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Heterobifunctional rotaxanes for asymmetric catalysis

Noël Pairault,[a] Hui Zhu,*[b] Dennis Jansen,[a] Alexander Huber,[a] Constantin G. Daniliuc,[c] Stefan Grimme[b] and Jochen Niemeyer*[a]

In memory of Prof. Carsten Schmuck

Abstract: Heterobifunctional rotaxanes serve as efficient catalysts for the addition of malonates to Michael-acceptors. We report a series of four different heterobifunctional rotaxanes, featuring an amine-based thread and a chiral 1,1´-binaphthyl-phosphoric acid based macrocycle. High-level DFT calculations provided mechanistic insights and enabled rational catalyst improvements, leading to interlocked catalysts that surpass their non-interlocked counterparts in terms of reaction rates and stereoselectivities.

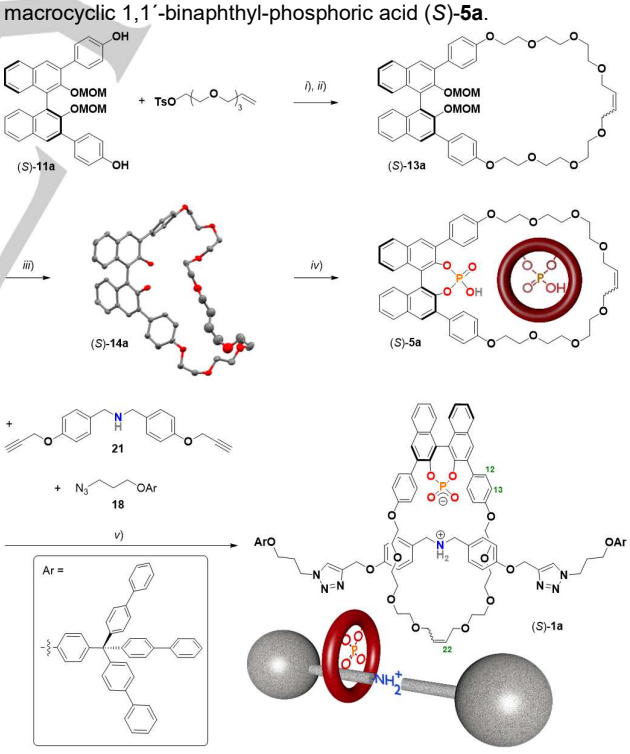
The mechanical bond[1] has emerged as a new design element for the generation of catalytically active species. The use of rotaxanes,[2] catenanes[3] or molecular knots[4] offers novel possibilities in catalysis, such as the development of switchable systems, the construction of highly congested reaction spaces or the linking of different functionalities via the mechanical bond.[5]

For an application in asymmetric catalysis, a number of chiral mechanically interlocked molecules (MIMs) have been developed.[6] In transition-metal catalysis, *Leigh* used rotaxanes with chiral diamine-based macrocycles for Ni-catalyzed enantioselective Michael-additions[7], while *Goldup* employed mechanically planar-chiral rotaxane ligands for Au-mediated cyclopropanations.[8] In the realm of organocatalysis, *Leigh* and *Berna* developed rotaxanes featuring nucleophilic secondary amines on the axle. Making use of either stereogenic centers in close vicinity to the amine[9] or by employing the macrocycle to achieve a desymmetrization of a (pseudo)-symmetric thread,[10] these rotaxane-catalysts were applied for enantioselective Michael-additions or α-functionalizations.

In a slightly different approach, *Takata* developed chiral rotaxanes in which a catalytically active nucleophile (e.g. a thiazole or pyridine) and a chiral BINOL-moiety are present on different subcomponents of the MIMs.[11] Nevertheless, the close vicinity of both components, brought about by the mechanical bond, allowed the use of these catalysts for enantioselective acylation reactions or in the benzoin-condensation. Our group has recently reported the mechanical linking of two chiral 1,1´-binaphthyl-phosphoric acids in a [2]catenane.[12] The resulting bifunctional system showed drastically enhanced stereoselectivities in comparison to the non-interlocked monophosphoric acids in the transfer-hydrogenation of quinolines.[13]

Herein, we now report the first application of a chiral acid/base-functionalized rotaxane for asymmetric catalysis. We have combined a Brønsted-acidic macrocycle based on a chiral 1,1´-binaphthyl-phosphate unit with a Brønsted-basic thread featuring a central secondary amine. We envisaged that the cooperative action of both functional groups in asymmetric catalysis would be enhanced by the mechanical bond, thus leading to enhanced reaction rates and stereoselectivities. Indeed, using a combined experimental and theoretical approach, we were able to generate rotaxanated catalysts that show markedly increased reaction rates and stereoselectivities in comparison to their non-interlocked counterparts.

For the synthesis of the first-generation bifunctional chiral rotaxane (*S*)-**1a** (see scheme 1), we started by generating the macrocyclic 1,1´-binaphthyl-phosphoric acid (*S*)-**5a**.



Scheme 1: Synthesis of rotaxane (*S*)-**1a** [*i*) (*S*)-**11a** (1 eq), *O*-allyl-triethyleneglycol-tosylate (3 eq), Cs_2CO_3, 80 °C, CH_3CN; 70%; *ii)* Grubbs-II catalyst, CH_2Cl_2, 0.5 mM, 54%; *iii)* conc. HCl, 70 °C, THF/MeOH, 99%; *iv*) $POCl_3$, pyridine, 60 °C, then H_2O, 95%; *v*) (*S*)-**5a** (1 eq), **21** (1.6 eq), **18** (3.3 eq), $[Cu(MeCN)_4PF_6]$, CH_2Cl_2, 0 °C, 33%] together with the structure of macrocycle (*S*)-**14a** in the solid state (hydrogen atoms omitted for clarity and thermal ellipsoids set at the 60% probability level).

[a] Dr. N. Pairault, M. Sc. D. Jansen, B. Sc. Alexander Huber, Dr. J. Niemeyer
Institute of Organic Chemistry and Center for Nanointegration Duisburg- Essen (CENIDE), University of Duisburg-Essen
Universitätsstrasse 7, 45141 Essen (Germany)
E-mail: jochen.niemeyer@uni-due.de
[b] Dr. Hui Zhu, Prof. Stefan Grimme
Mulliken Center for Theoretical Chemistry
Rheinische Friedrich-Wilhelms-Universität Bonn
Beringstrasse 4, 53115 Bonn, Germany.
E-mail: hui@thch.uni-bonn.de
[c] Dr. C. Daniliuc
Institute of Organic Chemistry
Corrensstr. 40, 48149 Münster, Germany

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This was performed by alkylation of (*S*)-**11a** with *O*-allyl-triethyleneglycol-tosylate, followed by ring-closing metathesis under dilute conditions (0.5 mM) to give the 38-membered macrocycle (*S*)-**13a**. Subsequent acid-induced MOM-deprotection and phosphorylation gave the desired macrocyclic phosphoric acid (S)-**5a** in good yield (36% over four steps). All compounds were fully characterized by standard analytical methods (see SI for details), in addition the macrocyclic diol **14a** could be analyzed by single-crystal X-ray analysis of a racemic sample.

Starting from macrocycle (*S*)-**5a**, we generated rotaxane (*S*)-**1a** in a passive-template approach. (*S*)-**5a** was mixed with the dialkynylated amine **21** to give the corresponding phosphate-ammonium pseudorotaxane-complex, which was stoppered with bulky azide **18** in the presence of Cu(I). To guarantee the isolation of pure zwitterionic NH_2^+/POO^- [2]rotaxane, the compound was washed by acidic then neutral aqueous solution after silica gel column chromatography, yielding (*S*)-**1a** in 33% yield.

NMR-analysis (see fig. 1) reveals distinct chemical shift changes for the rotaxane (*S*)-**1a** in comparison to the macrocycle (*S*)-**5a**, the thread **3** and the non-interlocked mixture of (*S*)-**5a** with **3**. Finally, the interlocked nature of the rotaxane was unambiguously shown by MS/MS-experiments, which show liberation of the thread upon fragmentation of the macrocycle (see SI fig. S23 – S24).

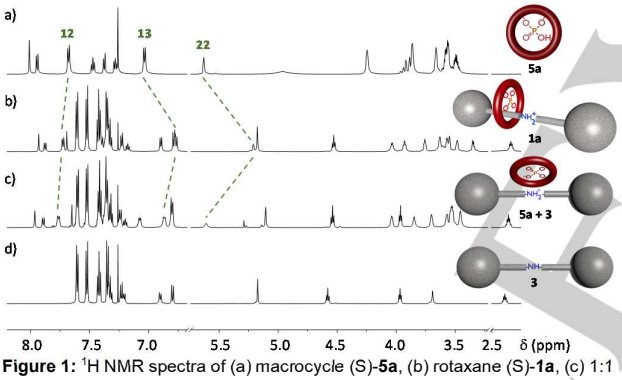
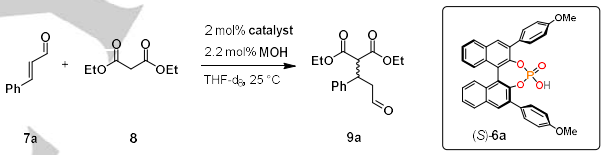


Figure 1: ^{1}H NMR spectra of (a) macrocycle (S)-**5a**, (b) rotaxane (S)-**1a**, (c) 1:1 mixture of macrocycle (S)-**5a** and (d) thread **3** (all: 600 MHz, $CDCl_3$, 298 K, for numbering see scheme 1).

With the [2]rotaxane (*S*)-**1a** in hand, we set out to investigate its application in asymmetric catalysis. Based on the bifunctional phosphate-ammonium structure, we envisaged its use for the asymmetric Michael-addition to α,β-unsaturated aldehydes. Such reactivity is known for non-interlocked phosphate-ammonium species (e.g. the TRIP-morpholine pair).[14] The generally accepted mechanism involves iminium-activation of the aldehyde by the nucleophilic amine, followed by stereoselective addition of the nucleophile to the chiral phosphate-iminium ion pair (thus termed as asymmetric counteranion-directed catalysis, ACDC).[15] For our investigation, we employed the addition of diethyl malonate **8** to cinnamaldehyde **7a**, which yields the chiral Michael-adduct **9a** (see table 1). Firstly, we employed the zwitterionic rotaxane (*S*)-**1a** as a catalyst, but almost no conversion was observed (<1% conversion after 7 days, see SI fig. S62-S104 for all conversion curves and chiral HPLC analyses). Assuming that a strong phosphate-ammonium pairing would not allow ammonium-deprotonation and thus block the reactivity of the amine, we generated the deprotonated rotaxane [(*S*)-**1a**]$^-$M$^+$ by addition of one equivalent of metal hydroxide MOH (M = K/Na/Li). Indeed, this gave catalytically active species, with the highest reaction rate observed in case of LiOH (59%/83%/91% conversion for M = K/Na/Li). Based on this, we could also demonstrate *on*/*off*/*on* switching of the catalyst by subsequent addition of LiOH/HCl/LiOH (see SI fig. S105). Significantly lower conversion was observed for the free thread **3** (used as the free amine R_2NH, 10% conversion), and no conversion at all was found for LiOH only or for the macrocycle/LiOH combination. These controls clearly indicate that both metal-phosphate and amine are required for the catalytic activity.

Next, we investigated the influence of the mechanical bond on the catalytic behavior by using the non-interlocked mixture of macrocycle (*S*)-**5a** and thread **3** as well as the mixture of acyclic phosphoric acid (*S*)-**6a** (see table 1) and thread **3** as a comparison. For all three metal-salts (KOH/NaOH/LiOH), we consistently observed the lowest conversion for the macrocycle/thread pairs, while slightly higher conversions were observed for the acyclic phosphoric acid/thread pairs. However, rotaxane (*S*)-**1a** was by far the most active catalyst in all cases, with reaction rates being 3.1 - 1.5 times higher in comparison to the acyclic phosphoric acid/thread mixtures and even 9.2 – 2.0 times higher than those of the macrocycle/thread mixtures.

Table 1: Catalytic results for rotaxane (S)-**1a** and its non-interlocked counterparts using different added bases (2 mol% catalyst, THF-d_8, 25 °C).[a]



Entry	Catalyst precursor	Added base MOH[b]	Conversion (%)[c]	*ee* (%)[d]
1	-	LiOH	<1	-
2	macrocyclic acid (*S*)- **5a**	LiOH	<1	-
3	thread **3**	-	10	-
4	rotaxane (*S*)-**1a**	-	<1	]
5		KOH	59	9
6		NaOH	83	16
7		LiOH	91	14
8	macrocyclic acid (*S*)-**5a** + thread **3**	KOH	8	0
9		NaOH	9	5
10		LiOH	45	22
11	acyclic acid (*S*)-**6a** + thread **3**	KOH	19	1
12		NaOH	30	5
13		LiOH	59	14

[a] THF-d_8 used as obtained (ca. 100 ppm H_2O). [b] Added as 1M solution to THF-solution of catalyst precursor, followed by drying in vacuo, prior to catalytic reaction. [c] Determined by ^{1}H-NMR after 7 days. [d] Determined by chiral HPLC for isolated products.

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With respect to stereoselectivities, both the rotaxane (*S*)-**1a** and its non-interlocked counterparts only afforded low enantioselectivities (see table 1). However, three trends were observed: In case of Na/K, the rotaxane-catalyst (*S*)-**1a** gave higher stereoselectivities (9%/16% *ee* for Na/K) than the non-interlocked catalysts (1%/5% and 0%/5% *ee* for Na/K). For the Li-case, however, stereoselectivities for interlocked and non-interlocked species were comparable (14%/14%/22% *ee*). Variation of the solvent (CD_2Cl_2, toluene-d_8 or DMSO-d_6) led to unchanged or decreased stereoselectivities (see SI table S1).

To the best of our knowledge, the phosphate-ammonium catalyzed Michael-addition has not yet been investigated theoretically.[16] We set out to explore the structures of rate- and stereo-determining intermediates and to rationalize the experimentally observed trends in reaction rates and stereoselectivities based on high-level DFT calculations. Our well established state-of-the-art DFT protocol (at the PW6B95-D3/def2-QZVP + COSMO-RS // TPSS-D3/def2-TZVP + COSMO level[17] in THF solution) was applied, and the final Gibbs free energies (at 298 K and 1 M reference concentration) are used in our discussion. The initial structures and reaction paths were explored with the efficient GFN-xTB method.[17]

Our DFT calculations (see fig. 2) show that the stoichiometric reaction between the non-interlocked model precatalyst **S⁻NmhH⁺** (phosphate-ammonium pair) and the strong base **Liw₂OH** ($Li(H_2O)_2OH$) is highly exergonic by −25.0 kcal/mol to form the lithium phosphate complex **SLiw₂** with two coordinated water molecules as well as the free amine base **Nmh** (or NMe_2H) in THF solution. The substrate **Meh** (malonate) binds through two ester groups to the lithium site of **SLiw₂** to replace one H_2O ligand, leading to a more C-H acidic malonate from which a proton can be transferred to the free amine base **Nmh**. This proton transfer reaction is only 1.0 kcal/mol endergonic over a low barrier of 8.4 kcal/mol thus may reversibly lead to the ammonium phosphate **S⁻NmhH⁺** along with the lithium-activated malonate **MeLiw** as potential Michael-donor. At this point, at least two pathways of Michael-addition to cinnamaldehyde **Pho** (cinnamaldehyde) are possible depending on if the asymmetric phosphate anion **S⁻** is involved:

In the first path, direct Michael-addition between **MeLiw** and **Pho** occurs via the transition structure **MeLiwPho_ts**, which is 22.1 kcal/mol endergonic over a barrier of 23.5 kcal/mol to form the zwitterionic adduct **MeLiwPho** (not shown in Figure 2), where the enolate-type addition product is bound to the Li-water cluster. In the presence of **S⁻NmhH⁺**, the adduct **MeLiwPho** can be stabilized by the binding of phosphate anion **S⁻** to Li, followed by facile proton transfer (via **SLiwMePhon_ts**) from **NmhH⁺** to the enolate α-carbon, eventually leading to the final Michael-addition product **MePhho** and regenerated **SLiw₂** and **Nmh** as actual catalyst.

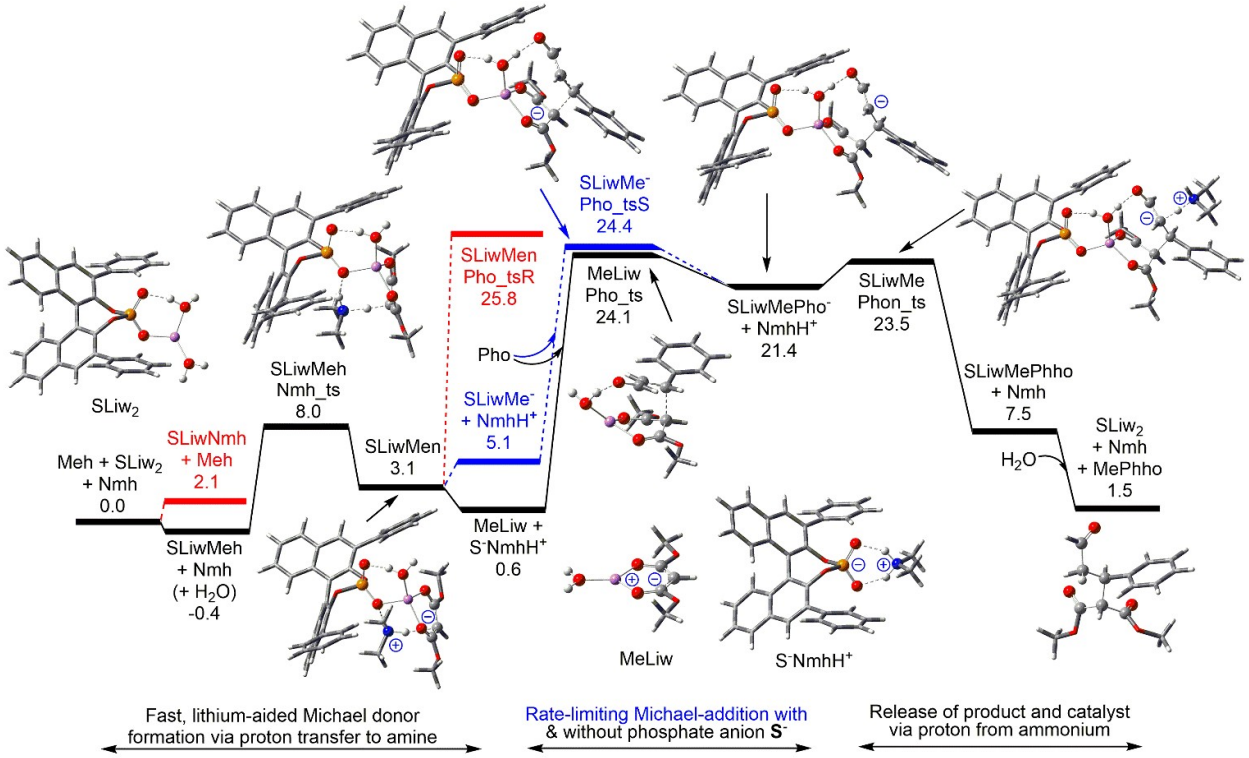

Figure 2. DFT computed reaction free energy paths (in kcal/mol, at 298 K, 1 M reference concentration) for the catalytic Michael-addition of model systems of dimethylmalonate **Meh** and cinnamaldehyde **Pho** (PhCH=CHCHO) using the acyclic lithium (*S*)-1,1'-biphenyl-phosphate **SLiw₂** and dimethylamine **Nmh** (NMe_2H) as catalyst, formed from the exergonic reaction of the ammonium phosphate salt pre-catalyst **S⁻NmhH⁺** and the strong base **Liw₂OH** ($Li(H_2O)_2OH$). The rotaxane-catalyst is mimicked by assuming an interaction of the amine/ammonium-thread and the Li-phosphate species (shown in red). Crucial P, O, N, C and H atoms are highlighted as violet, red, blue, grey and white balls along with grey carbon backbones while most hydrogen atoms are omitted for clarity.

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Such direct Michael-addition of free **MeLiw** may occur equally at both sides of the **Pho** substrate, eventually leading to *racemic* final adduct **MePhho** with an overall barrier of 24.5 kcal/mol (difference between **MeLiwPho_ts** and **SLiwMeh+Nmh**).

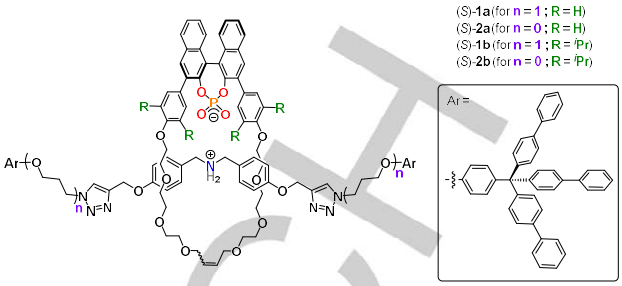
Alternatively, the (*S*)-symmetric phosphate anion **S**$^-$ may bind to the lithium site of **MeLiw** to form the unstable complex **SLiwMe**$^-$ before the nucleophilic addition to the **Pho** substrate, which may lead to the desired stereoselectivity. In addition to the strong O–Li coordination bond, **S**$^-$ may bind to **MeLiw** in two configurations either with or without an additional O···HO hydrogen-bond to the Li-bound H_2O ligand. In presence of the hydrogen-bond, the reaction is kinetically favored by 0.7 kcal/mol and leads to preferred formation of the (*S*)-product [(*S*)-**MePhho**] with an enantioselectivity of 1.4 kcal/mol. In contrast, the (*R*)-product is favored by 0.7 kcal/mol in the absence of the additional hydrogen bond.Yet, this phosphate-directed (*S*)-selective channel via **SLiwMe**$^-$**Pho_tsS** is still kinetically slightly less favorable (barrier of 24.8 kcal/mol, difference between **SLiwMe**$^-$**Pho_tsS** and **SLiwMeh+Nmh**) than the direct but *racemic* Michael-addition.

In order to take into account the rotaxanation in our calculations, we mimicked the high local concentration of functional groups in the interlocked structure by assuming an interaction between the amine/ammonium-thread and the Li-phosphate species (complexes **SLiwMenPho_tsR** and **SLiwNmh,** shown in red in figure 2). Such interaction results in a reduction of the overall barrier by about 0.8 kcal/mol for the pathway involving the ammonium-cation **Men** (barrier of 23.7 kcal/mol). This shows that for the interlocked catalyst, the reaction is kinetically competetive over the racemic pathway, although stereoselectivity for this pathway is small [(*R*)-product favored by 0.7 kcal/mol, see SI].

In summary, our DFT-computed mechanism is consistent with the observed catalytic role of amine, metal ions and phosphate anion, with small stereoselectivities observed mainly due to two reasons: (1) competing binding configurations between **S**$^-$ and the Michael-donor **MeLiw;** (2) lower **S**$^-$ affinity of **MeLiw** than **NmhH**$^+$. Note that the generally accepted mechanism of ACDC-type Michael-addition via the anion-bound iminium as key intermediate (instead of **SLiwMe**$^-$) was also considered in our DFT calculations but it encounters a much higher and chemically unrealistic barrier of about 35 kcal/mol for the **SLiw$_2$**-catalyzed iminium formation in the present case (see SI fig. S106).

According to the DFT-computed mechanism, the stereoselectivity of the addition reaction could be enhanced by introducing bulky substituents near the oxygen binding sites of **S**$^-$ that may favor single-mode **MeLiw** binding with enhanced affinity via stronger dispersion interactions. Such a modified phosphate anion **Sb**$^-$, featuring bulky ^{i}Pr-groups in the 3,5-positions, shows a 3.5 kcal/mol higher affinity to the malonate substrate **Meh** as well as an enhanced stereoselectivity (1.9 kcal/mol in favour of the (*S*)-product) for the asymmetric Michael-addition.

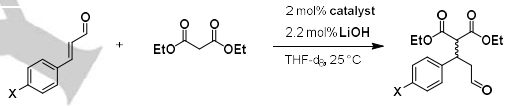
Based on these conclusions, we performed an evolution of the rotaxane-structure (*S*)-**1a** and synthesized three variants. In addition to introduction of bulky isopropyl-groups in the 3,5-positions (as suggested by DFT), we also designed a shorter thread in order to enhance the proximity between the relevant functional groups (phosphate and amine). The synthesis of the novel ^{i}Pr$_2$-substituted macrocycle (*S*)-**5b** and the novel rotaxanes (*S*)-**2a** (shorter thread only) and (*S*)-**1b**/**2b** (^{i}Pr$_2$-macrocycle with long/short thread, respectively) was performed in close analogy to the synthesis of (*S*)-**1a** (*vide supra*), giving three additional rotaxanes in 28-58% yield (see scheme 2, see SI for details and full characterization).



Scheme 2: Structures of [2]rotaxanes (*S*)-**1a**, (*S*)-**2a**, (*S*)-**1b** and (*S*)-**2b**.

Using the optimized reaction conditions (2 mol% catalyst, 2.2 mol% LiOH, THF-d_8, r.t.), we investigated the catalytic activity and stereoselectivity of rotaxanes (*S*)-**1a**/**2a**/**1b**/**2b** in comparison to the respective non-interlocked mixtures of macrocycle and thread (see table 2).[18] Catalysts **1a** and **2a**, which differ in the length of the thread, show no noticeable differences with regard to rate or stereoselectivity (91/92% conversion after 7 days, 14/14% *ee*), and the same is true for their non-interlocked counterparts (45/35% conversion, 22/23% *ee*).

Table 2: Catalytic results for different rotaxane-catalysts **1a**/**2a**/**1b**/**2b** and their non-interlocked counterparts.



Entry	Catalyst precursor	Aldehyde substituent X	Conversion (%)[a]	*ee* (%)[b]
1	rotaxane (*S*)-**1a**	H	91	14
2	macrocyclic acid (*S*)-**5a** + thread **3**	H	45	22
3	rotaxane (*S*)-**2a**	H	92	14
4	macrocyclic acid (*S*)-**5a** + thread **4**	H	35	23
5	rotaxane (*S*)-**1b**	H	88	53
6	macrocyclic acid (*S*)-**5b** + thread **3**	H	76	9
7	rotaxane (*S*)-**2b**	H	87	37
8	macrocyclic acid (*S*)-**5b** + thread **4**	H	78	7
9	rotaxane (*S*)-**1b**	OMe	54	44
10	macrocyclic acid (*S*)-**5b** + thread **3**	OMe	40	16
11	rotaxane (*S*)-**1b**	NO_2	92	49
12	macrocyclic acid (*S*)-**5b** + thread **3**	NO_2	56	14

[a] Determined by ^{1}H-NMR after 7 days. [b] Determined by chiral HPLC for isolated products.

In stark contrast to this, the $^{i}Pr_2$-substituted rotaxanes **1b**/**2b** give significantly higher stereoinduction without lowering the reaction rates (88/87% conversion, 53/37% *ee*), while their non-interlocked counterparts are slightly slower and significantly less stereoselective (76/78% conversion, 9/7% *ee*). The same trend can be observed upon variation of the substrate by using differently substituted Michael-acceptors **7b**/**c**, featuring *p*-OMe/*p*-NO_2 substituents, which show moderate stereoselectivity in case of rotaxane **1b** (44/49% *ee*), but poor stereoselectivity for the non-interlocked catalyst (16/14% *ee*).

Despite these clear trends and the enhanced stereoselectivities for the rotaxane-catalysts, we were wondering why the absolute stereoselectivity remains moderate. Based on DFT-calculations, it seems that the *racemic* Michael-addition between free **MeLiw** and **Pho** still remains kinetically competitive over nearly the same barrier as the channel involving the chiral phosphate, even in the new catalyst design. We will address this fact in due course by further modification of the rotaxane-structures.

In summary, we could show that the mechanical bond can indeed serve as an efficient tool for the modification and improvement of organocatalysts. The mechanical linking leads to a significant increase in reaction rates for all cases investigated here, which can be attributed to the high local concentrations of the functional groups in the [2]rotaxane-catalyst. In terms of stereoselectivity, we established that the length of the thread has no significant influence, while the exact substitution pattern of the macrocycle has a major impact. Introduction of bulky ^{i}Pr-groups led to a significant increase in stereoselectivity, however only in case of the mechanically interlocked catalysts. This finding may well pave the route for the generation of more selective interlocked catalysts for such organocatalytic transformations that have failed to be realized with high stereoselectivities up to date.

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Keywords: mechanically interlocked molecules • rotaxanes • organocatalysis • asymmetric catalysis • DFT

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[18] No further comparison with the combination of acyclic phosphoric acids + threads was conducted since these did not differ in stereoselectivity in the initial investigation using rotaxane **1a**.