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A Switchable [2]Rotaxane Asymmetric Organocatalyst That Utilizes an Acyclic Chiral Secondary Amine

Victor Blanco, David A. Leigh,* Vanesa Marcos, José A. Morales-Serna, and Alina L. Nussbaumer

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

Supporting Information

ABSTRACT: A rotaxane-based switchable asymmetric organocatalyst has been synthesized in which the change of the position of the macrocycle reveals or conceals an acyclic, yet still highly effective, chiral organocatalytic group. This allows control over both the rate and stereochemical outcome of a catalyzed asymmetric Michael addition.

Nature controls the rate of enzymatic synthesis through a variety of trigger-induced effects.[1] Such processes are inspiring the development of synthetic systems where a stimulus can be used to turn a catalyst's activity 'on' or 'off'.[2−4] However, enzyme-catalyzed reactions also often proceed with exquisite stereochemical control.[5] The Feringa group has described[3a] a molecular-machine-based organocatalyst that can be switched to bias catalysis of a conjugate addition in favor of either enantiomer (3:1 to 1:3 enantiomeric ratio (er)). Here we report on a [2]rotaxane[6] that acts as an effective asymmetric organocatalyst[7] in one state (>9:1 er) but is switched 'off' in the other state, by exploiting well-defined positional changes of the components to conceal or reveal a simple chiral organocatalytically active functional group.

The design of the rotaxane-based switchable asymmetric organocatalyst (*R*)-**1**·PF_6 consists of a dibenzo-24-crown-8 macrocycle and an axle bearing a triazolium ring and a chiral acyclic secondary amine derived from D-phenylalanine (Figure 1). Secondary amines employed as organocatalysts are usually cyclic,[8−10] but we had previously found[4] that pyrrolidine rings form perch, rather than threaded, complexes with crown ethers of this size which is not conducive for rotaxane formation. We were delighted, therefore, when model studies (see Tables 1 and 2 and the Supporting Information) showed that simple *acyclic* secondary amine derivatives of amino acids could very effectively catalyze asymmetric conjugated additions *via* iminium ion activation, often giving stereoselectivities as high as those obtained with commercial cyclic organocatalysts, albeit requiring longer reaction times. Such acyclic chiral moieties can be readily incorporated into a rotaxane thread.

The switching mechanism of the rotaxane relies on the macrocycle preferentially encapsulating the chiral secondary ammonium group, a better binding site for the macrocycle than the triazolium ring,[11] in the protonated form ((*R*)-**1**-H^+·$2PF_6^-$; Figure 1a). The macrocycle blocks access of reactants to the catalytic site. When the secondary amine of the rotaxane is not protonated ((*R*)-**1**·PF_6; Figure 1a), the triazolium group is the preferred binding site for the macrocycle[11] and the chiral

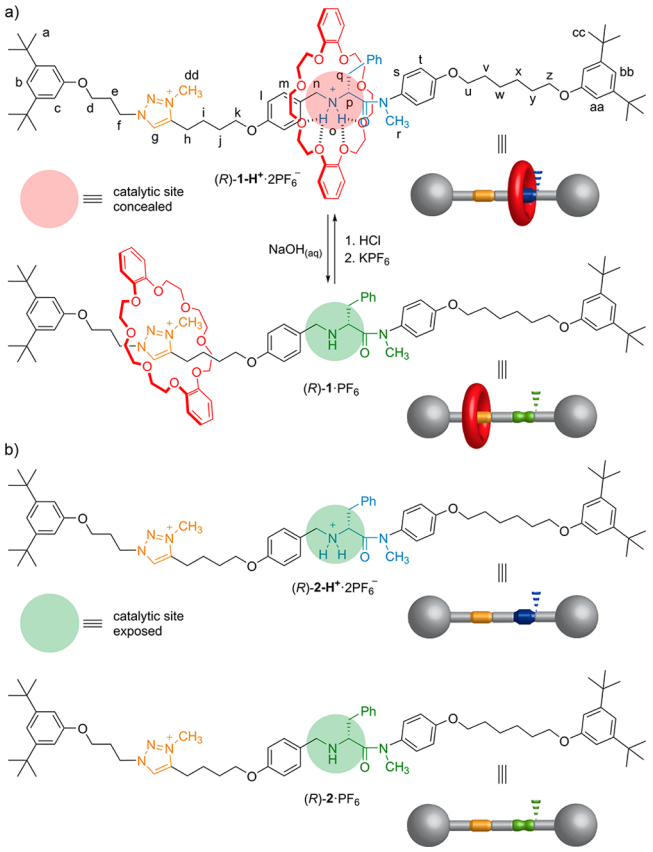

Figure 1. (a) Acid−base switching of the position of the macrocycle in chiral rotaxane (*R*)-**1**-H^+·$2PF_6^-$ (catalysis 'off')/(*R*)-**1**·PF_6 (catalysis 'on'). (b) Structure of threads (*R*)-**2**·PF_6 and (*R*)-**2**-H^+·$2PF_6^-$.

organocatalyst on the axle is exposed and available to participate in asymmetric catalysis.

The synthetic route toward rotaxane (*R*)-**1** relies on a CuAAC 'click' reaction[12] to covalently capture a threaded complex of dibenzo-24-crown-8 and an alkyne-functionalized ammonium axle with an azide-functionalized bulky 3,5-di-*tert*-butylphenyl derivative (see Supporting Information).

Switching of the preferred position of the macrocycle between the two binding sites is triggered by protonation/deprotonation of the amine/ammonium group (Figure 1a). A comparison of the ^{1}H NMR spectrum of (*R*)-**1**-H^+·$2PF_6^-$ (Figure 2b) to that of the protonated noninterlocked thread

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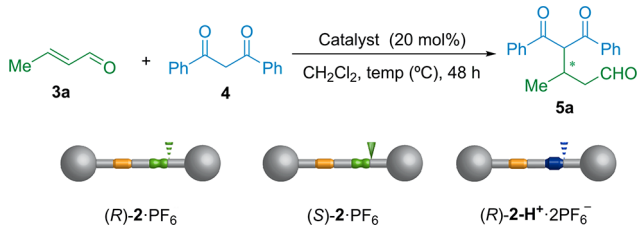
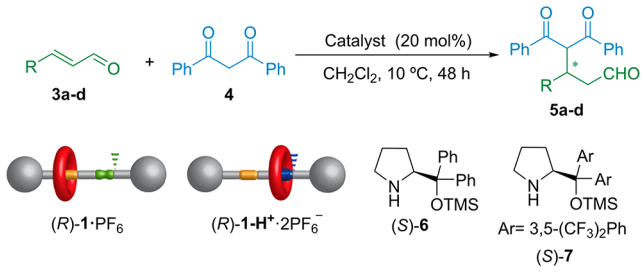
Table 1. Optimization of Conditions for the Asymmetric Michael Addition of 1,3-Diphenyl-1,3-propanedione (4) to *E*-Crotonaldehyde (3a)[a]



entry	catalyst	temp (°C)	conv[b] (%)	er (*R*:*S*)[c]
1	–	rt	0[d]	–
2	(*R*)-**2**·PF_6	rt	100	85:15
3	(*S*)-**2**·PF_6	rt	80	20:80
4	(*R*)-**2**·PF_6	−20	20	94:6
5	(*R*)-**2**·PF_6	0	45	94:6
6	(*R*)-**2**·PF_6	10	60	92:8
7	(*R*)-**2-H**$^+$·2PF_6^-	10	50	89:11

[a]Reaction conditions: 0.025 mmol of **4**, 0.05 mmol of *E*-crotonaldehyde (**3a**), and 0.005 mmol of catalyst (20 mol %) in 60 μL of CH_2Cl_2 at the indicated temperature. [b]Conversions determined by ^{1}H NMR after 24 h. [c]Enantiomeric ratios determined by chiral stationary phase HPLC. The reaction catalyzed with (*S*)-**7** (see Table 2) is known[13] to produce (*S*)-**5a** as the major enantiomer. [d]No reaction was observed during 24 h.

Table 2. Asymmetric Michael Addition of 1,3-Diphenyl-1,3-propanedione and α,β-Unsaturated Aldehydes Catalyzed by Rotaxane (*R*)-1 and Prolinol Derivatives (*S*)-6 and (*S*)-7[a]



entry	R (3)	catalyst	conv (%)	er (*R*:*S*)[c]
1	Me (**3a**)	(*R*)-**1**·PF_6	60[b]	90:10
2	Me (**3a**)	(*R*)-**1-H**$^+$·2PF_6^-	0[d]	–
3	Et (**3b**)	(*R*)-**1**·PF_6	70	94:6
4	*n*Pr (**3c**)	(*R*)-**1**·PF_6	65	93:6
5	Ph (**3d**)	(*R*)-**1**·PF_6	0[d]	–
6	Me (**3a**)	(*S*)-**6**	100[e]	32:68
7	Me (**3a**)	(*S*)-**7**	100[e]	8:92

[a]Reaction conditions: 0.05 mmol of **4**, 0.1 mmol of α,β-unsaturated aldehyde (**3a**–**d**), and 0.01 mmol of catalyst (20 mol %) in 125 μL of CH_2Cl_2 at 10 °C. [b]Conversions determined by ^{1}H NMR after 24 h. [c]Enantiomeric ratios determined by chiral stationary phase HPLC. The reaction catalyzed with (*S*)-**7** is known[13] to produce (*S*)-**5a** as the major enantiomer. [d]No reaction was observed during 24 h. [e]Conversions determined by ^{1}H NMR after 12 h.

(*R*)-**2-H**$^+$·2PF_6^- (Figure 2a) shows a downfield shift of the benzylic protons of the catalytic unit ($\Delta\delta H_n$ = 0.92 and 0.97 ppm; $\Delta\delta H_p$ = 0.11 ppm), and one of the protons of one of the aromatic rings of the benzylamine unit ($\Delta\delta H_m$ = 0.70 ppm), due to hydrogen bonding between the ammonium group and the crown ether. In addition, an upfield shift is observed for the signal of the amide methyl group ($\Delta\delta H_r$ = −0.67 ppm) and

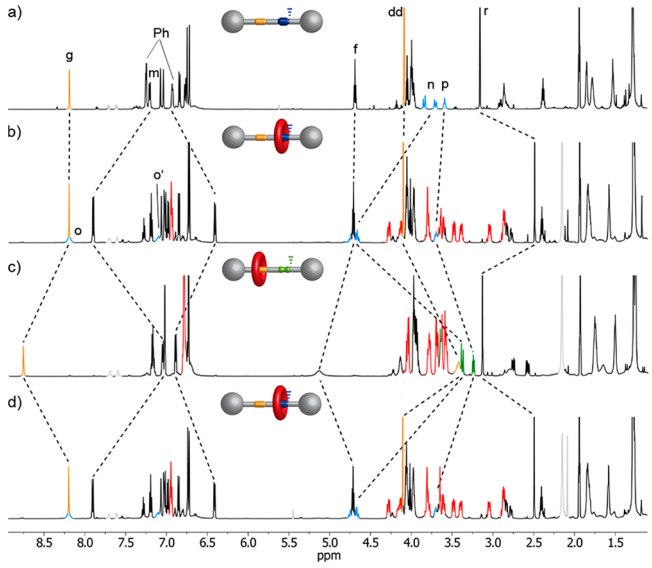


Figure 2. ^{1}H NMR spectra (600 MHz, CD_3CN, 293 K) of (a) thread (*R*)-**2-H**$^+$·2PF_6^-; (b) rotaxane (*R*)-**1-H**$^+$·2PF_6^-; (c) rotaxane (*R*)-**1**·PF_6; (d) solution (c) after addition of 1 equiv of HCl (1 M in Et_2O) and counterion exchange (KPF_6, CH_2Cl_2/acetone/water (1:4:2)). The lettering and color coding of the signals correspond to those shown in Figure 1.

one of the aromatic protons of the phenylalanine residue ($\Delta\delta H_{Ph}$ = −0.52 ppm) due to shielding by the aromatic rings of the macrocycle. In contrast, the signals of the triazolium protons (H_g and H_{dd}) appear at a similar chemical shift in both (*R*)-**1-H**$^+$·2PF_6^- and (*R*)-**2-H**$^+$·2PF_6^-. The observed chemical shifts strongly support the location of the macrocycle around the secondary ammonium site.

Deprotonation of rotaxane (*R*)-**1-H**$^+$·2PF_6^- with aqueous NaOH smoothly afforded (*R*)-**1**·PF_6, giving rise to significant changes in the ^{1}H NMR spectrum (Figure 2c). The benzylic protons of the benzylamine motif are shifted upfield ($\Delta\delta H_n$ = −1.17 and −1.28 ppm; $\Delta\delta H_p$ = −0.45 ppm), indicating that the amine group is not hydrogen bonding with the dibenzo-24-crown-8, and the amide methyl protons appear at the same chemical shift they do in the thread (*R*)-**2-H**$^+$·2PF_6^-. In contrast, the protons of the triazole ring and one of the CH_2 groups adjacent to the triazolium group are shifted downfield ($\Delta\delta H_g$ = 0.57 ppm; $\Delta\delta H_f$ = 0.43 ppm), indicating that they are now interacting with the crown ether, and the protons of the triazolium methyl group are shifted upfield ($\Delta\delta H_{dd}$ = −0.67 ppm) due to shielding by the macrocycle. The chemical shifts confirm the position of the macrocycle is around the triazolium unit, the preferred binding site now that the amine unit is no longer protonated. Upon reprotonation of the secondary amine group with a 1 M solution of HCl in Et_2O, the ^{1}H NMR spectrum of the rotaxane confirms that the original state, with the macrocycle residing over the ammonium unit, is restored (Figure 2d).

Having demonstrated that it is possible to control the position of the crown ether macrocycle on the axle in (*R*)-**1** by protonation/deprotonation of the secondary amine group, we investigated the efficacy of the rotaxane as an asymmetric organocatalyst. We chose as a reaction the Michael addition of 1,3-diphenyl-1,3-propanedione (**4**) to *E*-crotonaldehyde (**3a**), which can be catalyzed *via* iminium ion activation.[13] Initially, screening to optimize the reaction conditions was performed

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using the nonprotonated thread (*R*)-**2**·PF_6 as the catalyst (Table 1).

We confirmed that the reaction between **3a** and **4** in CH_2Cl_2 does not proceed at room temperature in the absence of the organocatalyst (Table 1, entry 1). The use of the nonprotonated thread (*R*)-**2**·PF_6 as the catalyst afforded the Michael adduct **5a** with excellent conversion and good stereoselectivity (Table 1, entry 2). When this reaction was catalyzed by (*S*)-**2**·PF_6, the enantiomer of the Michael adduct was obtained ((*S*)-**5a**[13]) (Table 1, entry 3). In order to optimize the enantioselectivity of the reaction, additional screening of the conditions was carried out (for solvent effects, see Supporting Information). Temperature proved to have a significant influence on the reactivity and enantioselectivity of the reaction (Table 1, entries 4−6). The reactions carried out at lower temperatures afforded better enantiomeric ratios, but at the expense of slower rates. The best results were found when the reaction was performed at 10 °C in CH_2Cl_2 affording **5a** with good conversion (60% after 24 h) and stereochemical control (92:8 er; Table 1, entry 6). When the reaction was catalyzed with the protonated thread (*R*)-**2**-H^+·$2PF_6^-$ using these conditions, **5a** was obtained with 50% conversion after 24 h in a 89:11 enantiomeric ratio (Table 1, entry 7), showing that the protonation of the catalyst does not inhibit catalysis to any significant extent.

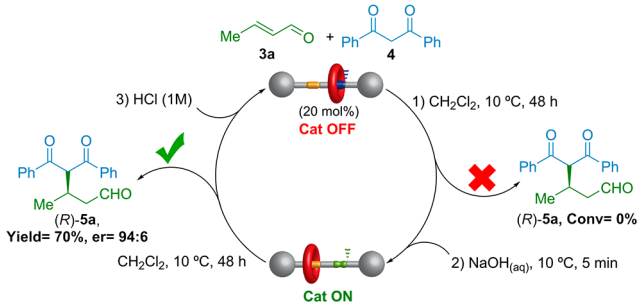
Once the optimized set of conditions was established, we investigated the asymmetric Michael addition between **3a** and **4** catalyzed by the nonprotonated and protonated rotaxanes (*R*)-**1**·PF_6 and (*R*)-**1**-H^+·$2PF_6^-$ (Table 2, entries 1−2).

The amine form of the rotaxane, (*R*)-**1**·PF_6, catalyzed the reaction as effectively as the amine form of the thread, (*R*)-**2**·PF_6, affording **5a** with good conversion and enantiomeric ratio (Table 1, entry 6 and Table 2, entry 1). However, in contrast to the catalysis by the protonated thread (Table 1, entry 7), the protonated (ammonium) form of the rotaxane, (*R*)-**1**-H^+·$2PF_6^-$, did not afford any Michael addition product **5a** (Table 2, entry 2) demonstrating that the switching 'off' of the asymmetric catalyst is extremely effective and is caused by the repositioning of the macrocycle to cover the catalytic site. Other alkyl-substituted α,β-unsaturated aldehydes (**3b,c**) with longer aliphatic chains also afforded the corresponding Michael adducts (**5b,c**) with good conversions and enantiomeric ratios (Table 2, entries 3 and 4). However, no reaction was observed using the aromatic α,β-unsaturated aldehyde **3d** (Table 2, entry 5).

In order to further evaluate the efficiency of the acyclic amine as an asymmetric organocatalyst in rotaxane (*R*)-**1**·PF_6, we compared its performance with the commercially available chiral prolinol organocatalysts (*S*)-**6** and (*S*)-**7** (Table 2, entries 6 and 7). Rotaxane (*R*)-**1**·PF_6 gave excellent control over the enantioselectivity of the reaction, generating a better enantiomeric ratio in the product than (*S*)-**6** (90:10 cf. 32:68; Table 2, entries 1 and 6) and similar to that of (*S*)-**7** (90:10 cf. 8:92; Table 2, entries 1 and 7). However, the rotaxane acyclic amine has significantly lower reactivity than the commercially available cyclic catalysts (60% conversion after 24 h compared to complete conversion after 12 h; Table 2, entries 1, 6, and 7).

Finally, the progress of the asymmetric Michael addition could also be controlled through *in situ* switching of the rotaxane catalyst (Scheme 1). After 48 h of stirring **3a** and **4** in the presence of 20 mol % rotaxane in its inactive, protonated, state ((*R*)-**1**-H^+·$2PF_6^-$) no conversion to product **5a** was observed (Scheme 1, part 1). Upon brief washing with 1 M aqueous NaOH, the rotaxane catalyst was switched 'on' affording **5a** in 70% yield and 94:6 er within 48 h (Scheme 1, part 2). The rotaxane catalyst could also be switched 'off' *in situ*: addition of 20 mol % of HCl (1 M) immediately stopped further formation of (*R*)-**5a** from **3a** and **4** (Scheme 1, part 3).

Scheme 1. *In Situ* Switching of Chiral Organocatalyst Rotaxane (*R*)-1 in the Michael Addition of 1,3-Diphenyl-1,3-propanedione (4) to Crotonaldehyde (3a)[a]



[a]See Supporting Information for experimental details.

In conclusion, rotaxane (*R*)-**1**·PF_6 is a switchable asymmetric organocatalytic system based on a simple acyclic secondary amine housed within a rotaxane architecture. The acyclic chiral secondary amine promotes an asymmetric Michael addition with stereochemical control comparable to, or better than, commercial cyclic amine organocatalysts at the expense of a slower rate of conversion. Biology uses molecular machines to control many aspects of chemical synthesis. Simultaneously employing different types of artificial switchable asymmetric catalysts may enable different products to be prepared from common pools of achiral building blocks, simply by switching the different catalysts 'on' and 'off'.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

David.Leigh@manchester.ac.uk.

Notes

The authors declare no competing financial interest.

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