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Exploring the Activation Modes of a Rotaxane-Based Switchable Organocatalyst

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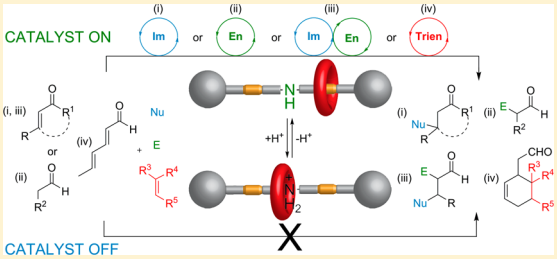
Supporting Information

ABSTRACT: The reactivity of a rotaxane that acts as an aminocatalyst for the functionalization of carbonyl compounds through HOMO and LUMO activation pathways has been studied. Its catalytic activity is explored for C−C and C−S bond forming reactions through iminium catalysis, in nucleophilic substitutions and additions through enamine intermediates, in Diels−Alder reactions via trienamine catalysis, and in a tandem iminium-ion/enamine reaction. The catalyst can be switched "on" or "off", effectively controlling the rate of all of these chemical transformations, by the *in situ* change of the position of the macrocycle between two different binding sites on the rotaxane thread.



1. INTRODUCTION

Enzymes are often regulated in nature through trigger-induced effects,[1] processes that are inspiring a growing number of synthetic catalysts for which an external stimulus can turn "on" or "off" the catalytic activity[2] or change the stereochemical outcome[3] of the system. However, the catalytic activity of most of the artificial switchable catalysts reported to date has only been tested with a limited number of reactions (usually one), and their scope has not been studied in detail. Understanding how switchable catalysts behave in their different states and how they participate in different reaction types could be important for their applications: for example with pools of differently functionalized building blocks that can react with the catalyst through different pathways or with catalysts where the "off" state leads to a reduced but not a zero level of catalytic activity with particularly reactive substrates. We recently described a switchable organocatalyst based on a rotaxane (**1**) able to control the rate of the Michael addition of an aliphatic thiol to *trans*-cinnamaldehyde (Figure 1).[4] Here we explore the efficacy of rotaxane **1**/**1**-H^+ as a switchable aminocatalyst in a variety of activation modes, including iminium, enamine, and trienamine catalysis, and in tandem iminium-enamine reactions.[5]

Rotaxane catalyst **1** consists of a dibenzo-24-crown-8 macrocycle locked onto an axle containing a dibenzylamine/ammonium moiety (the catalytic unit)[6] and a triazolium ring (Figure 1). The catalytic motif can be concealed or revealed, and its activity switched "off" or "on", by the acid/base-promoted change of the position of the macrocycle on the thread. When the rotaxane is protonated the macrocycle preferentially interacts with the ammonium unit (a better binding site than the triazolium ring), concealing it from the bulk, and the catalyst is in its "off" state (Figure 1, top).[7] When the secondary amine is not protonated the triazolium ring is the preferred binding site for the macrocycle so the catalytic center is exposed and available to participate in catalysis (Figure 1, bottom).[8]

Various types of secondary amines and ammonium groups (usually heterocycles) have previously been shown to participate in different types of covalent organocatalysis,[9] principally the functionalization of the α, β, γ, and ε position of carbonyl compounds through the three distinct activation pathways reported so far in aminocatalysis: LUMO (iminium ion),[10] HOMO (enamine, dienamine, and trienamine),[11−13] and SOMO[14] activation. However, acyclic secondary amines have been rarely studied as organocatalysts[15] and have only been shown to catalyze a limited number of reaction types. Furthermore, the masking of an axle site in a rotaxane is an intrinsically fluxional process; the dynamic nature of binding interactions and molecular level motions means that for some of the time the ammonium group of **1**-H^+ will be exposed and available to participate in reactions. It was therefore of interest to investigate both the ability of acyclic secondary amines to catalyze a variety of reaction types through different activation modes and the effectiveness of switching "off" catalysis through encapsulation using a rotaxane architecture.

Here we explore the scope of switchable rotaxane **1**/**1**-H^+ in a range of aminocatalytic processes and demonstrate its usefulness, efficiency, and robustness in iminium (Figure 2i) and enamine catalysis (Figure 2ii), in tandem iminium-enamine reactions (Figure 2iii), and in trienamine catalysis (Figure 2iv). The rotaxane did not catalyze reactions between α,β-unsaturated aldehydes and electrophiles or dienophiles through dienamine activation. In most, but not all, cases the switching mechanism is highly effective in turning catalytic activity "on" or "off".

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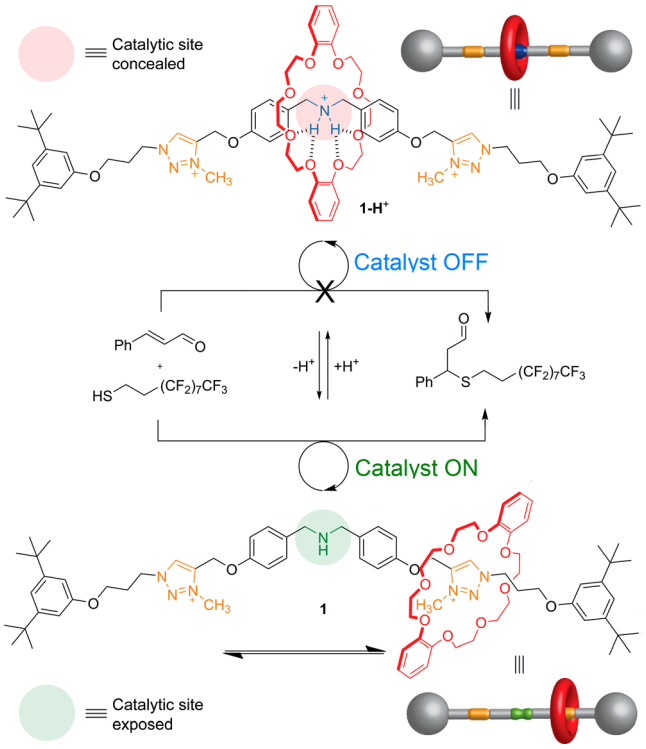


Figure 1. Rotaxane-based switchable organocatalyst **1**/**1**-H^+ and its application to control the rate of the Michael addition of an aliphatic thiol to *trans*-cinnamaldehyde through iminium activation.[4] The activity of the rotaxane catalyst can be switched "on" and "off" through the acid/base-promoted change of the position of the macrocycle between the different binding sites on the axle, revealing or concealing the organocatalytic dibenzylamine/ammonium group.

2. RESULTS AND DISCUSSION

2.1. Iminium Catalysis. The *β*-functionalization of carbonyl compounds through the Michael addition of a nucleophile is one of the most effective and well-studied examples of iminium activation organocatalysis.[10] In order to explore the generality of rotaxane **1** in iminium catalysis, we decided to investigate the Michael addition of a thiol[16] (Table 1) and activated methylene C-nucleophiles[17] (Table 2) to different *α*,*β*-unsaturated aldehydes and ketones (**2a**–**e**). Each of the reactions was investigated using both the putative active (**1**) and inactive (**1**-H^+) forms of the rotaxane catalyst and, as a control, carried out in the absence of the rotaxane (see Supporting Information).

Rotaxane **1** (catalysis ON) proved to be an excellent catalyst for the *β*-sulfenylation of *α*,*β*-unsaturated aldehydes, affording compounds **4a** and **4b** with high (95–98%) conversions (Table 1, entries 1 and 2). In contrast, the protonated rotaxane **1**-H^+ (catalyst OFF) did not show catalytic activity when using *trans*-cinnamaldehyde as the substrate and only a significantly reduced yield (14%) of product with *trans*-crotonaldehyde **2b**. The reaction also proceeded with excellent conversions using acyclic and cyclic *α*,*β*-unsaturated ketones as Michael acceptors with catalyst **1** (Table 1, entries 3–5), although when the reaction was carried out with cyclic ketones **2d** and **2e** the addition of NaOAc (a weak base that activates the nucleophile) was necessary to achieve high conversions. With rotaxane **1**-H^+ as catalyst no product formation was observed (Table 1, entries 4 and 5) other than modest (8%) conversion with **2c** (Table 1, entry 3).

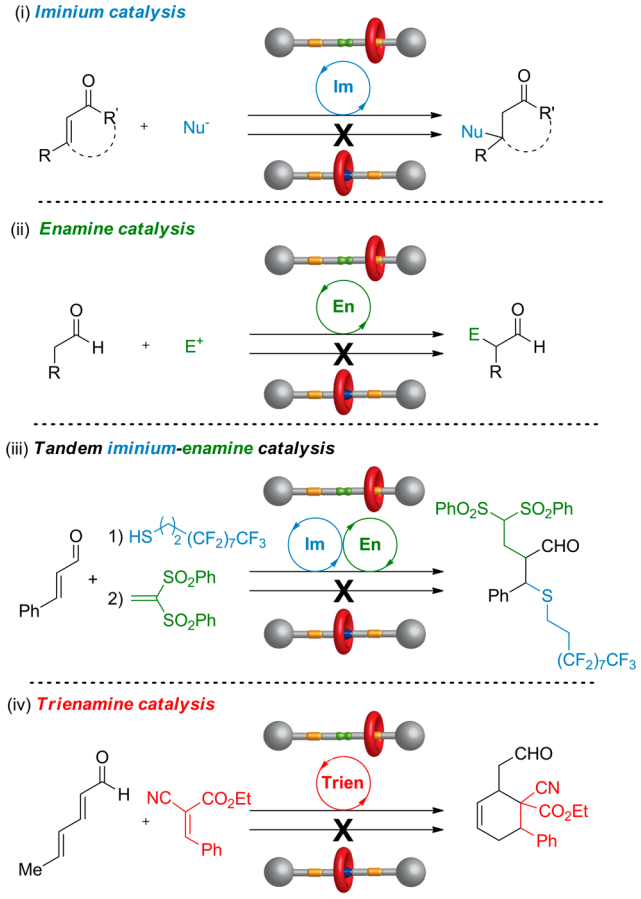
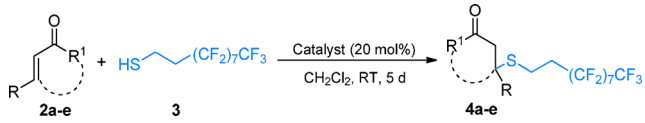
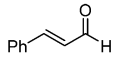
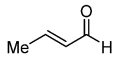
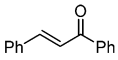
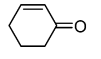


Figure 2. Scope of the rotaxane-based switchable organocatalyst **1** in (i) iminium catalysis (Im); (ii) enamine catalysis (En); (iii) tandem iminium-enamine catalysis; and (iv) trienamine catalysis (Trien).

Table 1. *β*-Sulfenylation of *α*,*β*-Unsaturated Carbonyl Compounds[a]



Entry	Carbonyl Compound		Conversion (%)[b] no cat	**1**	**1**-H^+
1		(**2a**)	n.r.[c]	95	n.r.[c]
2		(**2b**)	4	98	14
3		(**2c**)	n.r.[c,d]	82[d]	8[d]
4		(**2d**)	n.r.[c,e]	98[e]	n.r.[c,e]
5		(**2e**)	n.r.[c,e]	98[e]	n.r.[c,e]

[a]Reaction conditions: 0.1 mmol of **2a**,**b**,**d**,**e**, 0.05 mmol of thiol **3**, and 0.01 mmol of catalyst (**1** or **1**-H^+) (20 mol %) in 125 *μ*L of CH_2Cl_2 at rt. [b]Conversions determined by ^{1}H NMR. [c]No reaction observed. [d]Reaction carried out with 0.05 mmol of **2c**, 0.025 mmol of thiol **3**, and 5×10^{-3} mmol of catalyst (**1** or **1**-H^+) (20 mol %) in 150 *μ*L of CH_2Cl_2 at rt. [e]With NaOAc (20 mol %) as additive.

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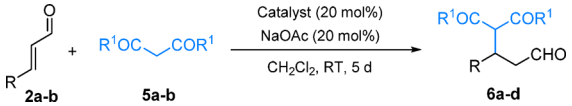
Table 2. Michael Addition of Activated Methylene Compounds to α,β-Unsaturated Aldehydes[a]



Entry	R (2)	R[1] (5)	Conversion (%)[b]		
			no cat	1	1-H$^+$
1	Me (**2b**)	Ph (**5a**)	n.r.[c]	95	n.r.[c]
2	Me (**2b**)	Me (**5b**)	n.r.[c]	98	n.r.[c]
3	Ph (**2a**)	Me (**5b**)	n.r.[c]	23	n.r.[c]
4	Ph (**2a**)	Ph (**5a**)	n.r.[c]	n.r.[c]	n.r.[c]

[a]Reaction conditions: 0.1 mmol of **2a,b**, 0.05 mmol of **5a,b**, 0.01 mmol of catalyst (**1** or **1**-H$^+$) (20 mol %), and 0.01 mmol of NaOAc (20 mol %) in 125 μL of CH_2Cl_2 at rt. [b]Conversions determined by ^{1}H NMR. [c]No reaction observed.

To probe the robustness of rotaxane **1** as an iminium activation catalyst for C−C bond formation, we investigated its catalytic activity in the Michael addition of 1,3-dicarbonyl compounds to α,β-unsaturated carbonyl compounds (Table 2).

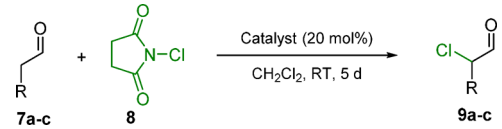
None of the Michael additions investigated with α,β-unsaturated aldehydes showed conversion to the corresponding β-substituted aldehyde in the absence of catalyst or with the inactive rotaxane **1**-H$^+$. In contrast, rotaxane **1** catalyzed the reaction between the aromatic and aliphatic substituted 1,3-dicarbonyl compounds (**5a**, **5b**) and *trans*-crotonaldehyde (**2b**) with excellent conversions (Table 2, entries 1 and 2). With *trans*-cinnamaldehyde (**2a**) the Michael adduct was only obtained with acetylacetone (**5b**) and with modest (23%) conversion (Table 2, entry 3). These reactions all required the presence of NaOAc. The reaction of 1,3-dicarbonyl compounds with α,β-unsaturated ketones under similar reaction conditions did not afford the Michael adducts.

The results in Tables 1 and 2 demonstrate the effectiveness of rotaxane **1** as an organocatalyst for iminium ion activation. To confirm that the switching process is effective *in situ*, we employed the interconversion of **1** and **1**-H$^+$ to control the progress of the sulfa-Michael addition of thiol **3** to *trans*-cinnamaldehyde (**2a**) and the Michael addition of 1,3-diphenyl-1,3-propanedione (**5a**) to *trans*-crotonaldehyde (**2b**). In both transformations, after 48 h in the presence of 20 mol % rotaxane in its inactive, protonated state (**1**-H$^+$) no conversion to products was observed. Upon brief washing with 1 M aqueous NaOH, the rotaxane catalyst was switched "on" to form **1**, leading to complete conversion of the reactants to the Michael addition products after 5 days. A control experiment, where the same procedure was carried out in the absence of the rotaxane catalyst, confirmed that the catalysis observed is due to the rotaxane organocatalyst (see Supporting Information).

2.2. Enamine Catalysis. The α-functionalization of saturated carbonyl compounds by their activation with secondary amines through an enamine intermediate that reacts with suitable electrophiles has been widely reported.[11] To evaluate the efficacy of the rotaxane switchable organocatalyst in enamine catalysis, we explored both nucleophilic substitution and nucleophilic addition reactions for the construction of C−X and C−C bonds in the α position of carbonyl compounds.

The nucleophilic substitution reaction investigated was the α-chlorination of aldehydes with *N*-chlorosuccinimide.[18] Using the active organocatalyst **1**, significant (40−61%) conversions were obtained (Table 3, entries 1−3) with both aliphatic and benzyl-substituted aldehydes (**7a**−**c**). In the absence of a

Table 3. α-Chlorination of Aldehydes[a]



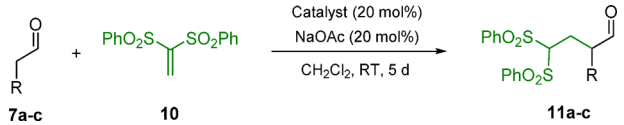
Entry	R (7)	Conversion (%)[b]		
		no cat	1	1-H$^+$
1	Me (**7a**)	n.r.[c]	43	n.r.[c]
2	*i*Pr (**7b**)	n.r.[c]	61	n.r.[c]
3	Bn (**7c**)	n.r.[c]	40	n.r.[c]

[a]Reaction conditions: 0.1 mmol of **7a**−**c**, 0.05 mmol of **8** and 0.01 mmol of catalyst (**1** or **1**-H$^+$) (20 mol %) in 125 μL of CH_2Cl_2 at rt. [b]Conversions determined by ^{1}H NMR. [c]No reaction observed.

catalyst or when using the inactive form of rotaxane (**1**-H$^+$) no conversion to products was observed. The α-chlorination of acyclic and cyclic ketone substrates was also investigated, but in these cases no conversion to products was observed.

As a representative example of an addition reaction proceeding through enamine catalysis, we chose the Michael addition of carbonyl compounds to vinyl bis-sulfone **10** (Table 4).[19] As before the control reactions of aliphatic and benzyl-

Table 4. Michael Addition of Aldehydes to Vinyl Bis-Sulfone 10[a]



Entry	R (7)	Conversion (%)[b]		
		no cat	1	1-H$^+$
1	Me (**7a**)	n.r.[c]	23	n.r.[c]
2	*i*Pr (**7b**)	n.r.[c]	43	n.r.[c]
3	Bn (**7c**)	n.r.[c]	70	n.r.[c]

[a]Reaction conditions: 0.1 mmol of **7a**−**c**, 0.05 mmol of **10**, 0.01 mmol of catalyst (**1** or **1**-H$^+$) (20 mol %), and 0.01 mmol of NaOAc (20 mol %) in 125 μL of CH_2Cl_2 at rt. [b]Conversions determined by ^{1}H NMR. [c]No reaction observed.

substituted aldehydes (**7a**−**c**) with **10** without catalyst or with protonated rotaxane **1**-H$^+$ did not afford the corresponding Michael adducts **11a**−**c**. In contrast the deprotonated rotaxane, **1**, catalyzed the formation of the desired products in the presence of NaOAc, with conversions in the range 23−70% (Table 4, entries 1−3).

As with the enamine substitution reactions, rotaxane **1** showed no activity in the nucleophilic addition of ketones (cyclic or acyclic) to vinyl bis-sulfone (**10**) under the investigated reaction conditions.

The *in situ* switching of the catalyst in enamine catalysis was demonstrated by controlling the progress of the nucleophilic addition of aldehyde **7c** to **10**. After 72 h of stirring **7c** and **10** in the presence of 20 mol % rotaxane in its inactive, protonated state (**1**-H$^+$) no conversion to product **11c** was observed. After brief washing with 1 M aqueous NaOH, the rotaxane catalyst

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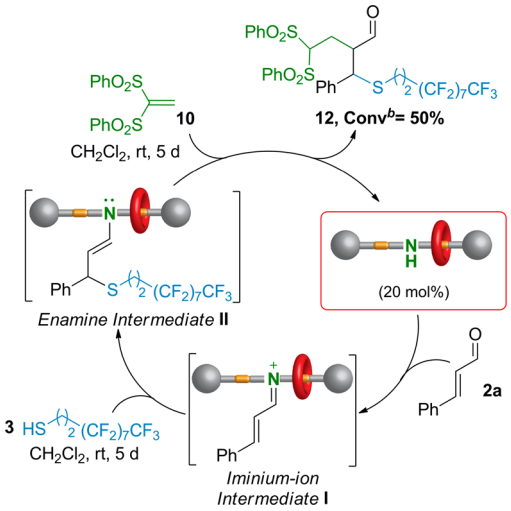
was switched "on", resulting in the formation of **11c** in a 70% conversion after 5 d. A control experiment, carrying out the reaction in the absence of the rotaxane, again confirmed that the conversion is due to the rotaxane organocatalyst (see Supporting Information).

In the enamine activation mode, the change of the position of the macrocycle on the rotaxane generally allows for greater control over the rate of the reaction than in iminium catalysis, as the "off" state of the system does not exhibit any observable catalytic activity at all. The active form of the rotaxane catalyst promotes both substitution and addition reactions, albeit with lower conversions than is found with the best iminium ion catalyzed reactions.

2.3. Tandem Iminium-Enamine Catalysis. The ability of rotaxane **1** to activate carbonyl compounds through both enamine and iminium-ion mechanisms makes this catalyst ideal for its application in tandem reactions,[20] where aldehydes substituted in both the α and β positions can be formed. Such reactions are based on the conjugated addition of nucleophiles to α,β-unsaturated aldehydes followed by the functionalization with an electrophile at the α position via the enamine intermediate. To demonstrate that this can be achieved with rotaxane **1**, we carried out the addition of thiol **3** to *trans*-cinnamaldehyde (**2a**) catalyzed by **1** through iminium formation, followed by subsequent addition of vinyl bis-sulfone **10** via enamine catalysis to afford compound **12** (Scheme 1).

Scheme 1. Tandem Iminium-Enamine Reaction: Michael Addition of 3 to *trans*-Cinnamaldehyde (2a) Followed by Nucleophilic Addition to Vinyl Bis-Sulfone 10[a]

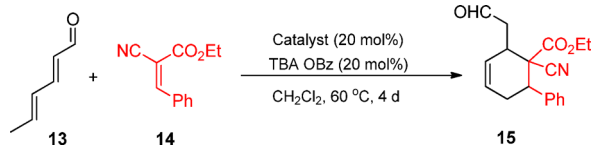


[a]Reaction conditions: 0.1 mmol of **2a**, 0.05 mmol of **3** and 0.01 mmol of catalyst (**1** or **1**-H^+) (20 mol %) in 125 μL of CH_2Cl_2 at rt. After 5 days, addition of 0.05 mmol of **10** in 125 μL of CH_2Cl_2 at rt. [b]Conversion determined by ^{1}H NMR.

Two new bonds, a C−S bond (by iminium ion catalysis) and a C−C bond (by enamine catalysis), are formed in 50% yield over the two steps. The reaction did not proceed in the absence of the organocatalyst or when using the protonated "off" form **1**-H^+ of the rotaxane.

2.4. Trienamine Catalysis. Recently it was discovered that some small-molecule amines could catalyze the Diels−Alder reactions of polyenals (which act as dienes) with dienophiles through trienamine intermediates.[13] Encouraged by the successful application of rotaxane **1** as an organocatalyst in iminium and enamine catalysis, we investigated whether the switchable rotaxane can be utilized as a catalyst for the Diels−Alder reaction between 2,4-dienals and cyanoacetates[13a] (Table 5). We confirmed that the reaction between polyenal **13** and

Table 5. Diels−Alder Reaction of 2,4-Dienal 13 and Cyanoacetate 14[a]



13 14 15

Entry	Catalyst	Conversion (%)[b]
1	no cat	n.r.[c]
2		n.r.[c]
3		84

[a]Reaction conditions: 0.075 mmol of **13**, 0.05 mmol of **14**, 0.01 mmol of catalyst (**1** or **1**-H^+) (20 mol %), and TBA OBz (tetrabutylammonium benzoate) (20 mol %) in 250 μL of CH_2Cl_2 at 60 °C. [b]Conversions determined by ^{1}H NMR. [c]No reaction was observed by ^{1}H NMR.

cyanoacetate **14** in CH_2Cl_2 does not proceed at 60 °C in the absence of the organocatalyst or using protonated rotaxane **1**-H^+ (Table 5, entries 1 and 2).[21] The use of the rotaxane **1** as catalyst in the presence of a small amount of tetrabutylammonium benzoate (TBA OBz) afforded the Diels−Alder adduct **15** in good yield (84%) after 4 days (Table 5, entry 3).

The progress of the Diels−Alder reaction was also effectively controlled by *in situ* switching of the rotaxane. After stirring **13** and **14** in the presence of 20 mol % rotaxane in its protonated form (**1**-H^+) and 20 mol % of TBA OBz for 5 days at 60 °C, no conversion to product **15** was observed. After washing with 1 M aqueous NaOH, the rotaxane catalyst was switched "on" resulting in the formation of **15** in 84% yield after 5 days. A control experiment without the catalyst generated no product (see Supporting Information).

Rotaxane **1**/**1**-H^+ proved to be an excellent switchable catalyst for trienamine catalysis, with a clear "off" state that does not display catalytic activity and an "on" state able to promote the transformation with good conversion.

3. CONCLUSIONS

We have demonstrated that a rotaxane which masks/exposes an acyclic secondary amine in response to acid/base exhibits broad scope as a switchable organocatalyst. The "on-state" of the rotaxane shows excellent catalytic activity (often 95−98% yields) in the β-functionalization of carbonyl compounds with C or S-nucleophiles through iminium activation, although the "off-state" of the reaction also promotes the most facile of these transformations to a lesser degree. The "on-state" of the rotaxane is somewhat less effective (40−61% conversions) at promoting nucleophilic addition or substitution reactions via enamine catalysis, but the switching is more effective, with the "off-state" of the catalyst showing no detectable catalytic activity in these reactions. The rotaxane catalyst is even able to promote tandem iminium-enamine reaction sequences with

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high efficiency and the Diels–Alder reaction of dienals through a trienamine activation pathway.

Understanding the efficacy and limitations of particular classes of switchable catalysts should prove useful in the development of systems, whereby pools of diverse building blocks can be induced to react in different ways, forming different products in multistep reaction sequences in one pot, simply by controlling the sequence through which latent catalysts are switched "on" and "off".

■ ASSOCIATED CONTENT

Supporting Information

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

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Notes

The authors declare no competing financial interest.

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