14

Scheme 12. a) Berna's prolinamide rotaxane organocatalyst. b) Asymmetric Michael addition of acetone to ß-nitrostyrene with either the rotaxane or the thread as catalyst.



Rotaxane	Conv (%)	dethreading possible?
16a	99	no
16b	85	no
16c	97	yes
16d	92	yes
16e	89	yes
16f	91	yes

Rotaxane	Conv (%)	stereoselectivity
18a	82	>99:1[a]
18b	84	6:1[a]
18c	72	93:7[b]

a) Diastereoselectivity for (*1R, 2S, 3R*)-**19** over (*1R, 2R, 3S*)-**19**
b) Enantioselectivity for (*2S, 3R*)-**19** over (*2R, 3S*)-**19**

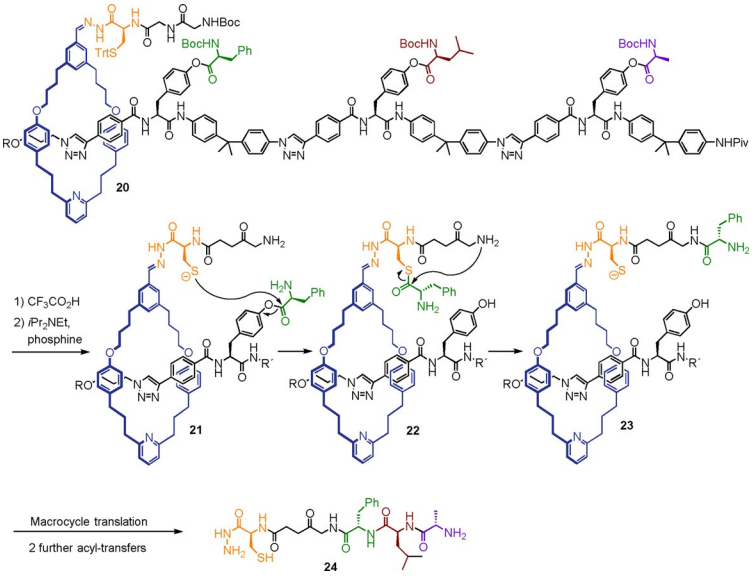
Scheme 13. Berna's intramolecular cyclisation of interlocked fumaramides. a) Non-chiral rotaxanes, b) Diastereoselective cyclisation, c) Chiral rotaxanes, d) Enantiospecific cyclization.

catalytically active macrocycle has also been termed as "processive catalysis".

In 2016, Berna and co-workers described a rotaxane composed of a bis(pyridinedicarboxamide) macrocycle and a fumardiamide thread. They found that the thread undergoes a cyclisation to give the corresponding β-lactam, which is strongly influenced by the presence of the macrocycle (Scheme 13).[35] The rotaxane (**16**) was shown to undergo intramolecular cyclisation in the presence of at least one *N*-benzyl substituent. In the presence of a base (Cs_2CO_3), the benzylic position is deprotonated giving rise to the corresponding ß-lactam (**17**) (Scheme 13 a) in excellent yields and exclusive diastereoselectivity towards the *trans*-products. When the thread contains one *N*-dibutylamine-terminus, the flexibility of the butyl substituents allows for a dethreading to give the non-interlocked components (Scheme 13 b).

Additionally, the team performed the reaction in an enantiospecific fashion.[35b] When a chiral *N*-((*R*)-1-phenylethyl substituent was employed as replacement for the *N*-benzyl group (rotaxanes **18**, Scheme 13 c), the exclusive diastereoselectivity (*trans*-product) of the ß-lactam product was maintained in addition to the resulting quaternary stereocentre. The preferred products depend on the chiral substituents used: (2*S*,3*R*)-products for the *N*-((*R*)-1-phenylethyl) substituents and (1*R*,2*S*,3*R*)-products for the *N*,*N*-bis((*R*)-1-phenylethyl) substituents (Scheme 13 d).

Based on the working principle of natural enzymes that perform sequence-specific syntheses, Leigh and co-workers reported a processive rotaxane that assembles specific reactive building blocks in a precise order (Scheme 14).[36] The macrocycle bears a Cys-Gly-Gly tripeptide sequence attached via a hydrazone linker and the thread contains three tyrosine-residues, each of which is linked to a different amino acid (Phe, Leu and Ala) via ester bonds. The active peptide synthesizer (**21**) is obtained by deprotection and addition of base. The nucleophilic thiolate present at the macrocycle binds the next amino acid (Phe) on the thread by transesterification, thus forming the thioester (**22**). The more stable amide is obtained by the intramolecular transfer to the terminal Gly residue on the macrocycle, yielding an extended tetrapeptide (Cys-Gly-Gly-Phe). Without the amino acid moiety, the tyrosine residue of the resulting rotaxane (**23**) is now small enough to permit the translocation of the macrocycle towards the next amino acid. The process is repeated giving a specific



Scheme 14. Leigh's sequence specific peptide synthesizer.

amino-acid sequence which corresponds to the order of the building blocks on the original path. Used for the transfer of three additional amino acids onto the original tripeptide, the corresponding H_2N-NH-Cys-Gly-Gly-Phe-Leu-Ala-NH_2 hexapeptide (**24**) is obtained after cleavage of the hydrazone-moiety. The concept has also been extended to oligo-peptides[37] and β-peptides.[38]

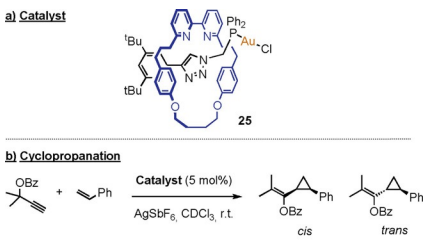
3. Rotaxane-based Transition Metal Catalysts

While rotaxanes have had great success in organocatalysis, partially because they often inherently feature organocatalytically active groups such as secondary amines, they can also be equipped with donor-groups for metal coordination. This opens up their application as a new type of ligand for transition-metal catalysis.

Similarly to the previous chapter, the discussed examples are grouped based on the function of their macrocyclic components: controlling reactivity (chapter 3.1), carrying of chiral information (chapter 3.2), introduction or modulation of chirality (chapter 3.3) and finally the use of the thread as the reaction substrate (chapter 3.4).[39]

3.1 Macrocycle controls reactivity

In 2005, Goldup and co-workers reported an example of Au-catalysis using a rotaxane with a diphenylphosphino group on the thread in combination with $Au^{I}Cl$ (Scheme 15a).[40] Used for the cyclopropanation of olefins with propargylic esters, the catalyst (**25**) showed no reactivity when activated by chloride abstraction using $AgSbF_6$. This was attributed to the fact that the Au^{+}-centre is buried in the macrocyclic unit (presumably by interaction with the bipyridine unit). However, the addition of metal ions, such as Cu^{I} or Zn^{II} led to an active species by competitive binding to the bipyridine, thus making the Au^{I}-centre available for catalysis. In this setup, the rotaxane catalyst affords the cyclopropanation products in good yields (76–93%) and high diastereoselectivity (up to 16:1). In contrast, the thread alone results in lower diastereoselectivity (up to 10:1, Scheme 15b).

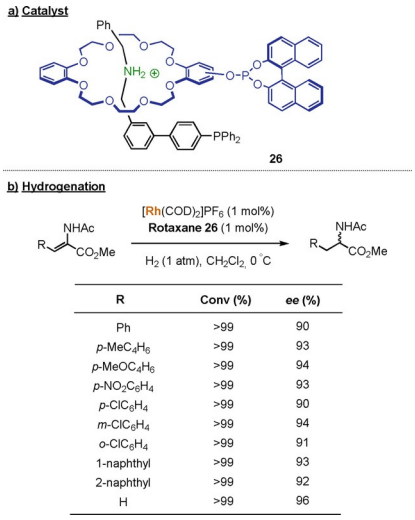


Catalyst	Additive	Conv (%)	*cis:trans*
25	-	-	-
25	$Zn(OTf)_2$	76	13:1
25	$[Cu(MeCN)_4]PF_6$	93	16:1
thread	-	85	10:1
thread	$Zn(OTf)_2$	86	10:1
thread	$[Cu(MeCN)_4]PF_6$	68	9:1

Scheme 15. a) Goldup's rotaxane-Au-complex. b) Au-catalysed cyclopropanation under different reaction conditions.

3.2 Macrocycle carries chiral information

A pseudorotaxane skeleton containing a chiral phosphite moiety attached to a crown ether macrocycle and a phosphine moiety connected to an ammonium containing thread (**26**, Scheme 16a) was introduced in 2007 by Nishibayashi, Fan and co-workers.[41] Although the components might dissociate, the threading is favoured in nonpolar solvent (like CH_2Cl_2 as employed here). Thus, simple mixing of the crown ether macrocycle with the ammonium-based thread can be used to generate a chiral bidentate ligand which possesses two coordination sites for binding the active metal centre (Rh). Applied to the hydrogenation of α-acetamidocinnamate, a number of differently substituted enamides were reduced to their corresponding chiral amides with excellent conversion (>99%) and good enantioselectivities of up to 96% (Scheme 16b). Unfortunately, no comparison was made to non-rotaxane ligands, so that the exact effect of pseudorotaxane-formation remains unknown.



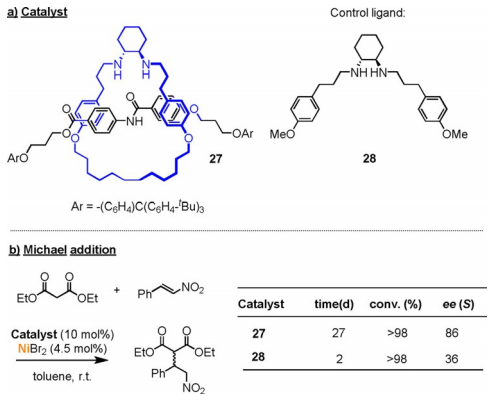
R	Conv (%)	ee (%)
Ph	>99	90
p-MeC_4H_6	>99	93
p-$MeOC_4H_6$	>99	94
p-$NO_2C_6H_4$	>99	93
p-ClC_6H_4	>99	90
m-ClC_6H_4	>99	94
o-ClC_6H_4	>99	91
1-naphthyl	>99	93
2-naphthyl	>99	92
H	>99	96

Scheme 16. a) Nishibayashi 's and Fans's pseudorotaxane ligand. b) Rh-catalysed asymmetric hydrogenation of different substrates.

In 2015, Leigh and co-workers reported a chiral rotaxane ligand for use in asymmetric catalysis.[42] They described the rotaxane (**27**) composed of an optically pure trans-1,2 diaminocyclohexane macrocycle (Scheme 17a). The diamine was applied as chiral ligand for Ni^{II} and the resulting complex tested for the enantioselective Michael addition of diethyl malonate to trans-ß-nitrostyrene. In contrast to the acyclic chiral ligand (**28**), the rotaxane (**27**) affords a longer reaction time, but a considerably higher enantioselectivity (86% *ee* for **27** vs. 36% *ee* for **28**, Scheme 17b).

3.3 An achiral macrocycle introduces or modulates chiral information

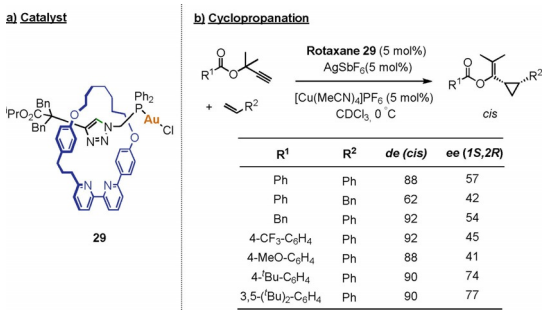
Generating a rotaxane by threading a non-symmetrical axle through a directional macrocycle provides a mechanically chiral interlocked molecule.[16] In a recent report, Goldup and



Catalyst	time(d)	conv. (%)	ee (S)
27	27	>98	86
28	2	>98	36

Scheme 17. a) Leigh's chiral diamine-based rotaxane. b) Ni-catalysed Michael-addition with either the rotaxane or the control compound as chiral ligands.

co-workers described the use of such a mechanically planar chiral rotaxane in enantioselective catalysis for the first time.[43] Similarly to their previous work, the team investigated cyclopropanation of olefins with propargylic esters (Scheme 18 a). The chiral rotaxane-Au complex **29** is active in the presence of $AgSbF_6$ and Cu^I additives, whose role is to bind the bipyridine unit in order to prevent the inhibition of the Au^I centre. Under these conditions, the rotaxane catalyst afforded high stereoselectivities toward the *cis*-isomer of the cyclopropane products for a range of different substituents (62–92 % *de*, 41–77 % *ee*).



R1	R2	de (cis)	ee (1S,2R)
Ph	Ph	88	57
Ph	Bn	62	42
Bn	Ph	92	54
4-CF3-C6H4	Ph	92	45
4-MeO-C6H4	Ph	88	41
4-tBu-C6H4	Ph	90	74
3,5-(tBu)2-C6H4	Ph	90	77

Scheme 18. a) Goldup's mechanical chiral rotaxane-Au-complex. b) Enantioselective Au-catalysed cyclopropanation of different substrates.

3.4 Macrocycle employs thread as substrate

Similar to the processive organocatalytic reactions described in chapter 2.4, metal-containing macrocycles have also been employed in processive catalysis.

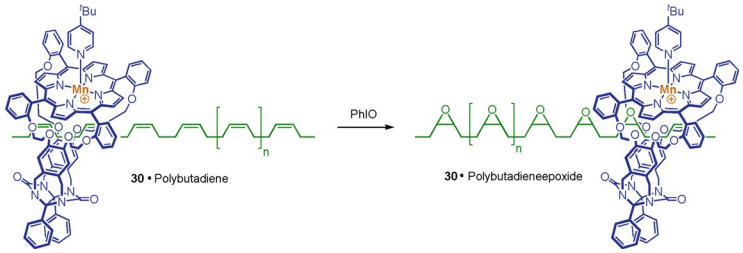
In the early examples, Nolte and co-workers reported the processive catalysis of a pseudorotaxane type structure (**30**, Scheme 19).[44a] They introduced a macrocyclic catalyst containing a porphyrin-Mn^{II} unit which encapsulates a polybutadiene substrate to yield a pseudorotaxane-structure. In the presence of PhIO as an oxidant, the Mn centre induces the epoxidation of the polybutadiene to polybutadieneepoxide in the macrocyclic cavity with high stereoselectivity (20:80 *cis*/*trans*). Meanwhile the use of an acyclic Mn-porphyrin catalyst without any binding cavity also proved efficient for the epoxidation reaction but with an opposite stereoselectivity (80:20 *cis*/*trans*, Scheme 19). In follow-up studies, the mechanism of threading and epoxidation were investigated in detail. As one result, it could be shown that the epoxidation occurs in random fashion, as opposed to a consecutive transformation of double-bonds on the polybutadiene-chain.[44] In more recent studies, this work was extended towards the oxidation of small-molecule guests and towards alternative catalyst structures, such as a urea-functionalised version of catalyst **30** or a cyclodextrin-conjugate of a Mn-porphyrin catalyst.[45]

Takata and co-workers reported another example of rotaxane-type processive reactions.[46] Here, a permanently interlocked rotaxane was presented which is based on an axle containing four allyl-carbamate units and a pyridine-diamide macrocycle. In the presence of Pd^{II}, heating the rotaxane (**31**) results in a cyclisation of the allyl carbamates units to oxazolidinones, thereby producing the rotaxane (**32**) (Scheme 20). With the macrocycle or the thread alone, no cyclisation product was observed, demonstrating that the cyclisation occurs exclusively inside the Pd-macrocycle cavity.

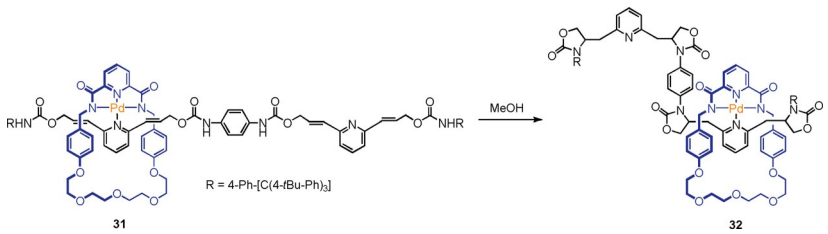
4. Conclusion and Outlook

The application of rotaxanes in catalysis has gained considerable attention in the last years. The research field has already come a long way, from the first proof-of-principle studies (e.g. the first examples for chiral rotaxane catalysts by Takata and the first examples for switchable catalysts by Leigh) to more sophisticated examples (e.g. the switchability between different reaction modes, the generation of highly congested reaction spaces or the introduction of mechanical chirality). This shows that rotaxanes offer exciting novel possibilities on a conceptual level, as we have tried to illustrate in the Minireview.

Still, rotaxane-catalysis (or catalysis using interlocked molecules in general) is still a young field. Many studies reported to date might be seen as proof-of-concept studies and more simple (and more efficient or selective) catalysts are available for many of the transformations that have been achieved with rotaxane-based catalysts so far. Also, the complexity and multistep syntheses of rotaxane-catalysts remain to be a problem. Yet, highly efficient and easily applicable protocols for rotaxane-synthesis have become available over the last years,[19] which will certainly help to make rotaxanated structures to become available for a broader community of scientists. We



Scheme 19. Nolte's pseudorotaxane polybutadiene epoxidation.



Scheme 20. Takata's Pd-catalyzed cyclisation of allyl carbamates.

believe that this will soon lead to the application of rotaxane-catalysts for such catalytic transformations that have not been achieved with sufficient selectivities when using non-interlocked catalysts so far.

The role of the macrocycle is one way to look at rotaxane-catalysis in order to understand the potential of rotaxane-catalysts for future research. We hope that this Minireview will aid the future development of rotaxane-based catalysts and we are certain that there is a bright future for rotaxane-catalysts in particular and for MIM-based catalysis as a whole.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: catalysis · chirality · macrocycles · mechanically interlocked molecules · rotaxanes

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