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# A Fluorescent and Switchable Rotaxane Dual Organocatalyst

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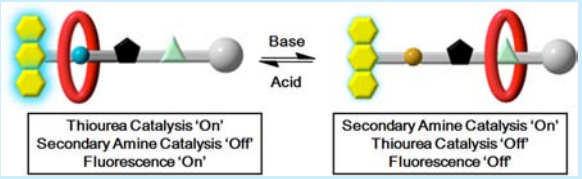
Supporting Information

**ABSTRACT:** Rotaxane organocatalysis presents a new direction toward controlled one-pot catalytic reactions. By combining molecular switches and catalysts, fluorescence and pH-responsive switching along with the exclusive selectivity of dual catalytic reactions are demonstrated. A newly designed [2]rotaxane catalyst containing an anthracene group was used to visualize the catalytic reaction process upon switching the macrocycle.




The idea of an artificial switchable catalyst[1] was inspired by enzymatic functions in nature. Rotaxane catalysis[2−4] is a potential candidate to realize this concept. This is an emerging chemical field that explores a single catalyst that catalyzes various reactions in a stepwise and cascade manner by shuttling the ring within the rotaxane molecule. This sophisticated molecular shuttling can be governed by pH,[5] temperature,[6] redox reactions,[7] competitive binding,[8] radiation,[9] *etc.* Studies on rotaxane catalysis were pioneered by Takata[2a] in 2004, demonstrating that rod-shaped thiazolium salt acts as a catalytic site, and the chiral binaphthyl macrocycle induces the stereoselectivity for asymmetric benzoin condensations. Leigh and his team later prepared acid−base switchable [2]rotaxane catalysts utilizing different activation modes of an amino group.[3a,b] According to the definition given by Leigh, rotaxane catalysts can be subcategorized into (i) a catalytic moiety on rotaxane scaffolds,[2] (ii) a switchable rotaxane catalyst,[3] and (iii) a processive rotaxane catalyst.[4] Recently, his group reported a rotaxane molecule that contains two catalytic sites[3c] bearing a secondary amine and a squaramide in the thread, which selectively catalyzes the Michael reaction between dibenzoylmethane, crotonaldehyde and *trans*-$\beta$-nitrostyrene in protonated and unprotonated forms.

Fluorescence switching is one of the observable tools used to characterize rotaxane shuttling. Various examples have shown that the florescence of [2]rotaxane can be changed upon triggering with pH stimuli.[5e] Additionally, the rotaxane architecture can be used to stabilize near-infrared dyes for bioimaging.[10] Meanwhile, only a few examples have been found of a fluorophore tagged within the catalyst molecule of an organocatalyst, and the only known application was in metal-containing coupling reactions without pure organic reactions.[11]

By applying the concept developed by Leigh,[3c] in this study, we report a new fluorescence tagged thiourea-based switchable [2]rotaxane dual catalyst by combining fluorescence and a switchable catalyst that are mediated by pH. This catalyst catalyzes different reactions within a mixture of substrates in which the simultaneous use of fluorescence under UV irradiation is employed to visualize the different positions of rotaxane's macrocycle with the manipulation of the specific catalytic site.

Urea-based rotaxane was first synthesized by Stoddart and coworkers in 1999[12] and was studied by Chiu's group.[13] The urea moiety within the rotaxane structure acts as a weak binding site[13c] for switching controllable organogels[13b] and a template for rotaxane synthesis.[13a] This process has not been applied in organocatalysis. We question whether it is possible to (1) synthesize a (thio)urea-based rotaxane and (2) employ thiourea in rotaxane organocatalysis. The design of thiourea-based rotaxane includes an anthracene fluorescent moiety with two potential catalytic sites, a secondary amine, and thiourea. Anthracene is a common fluorescent group emitting a blue fluorescence with an excitation wavelength of 368 nm in which the change in the fluorescence property can be concurrently correlated with catalysis. Theoretically, the secondary amine/ammonium group can be used as an iminium catalyst,[14] which is also a well-known binding site for the dibenzo[24]crown-8 (DB24C8) macrocycle. The thiourea group acts as another catalytic site in hydrogen-bond donor catalysis.[15] The [2]-rotaxane catalyst consists of a traditional DB24C8 macrocycle, a secondary amine/ammonium, a triazole ring, and a thiourea moiety and is stoppered with anthracene and 3,5-bis-(trifluoromethyl)-benzene.[5e] When rotaxane is in the protonated form (**1**-H·$PF_6$), ammonium is the best site for DB24C8, masking the iminium catalysis while the thiourea group is available for catalysis. In the deprotonated form (**1**), thiourea becomes the strongest binding site for DB24C8, turning off the thiourea catalytic property and enabling the iminium catalysis. Regarding rigidity, although an ethylene glycol unit is present in rotaxane, the triazole ring serves as a spacer to separate the two catalytic sites, thus preventing the back folding of thiourea with the amine/ammonium group.

The synthesis of thiourea-based rotaxane followed the conventional pathway, threading followed by stoppering,

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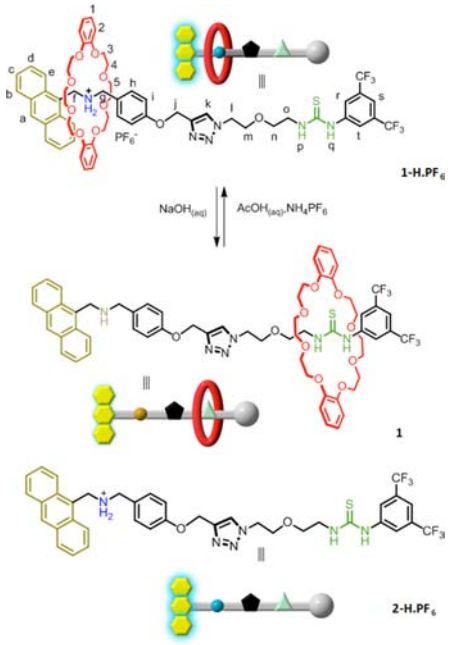
employing a modified CuACC click reaction.[16a] Two compounds, protonated aminomethylanthracene linked with acetylene (**S4**) and thiourea linked with azide (**3**), were synthesized accordingly. The DB24C8 first binds with the ammonium-H·$PF_6$ salt (**1**-H·$PF_6$) in dichloromethane, forming [2]pseudorotaxane (**1**-H·$PF_6$⊂DB24C8). Then, the thiourea side group functionalized with an azide group (**3**) is added, and the acid−base jointly promoted CuACC reaction[16b] occurs with the addition of AcOH/DIPEA (2:1 mol equiv) and $Cu(MeCN)_4PF_6$ (Scheme 1). Although the formation of a thiourea $Cu^+$ complex has been

**Scheme 1. Schematic Diagram of Acid−Base Switchable Fluorescent [2]Rotaxane Catalyst 1-H·$PF_6$, 1, and the Thread 2-H·$PF_6$**




reported,[17] we discovered that, in the presence of thiourea, the CuACC click reaction could still proceed. This is because thiourea could be easily hydrolyzed to urea via catalysis with a copper ion. In terms of mechanism, we presumed that the thiourea first coordinates with $d^{10}$ $Cu^+$, forming the homoleptic $[Cu^I(thiourea)_2(MeCN)_2]^+$. An observed color change from yellow to orange-red upon the addition of $Cu^+$ to the reaction mixture indicated the formation of copper−thiourea complexes without the presence of free $Cu^+$ (green) in the reaction mixture. At this stage, the acetylene displaced the MeCN ligand(s), thereby forming acetylide to continue the click reaction. This discovery can be further applied to the design and synthesis of new functional materials and biomolecules. The thiourea−copper complex can finally be worked up by washing with aqueous NaCN solution, yielding rotaxane **1**-H·$PF_6$, with a 59% yield after column chromatography.

The successful synthesis of **1**-H·$PF_6$ was confirmed by $^1$H NMR (see Supporting Information) and electrospray ionization-mass spectrometry (ESI-MS). By comparing the $^1$H NMR spectra of the click thread (**2**), protonated click thread (**2**-H·$PF_6$), and rotaxane (**1**-H·$PF_6$) (Figure 1a, b, e), the signals reveal the interaction of DB24C8 with ammonium within the rotaxane molecule. The protons adjacent to the ammonium ($H_f$ and $H_g$) were shifted downfield ($\Delta\delta H_f$ = 0.76 ppm and $\delta H_g$ = 1.13 ppm) in **1**-H·$PF_6$, corresponding to a strong hydrogen bond interaction

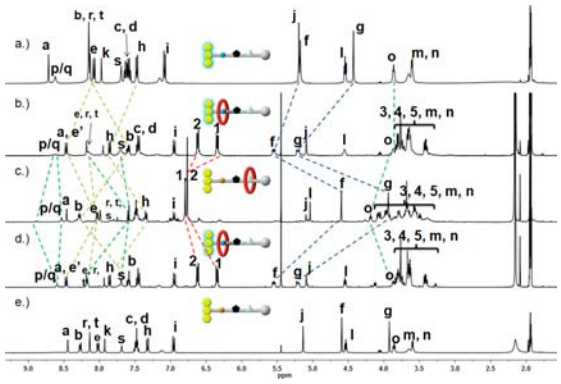



**Figure 1.** $^1$H NMR spectra (400 MHz, $CD_3CN$, 298 K) of (a) thread **2**-H·$PF_6$; (b) rotaxane **1**-H·$PF_6$; (c) rotaxane **1**-H·$PF_6$ after deprotonation with $NaOH_{(aq)}$ converted to rotaxane **1**; (d) rotaxane **1** reprotonation with AcOH/$NH_4PF_6$; and (e) thread **2**.

between ammonium and the oxygen of DB24C8. Meanwhile, the $H_f$ and $H_g$ signals changed from a singlet to a triplet, indicating that the ammonium became less labile. Additionally, the split signals of the DB24C8 aromatic ($H_1$, $H_2$) and aliphatic ($H_3$, $H_4$, $H_5$) protons ensured that the macrocycle was encircled in rotaxane due to the facing of two nonsymmetrical ends.

Although thiourea is a weaker binding site for DB24C8 compared with common rotaxane secondary sites, such as triazolium[18] and 4,4′-bipyridinium ($bipy^{2+}$),[5a−c,e] we found that thiourea can act as a switching station for DB24C8 upon base treatment in our [2]rotaxane molecule. When rotaxane **1**-H·$PF_6$ was subjected to deprotonation by washing with an aqueous NaOH solution (Scheme 1),[19] significant signal shifts were noticed in the $^1$H NMR spectrum (Figure 1b, c). The protons adjacent to the amine ($H_f$ and $H_g$) were shifted upfield ($\Delta\delta H_f$ = −0.94 ppm and $\Delta\delta H_g$ = −1.26 ppm) to the same positions as those in thread **2**. Protons next to the thiourea $H_o$ were downfield shifted ($\Delta\delta H_o$ = 0.35 ppm), and thiourea protons $H_p$ and $H_q$ appeared in the downfield area, suggesting the formation of hydrogen bonds with the crown ether oxygen atoms. Triazole proton $H_k$ showed a similar chemical shift after deprotonation, indicating that the macrocycle was not located in the triazole ring. Interestingly, the protons adjacent to triazole $H_I$ shifted downfield ($\Delta\delta H_I$ = 0.49 ppm), which could be due to the folding of the ethylene glycol toward the crown ether protons. The protons of 3,5-bis(trifluoromethyl)benzene $H_r$, $H_s$, and $H_t$ were shifted upfield, resulting in shielding by the ring current of the DB24C8 aryl groups. Moreover, the aromatic protons of anthracene shifted back to the same positions as those in thread **2**, assuring that the macrocycle is no longer localized next to the anthracene end group. When **1** was reprotonated with AcOH/$NH_4PF_6$, all signals were identical to the original spectrum (Figure 1d), indicating that the macrocycle shuttled back to the original site. The binding constant ($K_a$) between DB24C8 and the thiourea complex was calculated as $4.0 \times 10^3$ $M^{-1}$ using a single-point determination method (Figure S31 in MeCN from the $^1$H NMR spectrum). The use of the simple, commercially available macrocycle (DB24C8) and the straightforward synthetic scheme provides advantages for further applications in the catalysis, design, and modification of the molecules, as well as the future development of rotaxane catalysis.

With the successful switching of [2]rotaxane, we further investigated the intrinsic fluorescence properties of [2]rotaxane before and after the switching process. Catalytic reaction entry 1 shows an intense (local maximum) anthracene fluorescence,



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while entry 2 only shows a weakened (local minimum) anthracene fluorescence (Figure 2). Thus, [2]rotaxane is acid–base switchable. The pH switching processes of **1**-H·$PF_6$ and **1** with an acid/base were characterized by UV/vis spectroscopy and fluorescence spectroscopy (Figures S1–S13). The switching of the macrocycle of [2]rotaxane, which is correlated to their corresponding fluorescence and catalytic properties, can be visualized by conventional UV lamp irradiation.

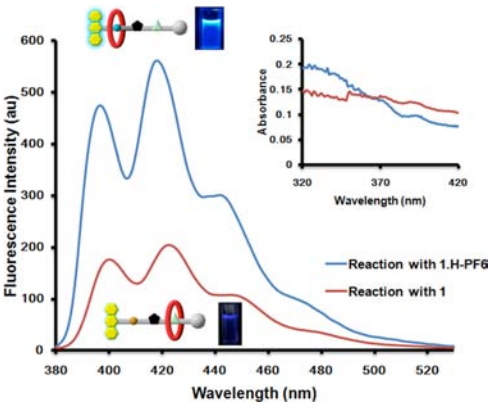
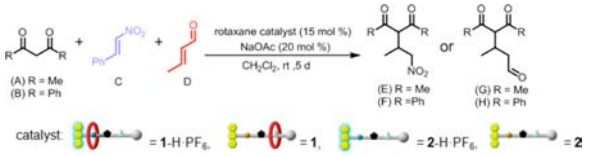



**Figure 2.** Fluorescence spectrum of **1**-H·$PF_6$ and **1** in the catalytic reaction entries 1 and 2 ($\lambda_{exc}$ = 368 nm, $1 \times 10^{-5}$ M) in $CH_2Cl_2$. Insert: UV/vis spectrum of **1**-H·$PF_6$ and **1** in the reaction entries 1 and 2.

We finally investigated the catalytic usage of [2]rotaxane (**1**-H·$PF_6$ and **1**) and the thread (**2**-H·$PF_6$ and **2**) as dual organocatalysts in a mixture of two and three components. We report eight sets of catalytic data (Table 1) in which the use of the specific mode of rotaxane catalyst (**1**-H·$PF_6$, **1**) can selectively catalyze different types of Michael addition reactions to give the desired products. Thiourea was used to activate the nitro-olefin of **C** via H-bond-donor catalysis to react with **A**/**B** (Scheme S1). The secondary amine/ammonium group was expected to catalyze the reaction between **A**/**B** and $\alpha,\beta$-unsaturated aldehyde **D** via iminium catalysis (Scheme S2). More substrate derivatives have been screened; however, they showed trace (Figure S26) or no conversions (Figures S27, S28) due to their low reactivities.

**Table 1. Catalysis Entry Using 1-H·$PF_6$, 1, 2-H·$PF_6$, and 2 in the Two- and Three-Component Systems**[a]




| entry | substrates | catalyst | yield (%) |
|---|---|---|---|
| 1 | A + C + D[b] | **1**-H·$PF_6$ | 81 (E), trace (G) |
| 2 | A + C + D[b] | **1** | trace (E), 50 (G) |
| 3 | A + C + D[c] | **2**-H·$PF_6$ | trace (E), 42 (G) |
| 4 | A + C + D[c] | **2** | trace (E), 52 (G) |
| 5 | B + C + D[b] | **1**-H·$PF_6$ | 55 (F), trace (H) |
| 6 | B + C + D[b] | **1** | trace (F), 80 (H) |
| 7 | B + C + D[c] | **2**-H·$PF_6$ | 21 (F), 47 (H) |
| 8 | B + C + D[c] | **2** | 20 (F), 60 (H) |
| 9 | B + C[de] | **1**-H·$PF_6$ | 71 (F) |
| 10 | B + D[d] | **1** | 70 (H) |
| 11 | A + C[d] | **1**-H·$PF_6$ | 98 (E) |
| 12 | A + D[d] | **1** | 69 (G) |

[a]Yields were determined by $^1$H NMR spectroscopy. [b]Reaction conditions: 0.1 mmol of **A**/**B**, **D**, 0.05 mmol of **C**, 15 mol % of catalyst, and 20 mol % of NaOAc in 125 $\mu$L of $CH_2Cl_2$ for 5 days at rt. [c]0.1 mmol of **A**/**B**, **D**, and **C**, 15 mol % of catalyst, and 20 mol % of NaOAc in 125 $\mu$L of $CH_2Cl_2$ for 5 days. [d]0.05 mmol of **A**/**B**, 0.1 mmol of **C**/**D**, 15 mol % of catalyst, and 20 mol % of NaOAc in 125 $\mu$L of $CH_2Cl_2$ for 3 days at rt. [e]After stirring for 5 days. The designation "trace" means the conversion was <5%.

For a three-component system, initially, **1**-H·$PF_6$ (thiourea exposed) catalyzed the reaction between **A** and **C** to give **E** in a yield of up to 81% with a trace amount of **G**. When using **1** (secondary amine exposed) as the catalyst in entry 2, a trace amount of product **E** and ~50% of **G** were observed. In entries 5 and 7, similar results were obtained in which **F** and **H** were observed with moderate yields (55–73%) and with high selectivity (only a trace amount of the other product was observed) using **1**-H·$PF_6$ and **1**, respectively. However, when using the noninterlocking threads (**2**-H·$PF_6$ and **2**) as the catalyst, different results were obtained. From entries 3 and 4, only a trace amount of **E** was obtained with a moderate yield of **G**. In entries 7 and 8, a moderate yield of **H** and a lower yield of **F** were observed. In entries 3, 4, 7, and 8, an equal amount of substrates was used, thus revealing the competition between substrates and catalyst by contrasting the yield of the two products. The amine/ammonium catalytic moiety was found to be dominant in the catalysis and reacted faster than that of the thiourea in the mixture of three substrates without selectivity. Unfortunately, acetylacetone and its intermediates were too reactive toward crotonaldehyde and the amine/ammonium catalyst, resulting in undesirable side reactions between these two compounds and lowering the total percent yield within the system (Figure S21). An *In situ* rotaxane catalyst switching experiment of substrates **B** + **C** + **D** was achieved by adding 20 mol % of triethylamine (TEA) with **1**-H·$PF_6$, revealing the catalyst can be deprotonated and activate the secondary amine catalytic site of **1** (Figure S22).

Second, rotaxane can also be applied to a two-component system[3a,b] (**A** + **C**, **A** + **D**, **B** + **C**, or **B** + **D**), giving the corresponding products in good yield within a shorter period compared with a three-component system (Table 1). Yields of 71–98% were observed in entries 9–12, readily giving the desired product within 3 days (except for entry 9, which required 5 days). This could be due to (1) no competition in a two-component system between the substrates' interaction with the catalyst and (2) no undesirable side reactions between the substrates with the intermediates, as well as the products. Furthermore, *in situ* experiments of entries 10 and 12 demonstrated (Table S1) the amine catalytic activity of **1** could be switched OFF by addition of trifluoroacetic acid (TFA). For entry 10 with **1**-H·$PF_6$ as the catalyst, the amine catalytic activity can be switched ON by addition of TEA. Kinetics studies (Figures S29–S33) showed a similar reaction rate (2.56–4.55 mM $h^{-1}$) in the presence of **1**-H·$PF_6$ or **1** in a two- or three-component system, except entry 11, due to the higher reactivity of the reaction (Figure S20).

In conclusion, a novel fluorescence-tagged switchable [2]-rotaxane catalyst with two catalytic sites (secondary amine and thiourea) was synthesized. The fluorescence of [2]rotaxane can be reversibly switched "ON" and "OFF" upon the addition of AcOH and TEA, which is correlated to the position of the rotaxane's macrocycle and the catalytic properties of either thiourea (ON) or amine (OFF). The rotaxane catalyst was also found to be acid–base switchable, exclusively masking the



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secondary amine or thiourea from DB24C8 in different pH environments. The rotaxane catalyst can be applied to a two- or three-component system, selectively giving the desired product. Four sets of three-component catalytic reaction systems of acetylacetone (**A**) or dibenzoylmethane (**B**) with *trans*-$\beta$-nitrostyrene (**C**) and (*E*)-crotonaldehyde (**D**) were catalyzed by the protonated rotaxane **1**-H·$PF_6$ and deprotonated rotaxane **1** with moderate conversion and high selectivity. Four sets of two-component catalytic reaction systems were reported with a better yield in a shorter period. *In situ* ON−OFF switching of the rotaxane catalyst has also been demonstrated.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03700.

Spectral analysis, catalysis, and additional characterization data (PDF)

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### Notes

The authors declare no competing financial interest.

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