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# Cation-Triggered Switchable Asymmetric Catalysis with Chiral Aza-CrownPhos**

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***Abstract:*** *An aza-crown ether, modified phosphoramidite ligand, has been designed and synthesized. The ON/OFF reversible switch of catalytic activity for its rhodium catalyst was thoroughly investigated in the asymmetric hydrogenation of dehydroamino acid esters modulated by host–guest interactions. In the OFF state, the catalyst is almost inactive (less than 1 % conversion) because of the formation of an intermolecular sandwich complex by two aza-crown ether moities and the cationic rhodium metal center. In using alkali-metal-cations as the trigger, the catalytic activity was turned ON and consequently resulted in full conversions and excellent enantioselectivities (up to 98 % ee).*

Switchable catalysis has gained increasing attention because of its potential to trigger or modulate catalytic activity and/or selectivity in situ with spatiotemporal control.[1] Nature can efficiently control an enzyme reaction rate through a variety of trigger-induced effects. Inspired by biocatalytic systems, a variety of synthetic switchable-catalysis systems,[2] such as photoswitchable catalysts,[2a–d] allosteric catalysts,[2e–h] molecular-machine-based catalysts,[2a] self-locking catalysts[2i,j] and so on,[2k–o] have been established over the past several years. Their catalytic activity and even stereoselectivity can be reversibly switched by external stimuli such as light, pH, ions, small molecules, etc. Despite great progress made in this field, only few examples have been reported for switchable asymmetric catalysis.[2a,f,l,o] In 2011, Feringa and co-workers described a chiral molecular motor-based bifunctional organocatalyst for asymmetric Michael addition. It was found that light or heat could turn "ON" or "OFF" the catalytic activity, and also change the stereochemical outcome. Most recently, a rotaxane-based switchable chiral organocatalyst was designed by the group of Leigh, and the secondary dibenzyl amine moiety was masked or exposed in response to acid/base regulations. This chiral rotaxane was successfully applied to catalyze asymmetric Michael addition reactions. To the best of our knowledge, the application of switchable chiral transition-metal catalysts having a clear cut between the ON and OFF states for asymmetric catalysis has not been demonstrated.[2f,o]

Herein we describe a new kind of switchable catalyst for transition-metal-catalyzed asymmetric catalysis which is triggered by external stimuli, that is, host–guest interactions. Transition-metal complexes containing a bidentate chiral ligand or two monodentate chiral ligands have proven to be powerful in numerous asymmetric catalytic reactions.[3] A number of them have a cationic metal center, which might be able to associate with electron-rich macrocyclic hosts.[4] We envisaged that if crown ether units are fixed on the proper position of the ligand, they may associate with the cationic metal center through cation–macrocycle interactions, thus leading to the formation of an intermolecular sandwich complex.[5] This host–guest interaction may thus block the catalytic center from substrates (Figure 1; state I). In contrast, adding proper alkali metal cations, which have stronger complexation with the crown ether, will decompose the original complexes to release the catalytic centers (Figure 1; state II). Furthermore, switching back to state I can also be realized by removing the alkali-metal cations with cryptands,[6] which have stronger binding affinities for alkali metal cations.

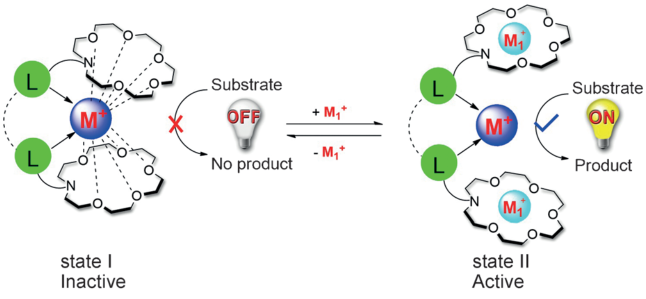

***Figure 1.*** Schematic representation of switchable catalysis triggered by host–guest interactions.

To exemplify our strategy for switchable asymmetric catalysis governed by host–guest interactions,[7] a new monodentate chiral phosphoramidite ligand [(*S*)-Aza-CrownPhos; Scheme 1], modified by an aza-crown ether, was designed and synthesized for this study (for details, see Scheme S1 in the Supporting Information).[8,9] With the ligand in hand, we then synthesized the precatalyst [Rh(Aza-CrownPhos)$_2$(NBD)]BF$_4$ from two equivalents of (*S*)-Aza-CrownPhos and one equivalent of Rh(NBD)$_2$BF$_4$. The $^1$H NMR study of

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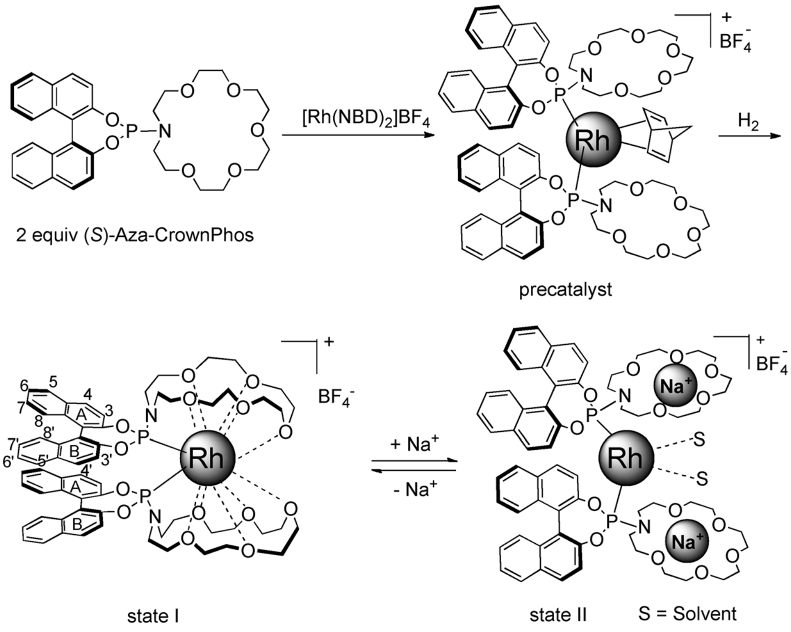
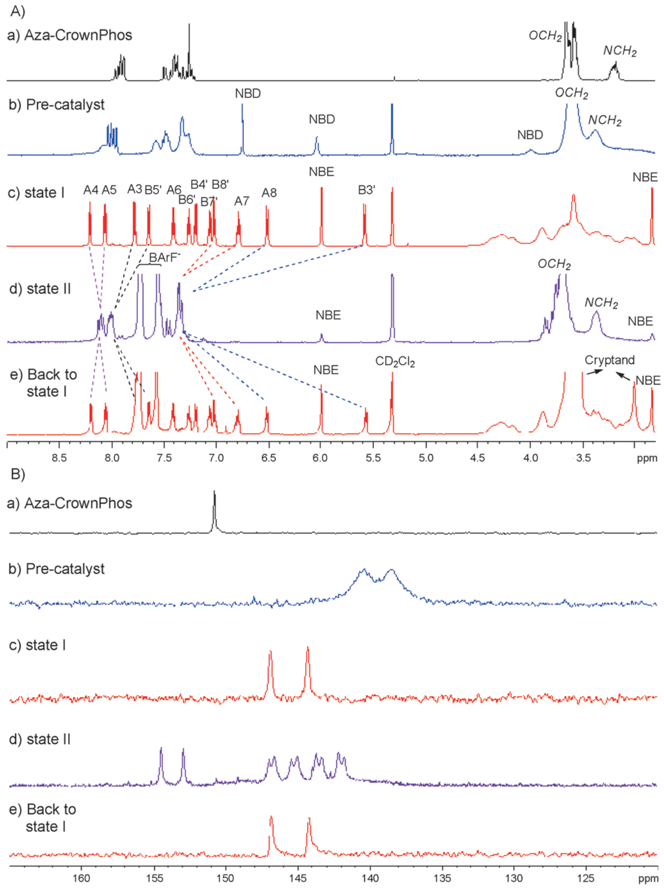


*Scheme 1.* Coordination structures of Rh/Aza-CrownPhos complexes in different states.

the precatalyst (Scheme 2Ab) showed that the signals of $NCH_2$ protons on Aza-CrownPhos shifted downfield because of the coordination of phosphorus ligand to rhodium. However, no obvious chemical shift changes were observed for the $OCH_2$ signals, thus revealing that the coordinated rhodium cation in the precatalyst was not bound to the aza-crown ether ring.[10] The $^{31}P$ NMR spectroscopic analysis (Scheme 2B b) showed two broad absorption peaks, which indicates that the precatalyst has two structural isomers which differ in the relative orientation of the two coordinated monodentate Aza-CrownPhos ligands. The two isomers interconverted at room temperature and showed broad absorptions both in $^1H$ NMR and $^{31}P$ NMR spectra.[11a]

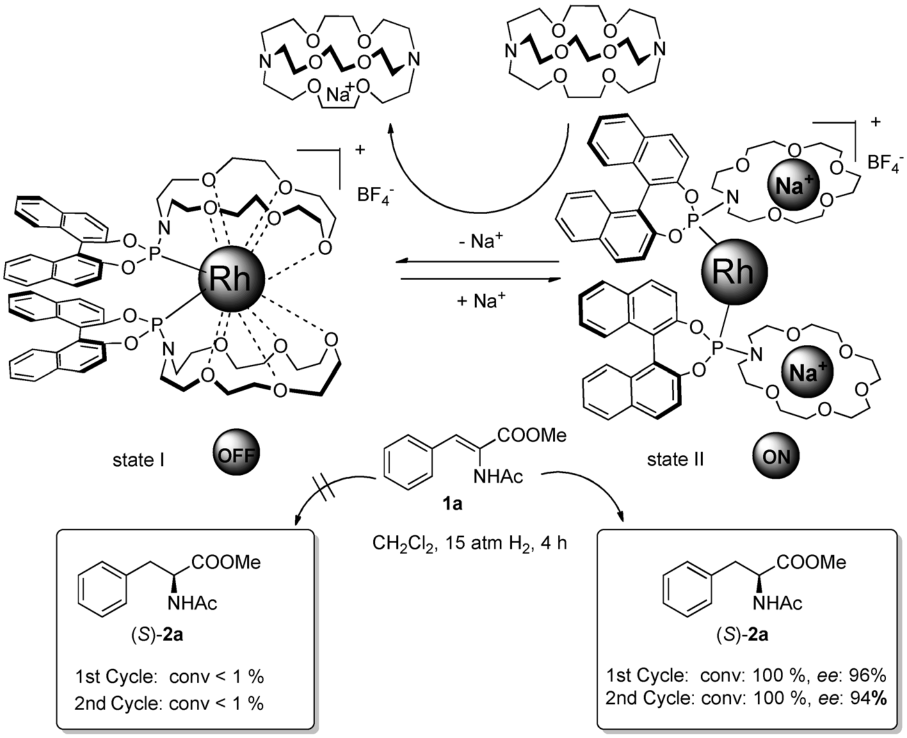
Subsequently, the precatalyst in $CD_2Cl_2$ was stirred under hydrogen gas for 1 hour to remove norbornadiene.[11a–d] As shown in Scheme 2Ac, the $^1H$ NMR spectrum showed an obvious signal splitting and broadening in the region $\delta = 2.8$–4.5 ppm, and are ascribed to the protons of aza-crown ether units. This result suggests a strong complexation between the aza-crown ether ring and cationic rhodium.[5] More impressively, the signals of the aromatic protons were separated into 12 sets with some of them shifted upfield. By following $^1H$-$^1H$ COSY and $^1H$-$^1H$ NOESY NMR investigations, the signals can be assigned (for details, see Figure S1) to the 12 different protons on the naphthalene unit, thus implying that the two naphthalene units are magnetically equivalent. Meanwhile, the obvious upfield shifts of the aromatic proton signals suggests that there is strong π–π stacking between the two naphthalene units.[12] In addition, only one doublet splitting signal was shown in the $^{31}P$ NMR spectrum ($\delta = 144.3$ ppm, $J_{PRh} = 319$ Hz; Scheme 2Bc), and indicates that the two Aza-CrownPhos units in this complex are equal with respect to the chemical environment. From all these results, it is naturally concluded that both aza-crown ether units participate in the association with the rhodium cation, and a sandwich structure is formed (state I). Furthermore, the result of ESI HR-MS confirms the formation of complex $[Rh(Aza\text{-}CrownPhos)_2]^+$ (see Figure S2).

By adding two equivalents of NaBArF (BArF = $[3,5\text{-}(CF_3)_2C_6H_3]_4B$) into the above $[Rh(Aza\text{-}CrownPhos)_2]BF_4$ system (state I), $[Rh(Aza\text{-}CrownPhos\cdot Na^+)_2]BF_4$ (state II) was formed spontaneously because of the stronger association ability of $Na^+$ with aza-crown ethers. $^1H$ and $^{31}P$ NMR studies showed the disassociation of $Rh^+$ from the aza-crown ether moieties, thus leading to the decomposition of the sandwich structure (for details see Figures S4 and S5). In addition, the peak at *m*/*z* 434.44221 in the ESI HR-MS spectrum strongly supports the formation of $[Rh(Aza\text{-}CrownPhos\cdot Na)_2]^{3+}$ with the experimental isotopic distribution neatly matching the calculated one (see Figure S3). The Job plot analysis of state I gave a host/guest molar ratio of 1:2 for $Na^+$, thereby indicating that $Na^+$ cations were bound to the aza-crown ethers (see Figure S7 in the Supporting Information). Thus, the switching from state



*Scheme 2.* $^1H$ NMR spectra (A; 600 MHz, $CD_2Cl_2$, 298 K, 10 mM) and $^{31}P$ NMR spectra (B; 500 MHz, $CD_2Cl_2$, 298 K, 50 mM) of a) Aza-CrownPhos; b) $[Rh(Aza\text{-}CrownPhos)_2(NBD)]BF_4$; c) $[Rh(Aza\text{-}CrownPhos)_2]BF_4$; d) $[Rh(Aza\text{-}CrownPhos\cdot Na^+)_2]BF_4$; e) $[Rh(Aza\text{-}CrownPhos)_2]BF_4$ regenerated from d) by adding 2 equivalents of cryptand-[2,2,2]. NBD = norbornadiene, NBE = norbornene.

I to state II is achieved by the triggering of alkali metal cations.



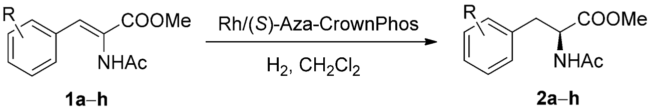
***Scheme 3.*** Control of the reversible switching in the asymmetric hydrogenation of **1a** by using the Rh/Aza-CrownPhos catalyst.

Switching from state II to state I was further realized by removal of $Na^+$ cations from their aza-crown ether complexes. Cryptand[2,2,2] is a better host molecule for $Na^+$ as compared with aza-18-crown-6.[6] The $^1H$ and $^{31}P$ NMR spectra indicate that the complex $[Rh(Aza\text{-}CrownPhos)_2]^+$ (state I) was regenerated (Scheme 2e versus Scheme 2c) upon the addition of 2 equivalents of the cyptand[2,2,2]. In addition, a strong peak for the $[cryptand{\cdot}Na]^+$ complex was detected by ESI HR-MS (see Section S4.4). Therefore, all the results obtained demonstrate that the catalyst transformation cycle between state I and state II can be successfully achieved by the modulation through host-guest interactions.

Having established the efficient and reversible transformations of the rhodium catalytic system, we then applied this switchable rhodium catalyst to the asymmetric hydrogenation of methyl α-acetamido cinnamate (**1a**; Scheme 3). As expected, the Rh/Aza-CrownPhos complex in state I is almost inactive, thus giving less than 1% conversion in 4 hours. In contrast, in state II, full conversion with 96% *ee* was obtained under the same reaction conditions. As shown in Scheme 3, two cycles of ON/OFF catalysis were achieved by sequentially adding $Na^+$ cations and cyptand[2,2,2] as additives (for details see Section S5).[13]

To further understand this cation-triggered asymmetric hydrogenation, the effects of different alkali metal cations were investigated. A great increase of enantioselectivity is observed for all cations tested, while the catalytic activity varied extremely. It was found that faster rates and higher conversions were obtained for smaller alkali metal cations, $Li^+$ and $Na^+$, in comparison to those using $K^+$ and $Cs^+$. The Job plot analyses of state I gave a binding ratio of 1:1 for both $K^+$ and $Cs^+$, thus differing from that of $Na^+$. These results show the importance of the matching between cation and aza-crown ether moiety to the efficacy of supramolecular modulation through cation–macrocycle interactions (for details see Figure S6 in the Supporting Information).[6,7,14]

***Table 1:*** Switchable asymmetric hydrogenation of dehydroamino acid esters by using Rh/Aza-CrownPhos catalyst.[a]



| Entry | Substrate | ON state Conv. [%][b] | ON state *ee* [%][b] | OFF state Conv. [%][b] |
|---|---|---|---|---|
| 1 | **1a** (R=H) | 100 | 98 | <1 |
| 2 | **1b** (R=2-OMe) | 100 | 98 | <1 |
| 3 | **1c** (R=3-OMe) | 100 | 95 | <1 |
| 4 | **1d** (R=4-OMe) | 100 | 95 | <1 |
| 5 | **1e** (R=2-Br) | 100 | 96 | <1 |
| 6 | **1f** (R=3-Cl) | 100 | 95 | <1 |
| 7 | **1g** (R=4-F) | 100 | 95 | <1 |
| 8 | **1h** (R=4-Me) | 100 | 92 | <1 |

[a] Reaction conditions: substrate (0.50 mmol), (S)-Aza-CrownPhos ($1.0\times10^{-3}$ mmol), $[Rh(NBD)_2]BF_4$ ($0.5\times10^{-3}$ mmol), NaBArF ($1.0\times10^{-3}$ mmol), 2 mL $CH_2Cl_2$, 15 atm $H_2$, 4 h, RT. [b] Conversions and *ee* values were determined by GC using a Varian Chirasil-L-Val column CP7495 (25 m×0.25 mm).

Finally, we investigated the asymmetric hydrogenation of a variety of dehydroamino acid esters by using this switchable catalytic system (Table 1). By using NaBArF as a trigger, all the hydrogenation reactions proceeded smoothly with complete conversions. Excellent *ee* values (92–98% *ee*) were obtained, and are comparable to the reported ones.[9c,e] Higher *ee* values were provided by *ortho*-substituted substrates in comparison to those for *meta*- and *para*-substituted ones. However, in the absence of NaBArF, the catalyst stayed in its inactive state, and conversions of less than 1% were observed. Therefore, this switchable catalytic system has shown a remarkable difference in activity between its ON and OFF state for asymmetric hydrogenation (with an ON/OFF ratio >100).

In summary, we have synthesized a new kind of phosphoramidite ligand modified by an aza-crown ether. The catalytic activity of its rhodium complex can be switched between the ON and OFF state through Na$^+$-triggered modulation using host–guest interactions. In the ON state, 100 % conversion and excellent enantioselectivity (up to 98 % *ee*) are obtained in the asymmetric hydrogenation of dehydroamino acid esters. In contrast, in the OFF state, the catalyst is almost inactive, thus giving less than 1 % conversion for all screened substrates. NMR spectroscopy and HR-MS studies and a set of control experiments indicate that the reversible cation–macrocycle interactions are responsible for this interesting activity-switching cycle (ON/OFF ratio $>100$). Further applications of this kind of chiral switchable catalysts in other catalytic reactions are currently in progress.

**Keywords:** asymmetric catalysis · cations · crown compounds · host-guest systems · hydrogenation

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