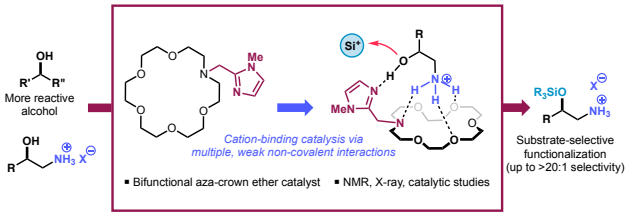
Ammonium-Binding Bifunctional Aza-Crown Ether Catalysts for Substrate-Selective Hydroxyl Functionalization

Austin G. Seilkop, Amaechi S. Odoh, Nicholas J. Coradi, Jacob I. Wright, Jorge Barroso, Byoungmoo Kim*

AUTHOR ADDRESS: Department of Chemistry, Clemson University, Clemson, South Carolina 29634, United States

KEYWORDS: Non-covalent interactions, cation-binding crown ether, substrate-selective silylation



ABSTRACT: Herein, we describe a new bifunctional macrocyclic catalyst that employs multiple weak non-covalent interactions to enable substrate-selective *O*-silylation of ammonium alcohols over more reactive aliphatic alcohols up to >20:1 substrate-selectivity. Our catalytic strategy merges i) the use of crown ethers as ammonium binding receptors and ii) the exploitation of *N*-methyl imidazole as a catalytic motif. Our collective mechanistic studies reveal the importance of receptor size, conformational preorganization, and the number of hydrogen-binding acceptor units needed to achieve high selectivity within the macrocyclic binding pocket.

Introduction

Inspired by nature's ability to perform highly selective enzymatic processes, the use of multiple weak non-covalent interactions (NCIs) has enabled significant advances in selective supramolecular catalysis. Molecular recognitions via NCIs employed in these applications often rely on the complementary shape and size between interacting partners, such as a pair of guest-host or substrate-catalyst. These complementary features can be fine-tuned to promote new chemical reactivities (e.g., anion-binding catalysis) or to achieve an array of selectivities (e.g., regio- or enantioselectivity)[1–6]. Most often, balancing the strength and reversibility of molecular recognition is essential for developing new catalytic processes.

Substrate-selective catalysis (Figure 1A) is a canonical characteristic of enzymatic reactions, and it has played important roles in industrial processes that manufacture commodity hydrocarbon chemicals.[7] Despite this, it is far less explored than regio- and enantioselective catalysis and the scope of substrate-selective catalysis has been mostly limited to nonpolar hydrocarbon substrates. To this end, we were inspired to design a catalyst that could enable the substrate-selective catalysis of molecular scaffolds bearing highly polar functional groups, such as amino alcohols, which are ubiquitous in bioactive molecules such as neurotransmitters, peptides, and antibiotics (Figure 1B). From a reactivity standpoint, the presence of amino alcohols in these molecules imparts challenges in developing substrate-selective catalysis. Although the use of transition metals or Lewis acid catalysts may be considered, their catalytic reactivity is likely to be hampered by the strong coordinative saturation by Lewis basic amino alcohols. This challenge may be circumvented by taking an approach that combines the use of protecting groups and NCIs, as elegantly demonstrated by Kawabata and co-workers (Figure 1C). They recently reported substrate-selective *O*-silylation of *N*-protected amino alcohols using a chiral 4-pyrrolidinopyridine catalyst.[8] An electron-withdrawing *N*-protecting group is required to unveil a strong H-bond donor in the protected amino alcohol substrate, which undergoes a key catalyst-substrate H-bonding interaction. Under their catalyst-controlled conditions, the *N*-protected 1,5-amino alcohols were preferentially *O*-silylated over different chain-length analogs. Although Kawabata and co-workers have impressively demonstrated high substrate-selectivities, the substrate scope of the silylation has been limited to simple linear amino alcohols, and the method suffers synthetic inefficiency due to the required protecting group manipulation. To date, a catalytic substrate-selective method for directly modifying unprotected amino alcohols remains elusive.

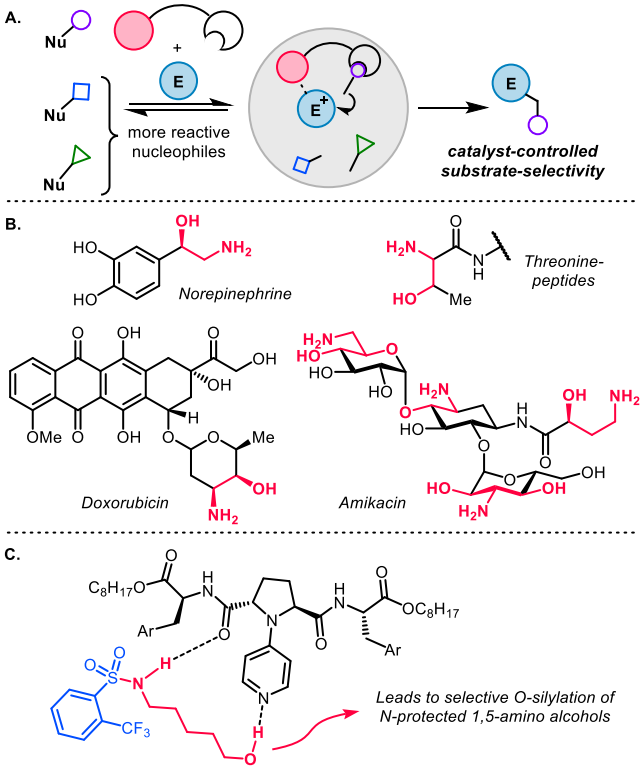


Figure 1. (A) General reaction scheme for substrate-selective catalysis. (B) Prevalence of amino alcohol motifs in diverse biomolecules. (C) Kawabata's proposed model for H-bond directed substrate-selective *O*-silylation of *N*-protected 1,5-amino alcohols.

To accomplish such challenging processes, we envisioned that a new supramolecular catalyst that employs multiple weak NCIs (e.g., H-bonds) will enable selective functionalization of amino alcohols. When considering the design of such a catalyst, we were drawn to Cram's pioneering work on rate acceleration of transacylation using the well-known molecular recognition between organic ammonium ions and crown ether receptors (Figure 2A).[9] Moreover, macrocyclic crown ethers are versatile catalysts capable of specific molecular recognition for sensing applications as well as recognition-driven reactions.[3,10–15] Inspired by these seminal works, we set out to develop new bifunctional aza-crown ethers (ACE) for substrate-selective, catalytic functionalization of amino alcohols by combining the following design elements (Figure 2B and C): i) the use of a proton as a simple, transient protecting group for amino alcohols to generate ammonium alcohol substrates, ii) the ability of crown ethers to bind ammonium ions, and iii) the incorporation of *N*-methyl imidazole (NMI) as a catalytic motif. We hypothesize that the macrocyclic conformation of the ACE catalyst would selectively bind to ammonium-bearing substrates via multiple H-bonding interactions. The pre-associated complex would then undergo proximity-induced *O*-functionalization via Brønsted base catalysis. Herein, we present our work on the synthesis and studies of new bifunctional macrocyclic catalysts for novel substrate-selective catalysis of unprotected amino alcohols via *O*-silylation.

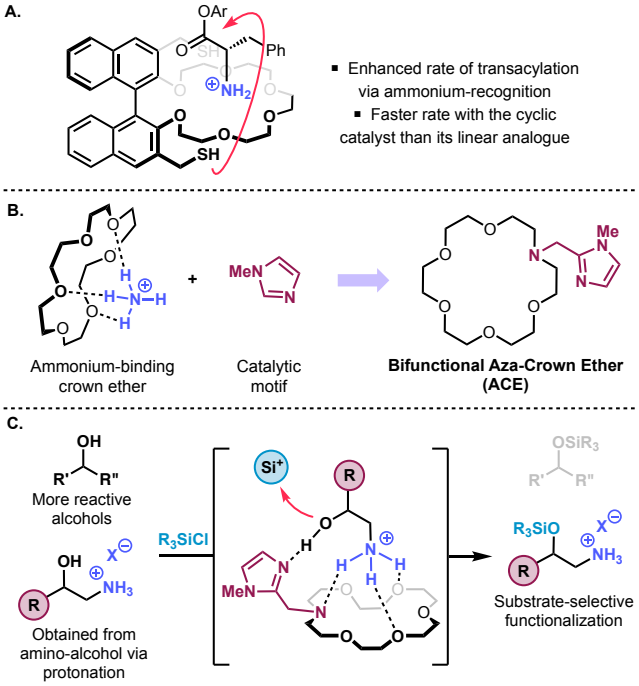


Figure 2. (A) Cram's pioneering work on accelerated transacylation using ammonium-binding crown ether. (B) Our catalyst design for molecular recognition-driven bifunctional ACE catalyst. (C) Our hypothesis for ammonium-directed substrate-selective *O*-silylation.

Results and Discussion

We envisioned that ACE that bears a secondary amine as a functional group handle is a suitable macrocyclic building block, which would allow us to covalently link the macrocycle and a catalytic motif in a modular way. Various ring sizes and analogs of ACE are commercially available as well. We synthesized several ACE catalysts via a single-step protocol using various ACEs and aldehyde-building blocks in good isolated yields (Figure 3A and see supporting information for details). Next, we evaluated the abilities of these ACE catalysts to interact with ammonium cations via multiple NCIs. First, ^{1}H NMR spectroscopy studies were performed by combining an equimolar amount of **C1** and NH_4PF_6 salt in MeCN solution at room temperature. We observed a set of peaks in which most of the proton signals of **C1** underwent notable downfield chemical shift changes (Figure 3B). This observation indicates the presence of multiple H-bonding interactions occurring between the ACE **C1** and NH_4 salt, leading to the fast association of the NH_4 under the NMR timescale or the formation of a single, stable complex. The proposed structure of the NH_4-bound **C1** complex and the multiple intermolecular H-bonding interactions were further confirmed by X-ray crystallographic analysis (Figure 3C). The distances of the H-bonds (D···A) were in the range of 2.856-2.999 Å, which indicates that these interactions in the solid state are moderately strong.[16–18] Also, we investigated the synthesis of *N*-benzyl-ACE **C2**, and analogous structural studies of the NH_4-bound **C2** revealed that the macrocycle alone can bind to the ammonium ion via moderately strong H-bonds (2.896-2.970 Å) and the NMI motif is not required for the molecular recognition. The formation of multiple H-bonds between **C2** and NH_4 ion in solution

was also supported by our ^{1}H NMR spectroscopy studies (see supporting information for details). In both cases, the H-bond lengths are consistent with the previously reported values for the NH_4PF_6–18-crown-6 complex.[19] Based on these structural data, we hypothesize that the macrocycle serves as the main molecular recognition site for ammonium species and the NMI motif may undergo a reversible H-bonding interaction, making the Lewis basic motif available for its catalytic activity.

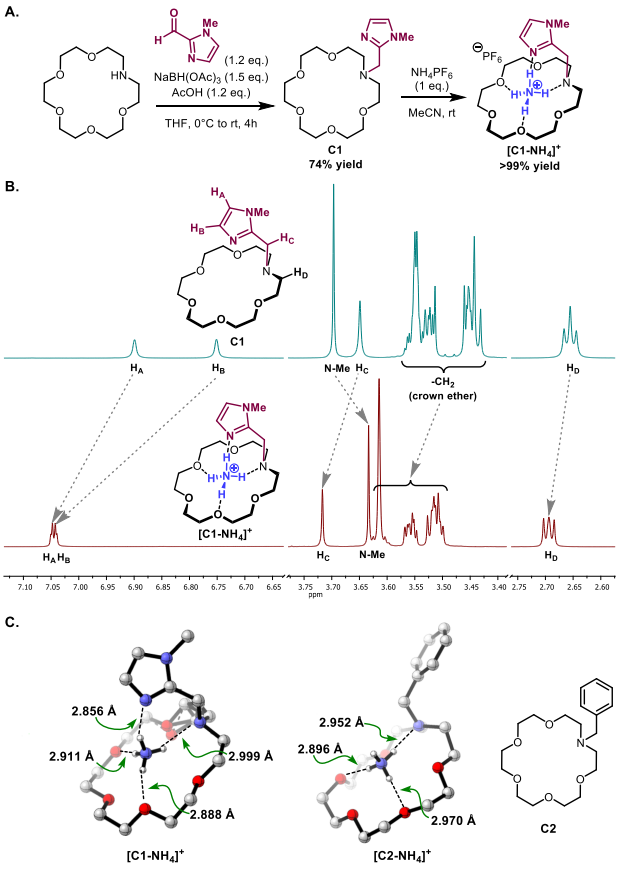


Figure 3. (A) Representative synthesis of bifunctional aza-crown ether catalyst and its NH_4-bound complex. (B) Comparison of ^{1}H NMR spectra (MeCN-d_3, 298K) between C1 (top) and its NH_4-bound complex (bottom, PF_6 anion was omitted for clarity). (C) X-ray structures of NH_4-bound C1 and C2 (left and right, respectively). The H-bonds (D···A) are indicated above (some hydrogen atoms and PF_6 anion were omitted for clarity).

This hypothesis then stimulated us to investigate if the Lewis basic NMI subunit provides a second binding site for an additional ammonium species by performing NMR titration studies. First, we chose an organic ammonium alcohol **1a** for ease of analysis and in anticipation that it would be a good candidate for exploring our substrate-selective catalysis. Analogous to our observation with the NH_4-bound **C1** (Figure 3), the ^{1}H NMR spectrum of an equimolar amount of the ammonium alcohol **1a** and **C1** showed the formation of a single species with considerable downfield chemical shift changes of the proton signals of **C1** (Figure 4A top and middle, and see supporting information for details). This indeed suggests that both the macrocycle and the Lewis basic arm are involved in the complexation via multiple H-bonding interactions.[20] Also, our NMR titration studies indicate that the association constant (K_a = 6.5 x 10^4 M^{-1}) is in agreement with the reported literature values for primary ammonium ion binding with crown ether (see supporting information for details).[10,21] Furthermore, we measured the association constant in the presence of 1 equivalent of Et_3N and obtained K_a value of 3.4 x 10^4 M^{-1}, which suggests that 1 equivalence of Et_3N does not significantly disrupt the ammonium-crown ether binding event. These collective data indicate a rapid complexation of the guest and the host with a binding stoichiometry of 1:1 ratio, even in the presence of an excess of compound **1a**. This may suggest both the macrocycle and NMI motifs are fully occupied by a single molecule of ammonium alcohol **1a**. Although we could not obtain a single crystal of the complex for X-ray crystallographic analysis to further support its structure, the solution state observations are consistent with two binding models in a dynamic H-bonding equilibrium, as depicted in Figure 4B. The binding model 1 involves both macrocycle and NMI subunits H-bonded to the ammonium motif (Figure 4B, left). For binding model 2, it is reasonable that these multiple H-bonds can be reorganized such that the NMI subunit engages in an H-bonding interaction with the hydroxyl group (Figure 4B, right). We performed DFT calculations to determine which one of the two models is more energetically feasible. Our results indicated that the binding model 2 is 4.0 kcal/mol more favorable than the binding model 1 (see supporting information for details). Therefore, we anticipate that such an H-bonding association of the NMI in the binding model 2 will serve as the Brønsted base activation of the hydroxyl group, which will enhance its reactivity in the substrate-selective catalysis.

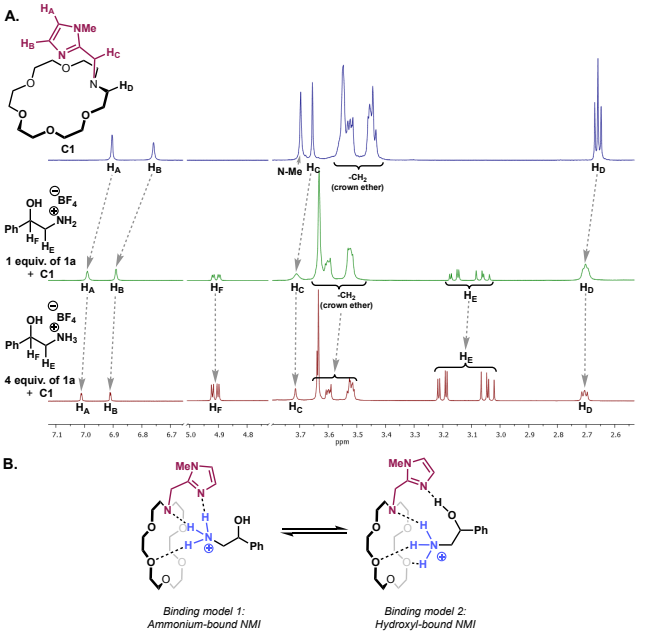


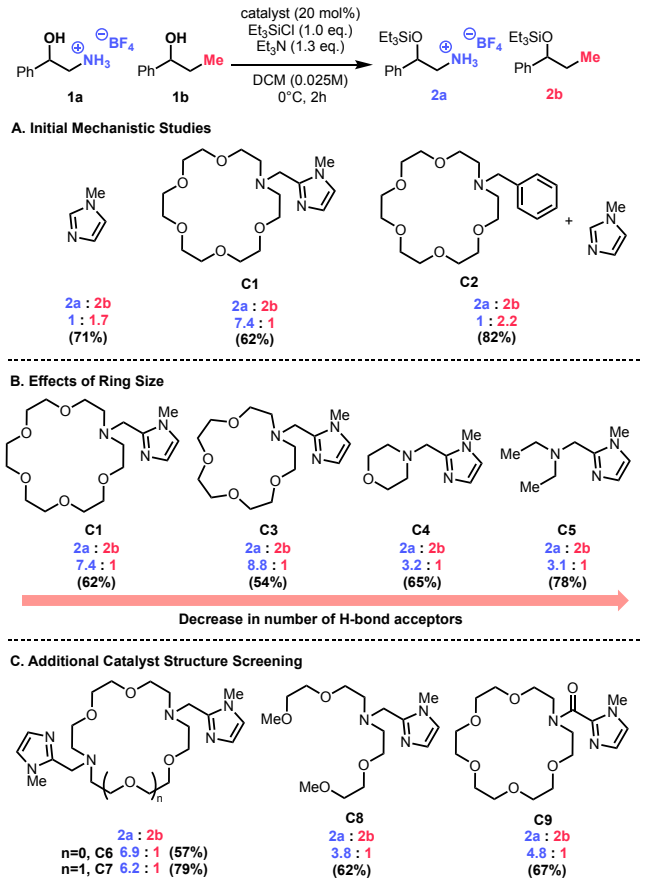
Figure 4. (A) Comparison of ^{1}H NMR spectra (MeCN-d_3, 298K) between (i) C1 (top), (ii) 1:1 ratio of organic ammonium alcohol 1a and C1 (middle), and (iii) 4:1 ratio of organic ammonium alcohol 1a and C1 (bottom). (B) Proposed binding models for the interaction of organic ammonium alcohol 1a and C1 (BF_4 anion was omitted for clarity).

These proposed binding models, along with our original hypothesis about the ammonium-directed *O*-functionalization, prompted us to evaluate the proposed bifunctionality and the key structural subunits on the catalytic efficacy of the ACE catalysts in substrate-selective catalysis. Building on our NMR titration studies, we chose the organic ammonium alcohol **1a** and its non-ammonium-counterpart **1b** as a pair of starting materials. Notably, the amino alcohol motif in **1a** is a common structural feature in many secondary metabolites.[22] We chose the BF_4 as a non-coordinating anion, which would allow the ammonium cation to be more accessible for binding to the ACE catalysts. Additionally, we reasoned that the well-studied *N*-heterocycle-catalyzed *O*-silylation[23–27] is a suitable and useful protection reaction to demonstrate the catalytic efficacy of NMI-bearing ACE catalysts in substrate-selective catalysis. For ease of reaction analysis using ^{1}H NMR spectroscopy, the reaction mixture was subsequently subjected to an acetylation condition at the end of the silylation reaction to furnish the corresponding acetates of the unreacted alcohols and amines (see the supporting information for details).

First, we began our study by evaluating the baseline competitive reactivity of substrate-selective silylation of the ammonium alcohol **1a** with its analogous non-ammonium alcohol **1b**. Under standard *O*-silylation conditions, using a catalytic amount of NMI, we observed that alcohol **1b** was the much faster-reacting substrate, producing a 1:1.7 ratio of *O*-silylated products **2a** and **2b** (Scheme 1A, left). In stark contrast, when our catalyst **C1** was used instead of NMI, a complete reversal in the substrate-selectivity of 7.4:1 ratio of **2a** and **2b** was observed, predominantly generating the desired product **2a** (Scheme 1A, middle). Subsequently, we tested the significance of covalently linking the macrocycle and the NMI subunit to investigate our proposed bifunctionality of the catalysts. In the presence of catalyst **C2** and NMI, we no longer observed the preference for the ammonium alcohol **1a**; instead, a similar level of substrate-selectivity as the NMI-catalyzed reaction was obtained (ratio of **2a**:**2b** = 1:2.2, Scheme 1A, right). This outcome strongly indicates that the ammonium-recognition event alone is insufficient for achieving selectivity for the ammonium alcohol substrate. During the survey of various reaction conditions, we observed increasing levels of substrate-selectivities for compound **2a** under strongly basic conditions (see Table S1, entries 8, 9, 15, and 16). This may suggest that the ammonium-binding catalysis is less operative, and it is likely that the observed selectivity favoring the formation of compound **2a** proceeds through an alternative pathway. Collectively, these results are consistent with our hypothesis for designing a new class of catalysts wherein the molecular recognition and Brønsted base catalysis are presumed to operate in tandem, leading to kinetically faster *O*-silylation of the ammonium alcohol substrate.

Next, we turned our attention to interrogating the number of H-bonding interactions between the ACE catalyst and ammonium substrate and their effect on the selectivity of the catalytic process. We anticipated that decreasing the number of H-bond acceptors in the crown ether subunit would reduce selectivity due to its diminished ability to effectively bind to an ammonium ion. First, we prepared a series of NMI-bearing catalysts with a range of crown ether sizes (Scheme 1B, compounds **C3-5**). As expected, catalysts **C4**-**C5** exhibited a trend whereby a decrease in ether oxygen atoms on the crown ether motif led to lower selectivity for compound **1a** (Scheme 1B). To our surprise, employing **C3** gave high selectivity (8.8:1) albeit lowest conversion (54%). The high substrate-selectivity exhibited by **C3** is consistent with the X-ray crystallographic structure of the ammonium-bound **C3** that revealed moderately strong H-bonds of 2.897-3.028 Å (Figure 5, left). Previous reports[28,29] have shown that the D_{3d} symmetry of 18-crown-6 ether has an ideal geometry for complementary H-bonding when complexing to the C_{3v} symmetry of the primary ammonium group RNH_3^+, which presumably enhances selectivity for silylation of ammonium alcohol **1a** as observed when using the **C1** catalyst. Interestingly, the comparison between NMI (Scheme 1A, left) and the catalyst **C5** (Scheme 1B, right) seems to suggest that the presence of a covalently linked tertiary amine subunit is important for selectivity. It is likely that the tertiary amine undergoes a sufficiently strong non-covalent interaction with **1a**, leading to notable alteration in the substrate-selectivity. In addition, we examined other catalyst scaffolds (Scheme 1C, compounds **C6-9**). For catalysts **C6** and **C7** that bear two NMI subunits, we initially expected an enhancement in substrate selectivity due to an increase in the number of catalytic subunits that are in proximity to the bound ammonium substrate. However, the observed selectivities (6.9:1 and 6.2:1 ratio, respectively, Scheme 1C, left) were found to be lower than their mono-NMI-ACE counterparts. This observation could be explained by the crytand-like encapsulation of an ammonium ion by catalysts **C6** and **C7**, which is revealed by our X-ray crystallographic structure of the ammonium-bound **C6** complex (Figure 5, right). Such a strong binding event is expected to suppress the productive bifunctional catalytic process.

Scheme 1. Investigation of the Bifunctionality of ACE Catalysts for substrate-selective silylation of ammonium alcohols[a]



[a]Reaction conditions, unless otherwise noted: **1a** (0.1 mmol), **1b** (0.1 mmol), catalyst (20 mol%), Et_3SiCl (0.1 mmol), Et_3N (0.13 mmol) in 2 mL of DCM were stirred at 0°C under N_2 for 2 h. For ease of reaction analysis, the reaction mixture was treated under an acetylation condition: DMAP (0.5 mmol) and Ac_2O (0.5 mmol) were added to the reaction mixture and stirred at rt for 2 h. Overall conversion (seen in parentheses) and selectivity ratios were determined by ^1H NMR spectroscopy.

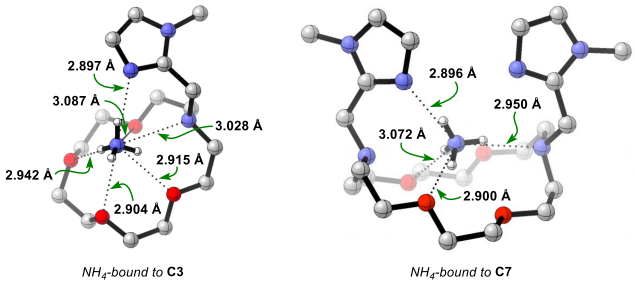


Figure 5. X-ray structures of NH_4-bound C3 and C7. The H-bonds (D···A) are indicated above (some hydrogen atoms and PF_6 anion were omitted for clarity).

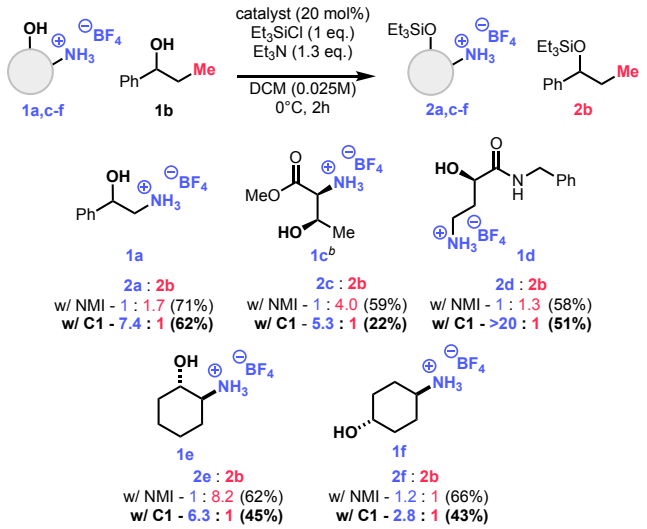
As a control, we investigated the importance of cyclic conformation of macrocyclic subunit in **C1** on reaction selectivity. We hypothesized that the pre-organized, rigid cyclic conformation is essential for effective ammonium-recognition to achieve selective silylation. In this light, we prepared acyclic catalyst **C8** and employed it under our reaction conditions (Scheme 1C). As we hypothesized, a lower level of substrate-selectivity was obtained (3.8:1 ratio, Scheme 1C, middle). Also, we observed that an amide-bearing catalyst **C9** exhibited a low selectivity (4.8:1, Scheme 1C, right), which is consistent with the fact that the electron withdrawing nature of the carbonyl moiety is expected to diminish both the strength of ammonium-catalyst interaction and the Lewis basicity of the NMI subunit. Lastly, we observed much lower selectivity for the ammonium substrate at low reaction temperature, giving a 1:2.7 ratio (see Table S1, entries 19-20). This can be explained by the increased strength of the H-bonds at low temperatures, which would shift the equilibrium of host-guest interactions towards association.[30]

To test the generality of the ACE-catalyzed substrate-selective silylation, we chose to examine diverse ammonium alcohols that are substructures of biomolecules, such as aminoglycosides and peptides (Scheme 2). We chose to employ **C1** due to its high substrate-selectivity and good reactivity. First, we observed that employing a catalytic amount of NMI to a mixture of substrates **1b** and threonine **1c** – an amino acid with an OH-side chain – gave mostly product **2b** (1:4.0 product ratio of **2c** and **2b**). However, when the same mixture was treated with catalyst **C1**, the inherent product distribution was overturned to give a ratio of 5.3:1, favoring the silylation of threonine **1c**. Similarly, a high level of overriding an inherent selectivity was observed for the 1,3-ammonium alcohol substrate **1d** – a hydroxybutyric acid subunit of amikacin. With NMI as a catalyst, a 1:1.3 ratio was observed, whereas catalyst **C1** showed excellent selectivity for the silylation of compound **1d** (>20:1 ratio).

Seeing the difference in the catalyst-controlled silylation ratios of trans-1,2-amino cyclohexanol **2e** and trans-1,4-amino cyclohexanol **2f** (6.3:1 and 2.8:1, respectively), it is evident that catalyst **C1** shows much better capabilities at overriding substrate selectivity of the NMI-catalyzed silylation of 1,2-amino alcohols. We suspect that the dimension of catalyst **C1** is more suitable for selectively silylating 1,2 and 1,3-ammonium alcohol substrates. In contrast, the conformationally restricted trans-1,4-ammonium alcohol **1f**, where the hydroxyl group is distal from the ammonium group, is not the ideal substrate-catalyst match and hence does not undergo recognition-driven, selective silylation. Additional studies are underway to identify the optimal complementary catalyst-substrate fit by modulating the linker length of the catalytic subunit.

We noticed that the product conversion is generally lower for the aza-crown ether catalyzed silylation than the NMI-catalyzed silylation. We postulate that the buildup of acidic protons in the silylation reaction medium may slow down the catalysis due to the protonation of the aza-crown ether catalyst, which bears a 3° alkyl amine motif. Also, it is plausible that the protonated 3° alkyl amine motif could engage in an intramolecular H-bonding interaction with the imidazole motif, hindering silylation of any alcohol substrates. Although this protonation is likely reversible, we anticipate that it may slow down the binding of the ammonium substrate. Nonetheless, these catalysts allow overturning of the substrate selectivity.

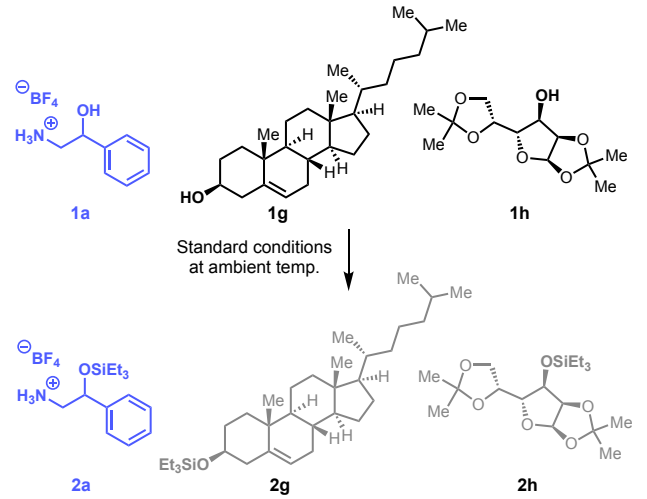
Scheme 2. Scope of BF_4-ammonium alcohols in substrate-selective silylation[a]



[a]Reaction conditions are the same as in Scheme 1. [b]Et_3SiCl (1.1 equiv), Et_3N (1.5 equiv), DCM:THF (9:1 v/v), 10 h.

Next, we evaluated the catalytic efficacy of **C1** in the presence of a more complex mixture of alcohol-bearing natural product substrates (cholesterol and protected α-D-allofuranose, Scheme 3). When comparing the product distribution of NMI and **C1**-catalyzed reactions, we observed a clear catalyst-controlled, recognition-driven selectivity where the product distribution for the target product **2a** was significantly increased from 14% to 68%. Employing these substrates under substrate-selective silylation conditions further strengthens our proposed mode of catalysis and reveals a consistent trend of the bifunctional catalyst overriding the inherent substrate-controlled selectivity.

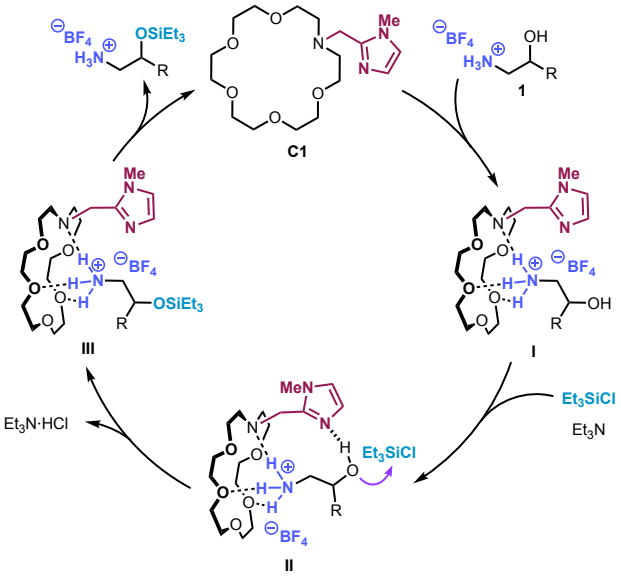
Scheme 3. Substrate-selective silylation of ammonium alcohol in the presence of more reactive biomolecules



NMR Conv.		Product Selectivity		
		2a	2g	2h
w/ NMI	85%	14%	78%	8%
w/ C1	72%	68%	27%	5%

On the basis of our studies, we propose a molecular recognition-driven catalytic cycle for the bifunctional catalysis (Scheme 4). First, the ammonium substrate binds to the macrocyclic catalyst via multiple H-bond interactions (complex **I**). Then, the NMI subunit of the catalyst initiates a Brønsted base activation of the hydroxyl group (complex **II**). The substrate then undergoes a nucleophilic attack towards the electrophile to give the silylated product (complex **III**). The ammonium substrate replaces the ammonium product to turn over the catalytic cycle. Alternatively, the NMI-catalyzed nucleophilic activation of TESCl may be operative.[25,31,32] We anticipate that this activation pathway will lead to the proximity-induced *O*-silylation of the ammonium substrate upon binding to the catalyst. Also, we considered the possibility of another mechanistic scenario involving the N to O silyl-migration pathway for the observed substrate-selectivity. Although we cannot completely rule out this possible alternative pathway, our control reactions using a catalytic amount of NMI have shown much higher selectivity for non-ammonium alcohol substrates. Thus, we suspect that this pathway is unlikely under our reaction condition.

Scheme 4. Proposed catalytic cycle



Conclusion

We have successfully developed a new class of bifunctional macrocyclic catalysts for recognition-driven, substrate-selective silylation of transiently protected, diverse amino alcohols. Our detailed mechanistic studies support an ammonium-directed *O*-silylation by the bifunctional ACE catalysts that utilize multiple cooperative NCIs for molecular recognition and catalytic activation. The results herein showcase potential for future applications in molecular recognition-based sensing, separations, and substrate-selective functionalization in a complex mixture of compounds. Also, this class of catalysts could have a wide range of applications for site-selective functionalization of complex biomolecules.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Detailed experimental procedures, analytical data for all new compounds, NMR titration data and X-ray crystal structures (PDF). FAIR Data is available as Supporting Information for this Publication and includes the primary NMR FID files for compounds 1-3, C1-C9.

Accession Codes

CCDC 2320974-2320977 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

AUTHOR INFORMATION

Corresponding Author

Byoungmoo Kim - Department of Chemistry, Clemson University, Clemson, South Carolina 29634, United States; Email: byoungk@clemson.edu

Author Contributions

A.G.S.: Conceptualization, synthesis, compound characterization, writing, and revision; A.S.O.: Synthesis, compound characterization, and revision; N.C and J.W.: Synthesis and compound characterization under the guidance of A.G.S. and A.S.O.; J.B.: Computational studies; B.K.: conceptualization, writing, and revision.

Notes

The authors declare no competing financial interests

ACKNOWLEDGMENT

B.K. gratefully acknowledges the financial support from Clemson University. B.K. thanks Prof. Daniel C. Whitehead (Clemson University) for his mentorship and helpful discussions. B.K., J.W., and N.C. gratefully acknowledge the financial support from NSF –Division of Chemistry, award CHE-2050042 (2021-2024). The authors would like to acknowledge Dr. Colin McMillen (Clemson University) for helping us to acquire X-ray crystallographic data and Dr. Rakesh Sachdeva (Clemson University) for helping us to acquire HRMS data.

REFERENCES

(1) Raynal, M.; Ballester, P.; Vidal-Ferran, A.; van Leeuwen, P. W. N. M. Supramolecular Catalysis. Part 1: Non-Covalent Interactions as a Tool for Building and Modifying Homogeneous Catalysts. *Chem. Soc. Rev.* **2014**, *43* (5), 1660–1733. https://doi.org/10.1039/C3CS60027K.

(2) Raynal, M.; Ballester, P.; Vidal-Ferran, A.; van Leeuwen, P. W. N. M. Supramolecular Catalysis. Part 2: Artificial Enzyme Mimics. *Chem. Soc. Rev.* **2014**, *43* (5), 1734–1787. https://doi.org/10.1039/C3CS60037H.

(3) Olivo, G.; Capocasa, G.; Del Giudice, D.; Lanzalunga, O.; Di Stefano, S. New Horizons for Catalysis Disclosed by Supramolecular Chemistry. *Chem. Soc. Rev.* **2021**, *50* (13), 7681–7724. https://doi.org/10.1039/D1CS00175B.

(4) Mayr, S.; Marin-Luna, M.; Zipse, H. Size-Driven Inversion of Selectivity in Esterification Reactions: Secondary Beat Primary Alcohols. *J. Org. Chem.* **2021**, *86* (4), 3456–3489. https://doi.org/10.1021/acs.joc.0c02848.

(5) Mayr, S.; Zipse, H. Annelated Pyridine Bases for the Selective Acylation of 1,2-Diols. *Eur. J. Org. Chem.* **2022**, e202101521. https://doi.org/10.1002/ejoc.202101521.

(6) Ashush, N.; Fallek, R.; Fallek, A.; Dobrovetsky, R.; Portnoy, M. Base- and Catalyst-Induced Orthogonal Site Selectivities in Acylation of Amphiphilic Diols. *Org. Lett.* **2020**, *22* (10), 3749–3754. https://doi.org/10.1021/acs.orglett.0c00830.

(7) Lindbäck, E.; Dawaigher, S.; Wärnmark, K. Substrate-Selective Catalysis. *Chem. Eur. J.* **2014**, *20* (42), 13432–13481. https://doi.org/10.1002/chem.201402548.

(8) Hashimoto, H.; Ueda, Y.; Takasu, K.; Kawabata, T. Catalytic Substrate-Selective Silylation of Primary Alcohols via Remote Functional-Group Discrimination. *Angew. Chem. Int. Ed.* **2022**, *61* (18), e202114118. https://doi.org/10.1002/anie.202114118.

(9) Chao, Y.; Cram, D. J. Catalysis and Chiral Recognition through Designed Complexation of Transition States in Transacylations of Amino Ester Salts. *J. Am. Chem. Soc.* **1976**, *98* (4), 1015–1017. https://doi.org/10.1021/ja00420a026.

(10) Späth, A.; König, B. Molecular Recognition of Organic Ammonium Ions in Solution Using Synthetic Receptors. *Beilstein J. Org. Chem.* **2010**, *6* (1), 32. https://doi.org/10.3762%2Fbjoc.6.32.

(11) Olivo, G.; Farinelli, G.; Barbieri, A.; Lanzalunga, O.; Di Stefano, S.; Costas, M. Supramolecular Recognition Allows Remote, Site-Selective C− H Oxidation of Methylenic Sites in Linear Amines. *Angew. Chem. Int. Ed.* **2017**, *129* (51), 16565–16569. https://doi.org/10.1002/anie.201709280.

(12) Olivo, G.; Capocasa, G.; Lanzalunga, O.; Di Stefano, S.; Costas, M. Enzyme-like Substrate-Selectivity in C–H Oxidation Enabled by Recognition. *Chem. Commun.* **2019**, *55* (7), 917–920. https://doi.org/10.1039/C8CC09328H.

(13) Olivo, G.; Capocasa, G.; Ticconi, B.; Lanzalunga, O.; Di Stefano, S.; Costas, M. Predictable Selectivity in Remote C− H Oxidation of Steroids: Analysis of Substrate Binding Mode. *Angew. Chem. Int. Ed.* **2020**, *59* (31), 12703–12708. https://doi.org/10.1002/anie.202003078.

(14) Romański, J.; Trzaskowski, B.; Piątek, P. Selective NaNO 2 Recognition by a Simple Heteroditopic Salt Receptor Based on L-Ornithine Molecular Scaffold. *Dalton Trans.* **2013**, *42* (43), 15271–15274.

(15) Martyanov, T. P.; Ushakov, E. N.; Nuriev, V. N.; Aleksandrova, N. A.; Sazonov, S. K.; Vedernikov, A. I.; Kuz'mina, L. G.; Klimenko, L. S.; Martyanova, E. G.; Gromov, S. P. Pseudodimeric Complexes of an (18-Crown-6)Stilbene with Styryl Dyes Containing an Ammonioalkyl Group: Synthesis, Structure, and Stereospecific [2 + 2] Cross-Photocycloaddition. *J. Org. Chem.* **2021**, *86* (4), 3164–3175. https://doi.org/10.1021/acs.joc.0c02514.

(16) Cheng, M.; Liu, X.; Luo, Q.; Duan, X.; Pei, C. Cocrystals of Ammonium Perchlorate with a Series of Crown Ethers: Preparation, Structures, and Properties. *Cryst. Eng. Comm.* **2016**, *18* (43), 8487–8496.

(17) Luo, Y.-H.; Wu, D.-E.; Song, W.-T.; Ge, S.-W.; Sun, B.-W. Positions of Amino Groups on Ammonium Salts Tunes the Conformations of Crown Ethers: Crystal Structures, Hirshfeld Surfaces and Spectroscopic Studies. *Cryst. Eng. Comm.* **2014**, *16* (24), 5319–5330. https://doi.org/10.1039/C4CE00150H.

(18) Wang, S.; Ding, X.-H.; Li, Y.-H.; Huang, W. Supramolecular Assemblies through Host–Guest Interactions of 18-Crown-6 with

Ammonium Salts: Geometric Effects of Amine Groups on the Hydrogen-Bonding Architectures. *Supramol. Chem.* **2015**, *27* (4), 213–223. https://doi.org/10.1080/10610278.2014.964238.

(19) Wu, D.-H.; Wu, Q.-Q. Ammonium Hexafluoridophosphate–18-Crown-6 (1/1). *Acta Cryst. E.* **2010**, *66* (8), o2132. https://doi.org/10.1107/S160053681002920X.

(20) Thordarson, P. Determining Association Constants from Titration Experiments in Supramolecular Chemistry. *Chem. Soc. Rev.* **2011**, *40* (3), 1305–1323. https://doi.org/10.1039/C0CS00062K.

(21) Maleknia, S.; Brodbelt, J. Cavity-Size-Dependent Dissociation of Crown Ether/Ammonium Ion Complexes in the Gas Phase. *J. Am. Chem. Soc.* **1993**, *115* (7), 2837–2843.

(22) Gupta, P.; Mahajan, N. Biocatalytic Approaches towards the Stereoselective Synthesis of Vicinal Amino Alcohols. *New J. Chem.* **2018**, *42* (15), 12296–12327.

(23) Worthy, A. D.; Sun, X.; Tan, K. L. Site-Selective Catalysis: Toward a Regiodivergent Resolution of 1,2-Diols. *J. Am. Chem. Soc.* **2012**, *134* (17), 7321–7324. https://doi.org/10.1021/ja3027086.

(24) Sun, X.; Lee, H.; Lee, S.; Tan, K. L. Catalyst Recognition of Cis-1,2-Diols Enables Site-Selective Functionalization of Complex Molecules. *Nat. Chem.* **2013**, *5* (9), 790–795. https://doi.org/10.1038/nchem.1726.

(25) Zhao, Y.; Rodrigo, J.; Hoveyda, A. H.; Snapper, M. L. Enantioselective Silyl Protection of Alcohols Catalysed by an Amino-Acid-Based Small Molecule. *Nature* **2006**, *443* (7107), 67–70. https://doi.org/10.1038/nature05102.

(26) Sun, X.; Worthy, A. D.; Tan, K. L. Scaffolding Catalysts: Highly Enantioselective Desymmetrization Reactions. *Angew. Chem. Int. Ed.* **2011**, *50* (35), 8167–8171.

(27) Hashimoto, H.; Ueda, Y.; Fujimura, K.; Takasu, K.; Kawabata, T. Approach Toward Reversal of Chemoselectivity in Catalytic Silylation of Pyranosides. *Eur. J. Org. Chem.* **2022**, 37, e202200949. https://doi.org/10.1002/ejoc.202200949.

(28) Rüdiger, V.; Schneider, H.-J.; Solov'ev, V. P.; Kazachenko, V. P.; Raevsky, O. A. Crown Ether–Ammonium Complexes: Binding Mechanisms and Solvent Effects. *Eur. J. Org. Chem.* **1999**, 8, 1847–1856. https://doi.org/10.1002/(SICI)1099-0690(199908)1999:8<1847::AID-EJOC1847>3.0.CO;2-Q.

(29) Lambert, S.; Bartik, K.; Jabin, I. Specific Binding of Primary Ammonium Ions and Lysine-Containing Peptides in Protic Solvents by Hexahomotrioxacalix[3]Arenes. *J. Org. Chem.* **2020**, *85* (15), 10062–10071. https://doi.org/10.1021/acs.joc.0c01294.

(30) Mukhopadhyay, R. D.; Das, G.; Ajayaghosh, A. Stepwise Control of Host–Guest Interaction Using a Coordination Polymer Gel. *Nat. Comm.* **2018**, *9* (1), 1987. https://doi.org/10.1038/s41467-018-04303-8.

(31) Manville, N.; Alite, H.; Haeffner, F.; Hoveyda, A. H.; Snapper, M. L. Enantioselective Silyl Protection of Alcohols Promoted by a Combination of Chiral and Achiral Lewis Basic Catalysts. *Nat. Chem.* **2013**, *5* (9), 768–774. https://doi.org/10.1038/nchem.1708.

(32) Patschinski, P.; Zhang, C.; Zipse, H. The Lewis Base-Catalyzed Silylation of Alcohols—A Mechanistic Analysis. *J. Org. Chem.* **2014**, *79* (17), 8348–8357. https://doi.org/10.1021/jo5016568.