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 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]rotaxane6 that acts as an effective asymmetric organocatalyst7 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·PF₆ 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 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 chiral moieties can 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 group,11 in the protonated form ((R)-1-H⁺·2PF₆⁻; Figure 1a). The macrocycle blocks access of reactants to the catalytic site. When the secondary amine of the rotaxane is not protonated ( (R)-1·PF₆; Figure 1a), the triazolium group is the preferred binding site for the macrocycle11 and the chiral organocatalyst on the axle is exposed and available to participate in asymmetric catalysis.

The synthetic route toward rotaxane (R)-1·PF₆ relies on a CuAAC ‘click’ reaction12 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 ¹H NMR spectrum of (R)-1-H⁺·2PF₆⁻ (Figure 2b) to that of the protonated noninterlocked thread

Received: February 19, 2014
Published: March 20, 2014
Table 1. Optimization of Conditions for the Asymmetric Michael Addition of 1,3-Diphenyl-1,3-propanedione (4) to E-Crotonaldehyde (3a)∗

| entry | catalyst | temp (°C) | conv (%) | er (R:S) |
|-------|----------|-----------|----------|----------|
| 1     | –        | rt        | 0        | –        |
| 2     | (R)·2·PF6 | rt        | 100      | 85:15    |
| 3     | (S)·2·PF6 | rt        | 100      | 20:80    |
| 4     | (R)·2·PF6 | 20        | 0        | 94:6     |
| 5     | (R)·2·PF6 | 0         | 45       | 94:6     |
| 6     | (R)·2·PF6 | 20        | 10       | 60       |
| 7     | (R)·2·PF6 | 10        | 50       | 92:8     |

∗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 CH2Cl2 at the indicated temperature. ∗Conversions determined by 1H NMR after 24 h. ∗Enantiomeric ratios determined by chiral stationary phase HPLC. The reaction catalyzed with (S)-7 (see Table 2) is known13 to produce (S)-5a as the major enantiomer. ∗No reaction was observed during 24 h.

Table 2. Asymmetric Michael Addition of 1,3-Diphenyl-1,3-propanedione and αβ-Unsaturated Aldehydes Catalyzed by Rotaxane (R)-1 and Prolinol Derivatives (S)-6 and (S)-7∗

| entry | R (3)     | catalyst   | conv (%) | er (R:S) |
|-------|-----------|------------|----------|----------|
| 1     | Me (3a)   | (R)·1·PF6  | 60       | 90:10    |
| 2     | Me (3a)   | (R)·1-H+·2PF6- | 0        | –        |
| 3     | Et (3b)   | (R)·1-H+·2PF6- | 70       | 94:6     |
| 4     | nPr (3c)  | (R)·1·PF6  | 65       | 93:6     |
| 5     | Ph (3d)   | (R)·1·PF6  | 0        | –        |
| 6     | Me (3a)   | (S)·6      | 100      | 32:68    |
| 7     | Me (3a)   | (S)·7      | 100      | 8:92     |

∗Reaction conditions: 0.01 mmol of 4, 0.1 mmol of αβ-unaturated aldehyde (3a–d), and 0.005 mmol of catalyst (20 mol %) in 125 μL of CH2Cl2 at 10 °C. ∗Conversions determined by 1H NMR after 24 h. ∗Enantiomeric ratios determined by chiral stationary phase HPLC. The reaction catalyzed with (S)-7 is known13 to produce (S)-5a as the major enantiomer. ∗No reaction was observed during 24 h. ∗Conversions determined by 1H NMR after 12 h.

(R)-2-H+·2PF6- (Figure 2a) shows a downfield shift of the benzylic protons of the catalytic unit (ΔδHr = 0.92 and 0.97 ppm; ΔδHf = 0.11 ppm), and one of the protons of one of the aromatic rings of the benzylamine unit (ΔδHm = 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 (ΔδHf = −0.67 ppm) and one of the aromatic protons of the phenylalanine residue (ΔδHph = −0.52 ppm) due to shielding by the aromatic rings of the macrocycle. In contrast, the signals of the triazolium protons (Hr and Hdd) appear at a similar chemical shift in both (R)-1-H+·2PF6- and (R)-2-H+·2PF6-. The observed chemical shifts strongly support the location of the macrocycle around the secondary ammonium site.

Deprotonation of rotaxane (R)-1-H+·2PF6- with aqueous NaOH smoothly afforded (R)-1·PF6, giving rise to significant changes in the 1H NMR spectrum (Figure 2c). The benzylic protons of the benzylamine motif are shifted upfield (ΔδHr = −1.17 and −1.28 ppm; ΔδHf = −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+·2PF6-. In contrast, the protons of the triazole ring and one of the CH2 groups adjacent to the triazolium group are shifted downfield (ΔδHm = 0.57 ppm; ΔδHf = 0.43 ppm), indicating that they are now interacting with the crown ether, and the protons of the triazolium methyl group are shifted upfield (ΔδHm = −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 Et2O, the 1H 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.15 Initially, screening to optimize the reaction conditions was performed...
using the nonprotonated thread (R)-2-PF₆ as the catalyst (Table 1).

We confirmed that the reaction between 3a and 4 in CH₂Cl₂ does not proceed at room temperature in the absence of the organocatalyst (Table 1, entry 1). The use of the nonprotonated thread (R)-2-PF₆ 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-PF₆, the enantiomer of the Michael adduct was obtained ((S)-5a) (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 CH₂Cl₂ 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⁺-2PF₆⁻ 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-PF₆ and (R)-1-H⁺-2PF₆⁻ (Table 2, entries 1–2).

The amine form of the rotaxane, (R)-1-PF₆ catalyzed the reaction as effectively as the amine form of the thread, (R)-2-PF₆ 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⁺-2PF₆⁻, 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 (Sb,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-PF₆, 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-PF₆ 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⁺-2PF₆⁻) 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: adduction of 20 mol % of HCl (1 M) immediately stopped further formation of (R)-5a from 3a and 4 (Scheme 1, part 3).

In conclusion, rotaxane (R)-1-PF₆ 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.

■ ACKNOWLEDGMENTS
This research was funded by the EPSRC. We are grateful to the following organizations for postdoctoral fellowships: The European Union seventh Framework Marie Curie Intra European Fellowship Program (to V.B.), Royal Society-British Academy Newton International Fellowship and CONACyT-Mexico Fellowship (to J.A.M.S.), and Swiss National Science Foundation (Grant Nr. PBBEP2_144839 to A.L.N.).

■ REFERENCES
(1) Traut, T. Allotro Regulatory Enzymes; Springer: New York, 2008.
(2) For examples of artificial catalysts that can be switched ‘on’ and ‘off’ by a specific stimulus, see: (a) Wirthner, F.; Rebek, J. Jr. Angew. Chem., Int. Ed. Engl. 1995, 34, 446. (b) Yoon, H. J.; Kuwabara, J.; Kim, J.-H.; Mirkin, C. A. Science 2010, 330, 66. (c) Sohtome, Y.; Tanaka, S.
Communication

Takada, K.; Yamaguchi, T.; Nagasawa, K. Angew. Chem., Int. Ed. 2010, 49, 9254. (d) Zairngast, M.; Pump, E.; Leitgeb, A.; Albering, J. H.; Slagovc, C. Chem. Commun. 2011, 47, 2261. (e) Berryman, O. B.; Sather, A. C.; Lledó, A.; Rebek, J. Jr. Angew. Chem., Int. Ed. 2011, 50, 9400. (f) Neilson, B. M.; Bielawski, C. W. J. Am. Chem. Soc. 2012, 134, 12693. (g) Schmittel, M.; De, S.; Pramanik, S. Angew. Chem., Int. Ed. 2012, 51, 3832. (h) Schmittel, M.; Pramanik, S.; De, S. Chem. Commun. 2012, 48, 11730. (i) Wilson, D.; Branda, N. R. Angew. Chem., Int. Ed. 2012, 51, 5431. (j) Vielmann, P.; Hecht, S. Beilstein J. Org. Chem. 2012, 8, 1825. (k) Lüning, U. Angew. Chem., Int. Ed. 2012, 51, 8163. (l) Neilson, B. M.; Bielawski, C. W. Chem. Commun. 2013, 49, 4543. (m) Neilson, B. M.; Bielawski, C. W. Organometallics 2013, 32, 3121. (n) Neilson, B. M.; Bielawski, C. W. ACS Catalysis 2013, 3, 1874.

(3) For switchable catalysts able to change the stereochemical bias of an organocatalytic reaction, see: (a) Wang, J.; Feringa, B. L. Science 2011, 331, 1429. (b) Mortezai, S.; Catarineu, N. R.; Canary, W. J. J. Am. Chem. Soc. 2012, 134, 8054.

(4) Blanco, V.; Carlone, A.; Häni, K. D.; Leigh, D. A.; Lewandowski, B. Angew. Chem., Int. Ed. 2012, 51, 5166.

(5) Gotor, V.; Alfonso, I.; García-Urdiales, E. Asymmetric Organic Synthesis with Enzymes; Wiley-VCH: Weinheim, Germany, 2008.

(6) For rotaxanes incorporating catalytic centers, see: (a) Thordarson, P.; Bjisterfeld, E. J.; Rowan, A. E.; Nolte, R. J. Nature 2003, 424, 915. (b) Tachibana, Y.; Kihara, N.; Takata, T. J. Am. Chem. Soc. 2004, 126, 3438. (c) Miyagawa, N.; Watanabe, M.; Matsuyama, T.; Koyama, Y.; Morichi, T.; Hirao, T.; Furusho, Y.; Takata, T. Chem. Commun. 2010, 46, 1920. (d) Suzuki, Y.; Shimada, K.; Chihara, E.; Saito, T.; Tsuchido, Y.; Osakada, K. Org. Lett. 2011, 13, 3774. (e) Lewandowski, B.; De Bo, G.; Ward, J. W.; Papmeyer, M.; Kuschel, S.; Aldegunde, M. J.; Gmelich, P. M. E.; Heckmann, D.; Goldup, S. M.; D’Souza, D. M.; Fernandes, A. E.; Leigh, D. A. Science 2013, 339, 189.

(7) For recent reviews on organocatalysis, see: (a) MacMillan, D. W. C. Nature 2008, 455, 304. (b) Melchiorre, P. Angew. Chem., Int. Ed. 2009, 48, 1360. (c) Bertelsen, S.; Jørgensen, K. A. Chem. Soc. Rev. 2009, 38, 2178. (d) Grondal, C.; Jeanty, M.; Enders, D. Nat. Chem. 2010, 2, 167. (e) Marquès-López, E.; Herrera, R. P.; Christmann, M. Nat. Prod. Rep. 2010, 27, 1138. (f) Cheong, P. H. Y.; Legault, C. Y.; Um, J. M.; Celebi-Olecum, N.; Houk, K. N. Chem. Rev. 2011, 111, 5042. (g) Jensen, K. L.; Dickmeiss, G.; Jiang, H.; Albrecht, K. Angew. Chem., Int. Ed. 2012, 45, 248. (h) Meninno, S.; Lattanzi, A. Chem. Commun. 2013, 49, 3821. (i) Alemán, J.; Cabrera, S. Chem. Soc. Rev. 2013, 42, 774. (j) Albrecht, L.; Jiang, H.; Jørgensen, K. A. Chem. Eur. J. 2014, 20, 358.

(8) The rationale is that the geometry of five-membered rings increases the nucleophilicity of the amine and the cyclic scaffold limits bond rotation, fixing pendant groups in space and intended to provide a well-expressed chiral environment.

(9) For amino acid derivatives as organocatalysts, see: (a) Ibrahim, I.; Zou, W.; Engvist, M.; Xu, Y.; Córdova, A. Chem.—Eur. J. 2005, 11, 7024. (b) Xu, Y.; Córdova, A. Chem. Commun. 2006, 460. (c) Arróniz, C.; Escolano, C.; Luque, F. J.; Bosch, J.; Amat, M. Org. Biomol. Chem. 2011, 9, 5079. (d) Chai, Z.; Zhao, G. Catal. Sci. Technol. 2012, 2, 29.

(10) For selected reviews and publications on conjugated addictions using iminium-ion activation see, for example: (a) Lelais, G.; MacMillan, D. W. C. Aldrichimica Acta 2006, 39, 79. (b) Brandau, S.; Landa, A.; Fränzén, J.; Marigo, M.; Jørgensen, K. A. Angew. Chem., Int. Ed. 2006, 45, 4305. (c) Carlone, A.; Marigo, M.; North, C.; Landa, A.; Jørgensen, K. A. Chem. Commun. 2006, 4928. (d) Erkkiš, A.; Majander, I.; Pihko, P. M. Chem. Rev. 2007, 107, 5416. (e) Tsogoeva, S. B. Eur. J. Org. Chem. 2007, 1701. (f) Almasi, D.; Alonso, D. A.; Nájera, C. Tetrahedron: Asymmetry 2007, 18, 299. (g) Carlone, A.; Cabrera, S.; Marigo, M.; Jørgensen, K. A. Angew. Chem., Int. Ed. 2007, 46, 1101. (h) Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. Angew. Chem., Int. Ed. 2008, 47, 6138. (i) Shimizu, M.; Hachiya, I.; Mizota, I. Chem. Commun. 2009, 874. (j) García Ruano, J. L.; Marcos, V.; Alemán, J. Chem. Commun. 2009, 4435. (k) Lathrop, S. P.; Kihara, N.; Takata, T.; Yu, Y. W.; Liu, T. F.; Liu, H. B.; Li, Y. L. Org. Biomol. Chem. 2011, 9, 6022. (h) Romundo, C.; Aðvar, A.; Clavel, D.; Jiménez-Barbero, J.; Coutrot, F. Chem. Soc. 2012, 3, 1851. (i) Busseron, E.; Coutrot, F. J. Org. Chem. 2013, 78, 4099. (j) Clavel, C.; Romundo, C.; Brabet, E.; Coutrot, F. Chem. Eur. J. 2013, 19, 2982. (k) Clavel, C.; Fournel-Marotte, K.; Coutrot, F.; Molecules 2013, 18, 11553.

(12) (a) Tornøe, C. W.; Christensen, C.; Meldal, M. J. Org. Chem. 2002, 67, 3057. (b) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. Angew. Chem., Int. Ed. 2002, 41, 2596. (c) Hänli, K. D.; Leigh, D. A. Chem. Soc. Rev. 2010, 39, 1240. (13) García Ruano, J. L.; Marcos, V.; Suanzes, J. A.; Marzo, L.; Alemán, J. Chem.—Eur. J. 2009, 15, 6576.