Chiral Amide Directed Assembly of a Diastereo- and Enantiopure Supramolecular Host and its Application to Enantioselective Catalysis of Neutral Substrates

Chen Zhao, Qing-Fu Sun, William M. Hart-Cooper, Antonio G. DiPasquale, F. Dean Toste,* Robert G. Bergman,* and Kenneth N. Raymond*

Chemical Sciences Division, Lawrence Berkeley National Laboratory, and Department of Chemistry, University of California, Berkeley, California 94720, United States

Supporting Information Placeholder

ABSTRACT: The synthesis of a novel supramolecular tetrahedral assembly of $K_{12}Ga_4L_6$ stoichiometry is reported. The newly designed chiral ligand exhibits high diastereoselective control during cluster formation, leading exclusively to a single diastereomer of the desired host. This new assembly also exhibits high stability toward oxidation or a low pH environment, and is a more robust and efficient catalyst for asymmetric organic transformations of neutral substrates.

Inspired by nature, recent work in supramolecular chemistry has focused on the design and construction of assemblies that imitate the properties of enzymes.[1] Many such synthetic nanovessels can function in aqueous environments at physiological pH,[2] contain well-defined cavities for selective guest encapsulation and recognition,[3] and have been shown to stabilize otherwise reactive and unstable species.[4] Furthermore, many supramolecular hosts have proven to be efficient catalysts that increase both the rate and selectivity of a variety of chemical reactions.[5] Raymond and co-workers have developed tetrahedral supramolecular assembly **1** of $K_{12}Ga_4\mathbf{2}_6$ stoichiometry, where **2** = *N*,*N*-bis(2,3-dihydroxybenzoyl)-1,5-diaminonaphthalene.[6] The highly charged anionic host **1** has been shown to encapsulate a variety of cationic and neutral guests;[7] however, to date, its use in enantioselective catalysis has been limited to the charged substrates of the Aza-Cope rearrangement.[8] While Fujita and coworkers have reported the [2+2] cycloaddition of neutral guests in stoichiometric chiral hosts,[9] the use of nanoscale molecular flasks possessing chiral cavities as catalysts for asymmetric transformations of neutral guests remains elusive.[8-10]

Complex **1** is a chiral species because the three catecholates coordinate to a given gallium atom can form either a right (Δ)- or a left (Λ)-handed helicity at each metal center. Enforced by mechanical coupling that leads to chirality transfer between the four vertices,[11] complex **1** is formed as a racemic mixture of two homochiral enantiomeric forms, namely ΛΛΛΛ-**1** and ΔΔΔΔ-**1**. Resolution of the racemate was realized using (-)-*N*'-methylnicotinium iodide, giving access to enantiopure ΛΛΛΛ-(*S*-nic ⊂ **1**) and ΔΔΔΔ-(*S*-nic ⊂ **1**) stereoisomers.[12] Sequential ion exchange chromatography with large excess amounts of tetramethylammonium and potassium iodides salts then afforded "empty" and enantiopure clusters. However, the instability of the isolated cationic guest-free or K^+-filled ΛΛΛΛ-**1** and ΔΔΔΔ-**1** clusters warrant improvements.[12] We describe herein the design and synthesis of a new enantiopure supramolecular Ga_4L_6 cluster that spontaneously self assembles. In addition to circumventing the need for resolution, these new assemblies provide enhanced stability and catalytic reactivity required for asymmetric organic transformations of neutral guests.

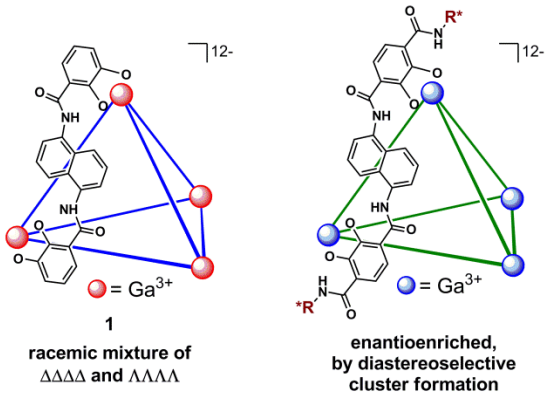


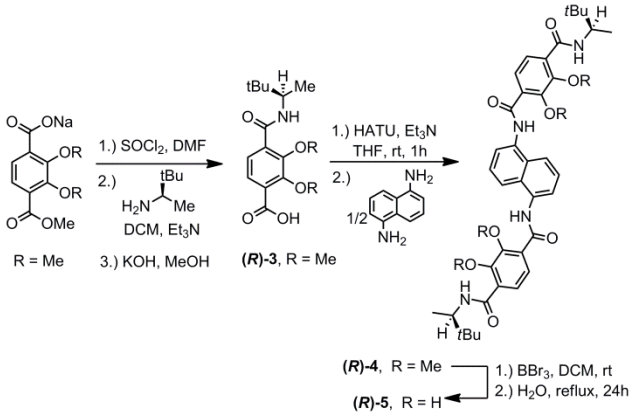
Figure 1. Relationship of racemic **1** to diastereo- and enantioenriched Ga_4L_6 supramolecular assembly

Our strategy for achieving an enantiopure supramolecular M_4L_6 assembly without resolution involves the addition of an amide-containing chiral directing group at the vertex of ligand **2**, as shown in Figure 1. We envisioned that this chiral source would control the helical configuration of the proximal metal center during cluster formation and direct a highly diastereoselective process in which the desired M_4L_6 supramolecular assemblies

would be formed enantioenriched rather than as a racemate. We also suspected that this additional amide functional group would stabilize the resulting assembly via hydrogen bonding with the catecholates and could prevent ligand oxidation and decomposition due to its electron withdrawing nature.

Ligand **(*R*)-5** was prepared as shown in Scheme 1. The terephthalate sodium salt was converted to the corresponding acyl chloride. This was followed by amide bond formation with commercially available chiral amine (*R*)-(-)-3,3-dimethyl-2-butylamine and subsequent saponification with KOH in methanol to afford the desired intermediate **(*R*)-3**. Reaction between **(*R*)-3** and 1.2 equiv. of HATU, (O-(7-azabenzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium hexafluorophosphate), in THF for 1h at room temperature followed by addition of 1,5-diaminonapthalene gave the desired methyl-protected chiral ligand **(*R*)-4**. Methyl group deprotection of **(*R*)-4** was achieved by treatment with BBr_3 and hydrolysis of the resulting borate to produce the desired terephthalamide-based chiral ligand **(*R*)-5** in 52% yield over 5 steps. The enantiomer **(*S*)-5** was also synthesized according to the procedures shown in Scheme 1.

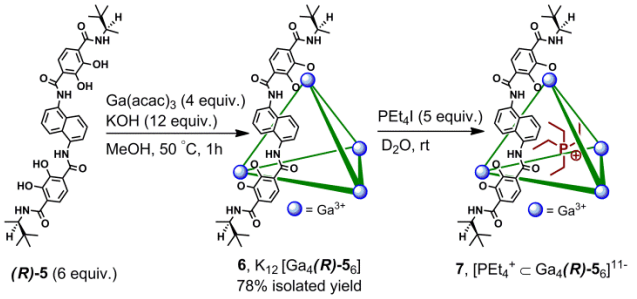
Scheme 1 – Synthesis of ligand **(*R*)-5**



We next investigated whether ligand **(*R*)-5** would form the desired tetrahedral supramolecular assembly. The initial reaction between 4 equiv. of $Ga(acac)_3$, 6 equiv. of ligand **(*R*)-5**, and 12 equiv. of KOH in methanol at room temperature, in the absence of any cationic species as a template, gave a mixture of products as analyzed by ^{1}H NMR spectroscopy (see Supporting Information). However when the reaction was repeated at 50°C for 1h, highly-symmetric complex **6**, as suggested by the simplicity of its ^{1}H NMR spectrum (see Supporting Information), was isolated as a yellow solid in 78% yield. Analysis of **6** by ESI mass spectrometry confirmed its stoichiometry as $K_{12}Ga_4$**(*R*)-5**$_6$. Furthermore, when 5 equiv. of PEt_4I was added to a D_2O solution of **6**, encapsulation of PEt_4^+ was observed as indicated by the proton resonances at δ = -1.45 and -1.78 ppm (see Supporting Information). This observation can also be taken as an indication of the successful formation of the desired tetrahedral assembly **6**.[6] Furthermore, **6**-$K_{12}Ga_4$**(*R*)-5**$_6$ was synthesized without the use of any cationic species as a template, whereas enantiopure **1** could only be obtained as a stable species after treatment with excess amount of NMe_4^+ as the template and counterion. Complex **6**-$K_{12}Ga_4$**(*S*)-5**$_6$, the enantiomer of **6**-$K_{12}Ga_4$**(*R*)-5**$_6$, was also synthesized by using ligand **(*S*)-5**, $Ga(acac)_3$ and KOH following a procedure directly analogous to that outlined in Scheme 2.

Complex **6** was also found to be bench-top stable in the solid state and in solution state at elevated temperature, whereas complex **1** was sensitive to oxidation and relatively less stable at 40 °C in the absence of a strong binding guest in solution over time. More importantly, complex **6** proved to be stable in aerobic D_2O at pD 5 and readily encapsulates PEt_4^+ even after heating at 70 °C for 6h, while complex **1** and $(NEt_4)_{12}$**1** dissociate in anaerobic D_2O immediately at the same pD (see Supporting Information). This property is a consequence of the lower basicity of the terephthalamide functionality relative to catecholate.[13]

Scheme 2 – Synthesis of supramolecular assembly **6** and its encapsulation of PEt_4^+ cation



It was reported previously that the UV π–π* transitions of the catechol moiety of assembly **1** produced a strong and distinct exciton couplet.[14] This property enabled the determination of absolute configuration of the resolved enantioenriched parent assembly **1** by circular dichroism spectroscopy.[12] When assemblies **6**-$K_{12}Ga_4$**(*R*)-5**$_6$ and **6**-$K_{12}Ga_4$**(*S*)-5**$_6$ were examined by CD spectroscopy, the spectra of the two enantiomers proved to be perfect mirror images of each other and contain a shape and sign of the Cotton effect similar to those of ΔΔΔΔ-**1** and ΛΛΛΛ-**1** (see Supporting Information).[12] Thus, we infer by comparison and assign complex **6**-$K_{12}Ga_4$**(*R*)-5**$_6$ as the ΔΔΔΔ stereoisomer and **6**-$K_{12}Ga_4$**(*S*)-5**$_6$ as the ΛΛΛΛ stereoisomer.

The absolute stereochemical assignment of ΔΔΔΔ-**6** was further supported by X-ray crystallographic analysis. Single crystals were obtained by slow diffusion of THF vapor into a water solution of ΔΔΔΔ-**6** without any strong-binding and cationic guest molecules under aerobic conditions. The structure conforms to the chiral space group R3 with three molecules of the enantiopure complex in the unit cell, each with crystallographic 3-fold symmetry. As shown in Figure 2, all four gallium centers adopt the Δ configuration, with an average Ga–Ga distance of 12.6 Å, similar to that found in the resolved parent assembly **1**.[6,12] The chiral directing groups bury the metal vertices of the cage with additional intramolecular hydrogen bonds between the amide proton and catecholate oxygen, which could be responsible for the observed stability of this new cluster. By crystal packing, each cage is part of a larger network of 12 neighboring cages, forming a 3-dimensional molecular organic framework. A huge solvent accessible void of 25000 Å^3 is calculated for the unit cell (65% of total unit cell vol-

ume), as a result of the large channels found along both the *a* and *b* axes of the crystal.

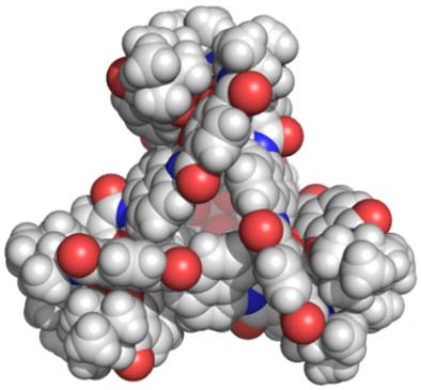


Figure 2. X-ray structure of ΔΔΔΔ-**6.**

As a further probe of the stereochemistry of ΔΔΔΔ-**6** and ΛΛΛΛ-**6**, we investigated their host-guest chemistries individually with both enantiomers of ammonium salt **8**. As illustrated in Figure 3, host-guest complex **9**, or ΔΔΔΔ-[(***S***)-**8** ⊂ **6**], should have different and distinguishable properties from complex **10**, ΔΔΔΔ-[(***R***)-**8** ⊂ **6**], due to their diastereomeric relationship. ^{1}H NMR spectroscopy (Figure. 3) reveals that the two complexes are indeed different, most notably in the encapsulation region of the spectra. On the other hand, complex **11**, ΛΛΛΛ-[(***R***)-8 ⊂ **6**], and complex **9** are enantiomers, and exhibit exactly the same spectroscopic behaviors when analyzed by ^{1}H NMR; the same result was also observed for complexes **10** and **12**. This evidence, combined with results from X-ray crystallography and CD spectroscopy, demonstrate that complex **6** is highly enantioenriched. The chiral group of ligand **5** exhibits strong control during cluster formation to give the desired supramolecular $K_{12}Ga_4$**5**$_6$ cluster as *a single diastereomer*.[15]

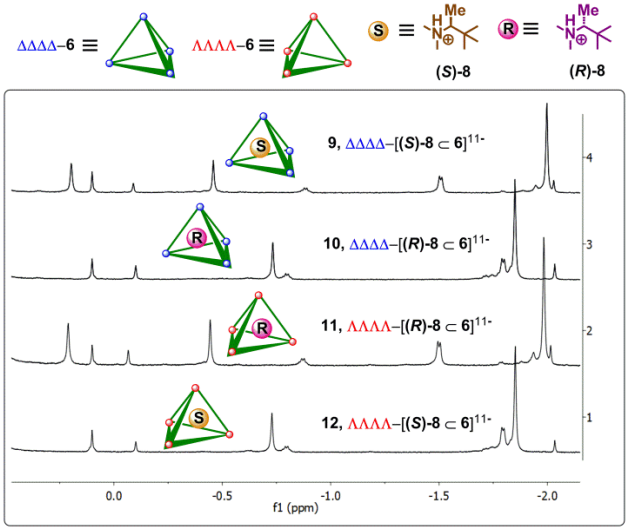
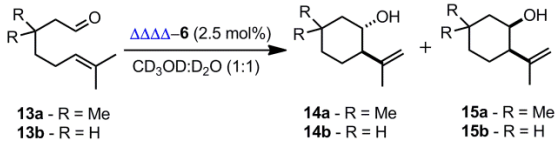


Figure 3. ^{1}H NMR spectra (encapsulation region) of complexes from host-guest chemistry of ΔΔΔΔ-**6** and ΛΛΛΛ-**6** individually with chiral ammonium salts (*S*)-**8** and (*R*)-**8**

One challenge to the development of asymmetric organic reactions catalyzed by enantiopure host ΔΔΔΔ-**1** is the requirement for cationic starting material or substrates that are more tightly bound than is NMe_4^+ to the cavity of ΔΔΔΔ-**1**. Since ΔΔΔΔ-**6** was synthesized without the use of any templates or cationic species, this new supramolecular host makes possible the enantioselective transformations of neutral compounds.

We recently reported the chemoselective carbonyl-ene cyclization of compounds **13a** and **13b** catalyzed by complex **1** to give exclusively products **14a,b** and **15a,b** respectively as compared to reaction performed in bulk solution.[16] When the reaction was repeated with 10 mol% of $(NMe_4)_{12}$**1** at 60 °C in D_2O buffered at pD 8 for 14h, no desired products were observed. On the other hand, when compound **13a** was treated with 2.5 mol% of ΔΔΔΔ-**6** in a solvent mixture of CD_3OD and D_2O buffered at pD 8 at room temperature, the desired products **14a** and **15a** were obtained in 92% NMR yield with a *trans:cis* ratio of 8:1 and 60% ee for **14a** over two days (Table 1, entry 1). Compared to reaction with complex **1** as the catalyst at the same pD, cyclization of **13a** in the presence of a catalytic amount of ΔΔΔΔ-**6** proved to be faster by 7-fold (see Supporting Information). Since complex ΔΔΔΔ-**6** is stable at low pD, attempts to effect the cyclization of **13a** at pD 5 led to faster conversion compared to reaction at pD 8 (Table 1, entry 2). The stability and turnover capability of catalyst ΔΔΔΔ-**6** was further illustrated as only 0.3 mol% of the complex is required to achieve 33% yield of **14a** and **15a** with no loss in enantiomeric excess of **14a** (Table 1, entry 4), representing 98 TON of the catalyst. Interestingly, carbonyl-ene cyclization of **13b** proceeded with complex **6** at pD 8 over 16h at 60 C to give the desired products in only 12% yield (Table 1, entry 5), whereas reaction at pD 5 led to much better conversion over the same reaction time to give the desired product mixture in 92% yield and 65% ee of **14b**.[17,18]

Table 1 – Enantioselective and chemoselective monoterpene-like cyclization of neutral substrates catalyzed by ΔΔΔΔ-**6**



entry	R	pD	temp (°C)	time (h)	yield (*trans:cis*)	*ee* of **14**
1	Me	8	25	50	92% (8:1)	61%
2[a]	Me	5	25	16	94% (7.5:1)	-58%
3	Me	5	-20	168	70% (8:1)	69%
4[b]	Me	5	60	24	33% (8:1)	58%
5	H	8	60	16	12% (nd)	nd
6[a]	H	5	60	16	92% (8:1)	65%

[a] Reaction performed with ΛΛΛΛ–**6** (2.5 mol%). [b] 0.3 mol% of ΔΔΔΔ–**6** was used (98 TON).

In conclusion, a new enantiopure supramolecular $K_{12}Ga_4L_6$ assembly has been synthesized, fully characterized, and applied as a rare example of chiral host catalyzed enantioselective transformations of neutral guests. The chiral amide in the terephthalamide-based ligands (***R***)-**5** and (***S***)-**5** direct cluster formation to afford highly diastereo- and enantiomerically enriched complexes. Remarkably, cationic guest-free variants of complexes ΔΔΔΔ-**6** and ΛΛΛΛ-**6**, which in comparison to **1** vary only in modification to the exterior of the assembly, show increased sta-

bility towards air oxidation in both the solid and solution states, and to low pH in solution. These features allow complexes ΔΔΔΔ-**6** and ΛΛΛΛ-**6** to serve as efficient catalysts for chemo-, diastereo- and enantioselective carbonyl-ene cyclization.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

fdtoste@berkeley.edu; rbergman@berkeley.edu; raymond@

socrates.berkeley.edu

Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

This research was supported by the Director, Office of Science, Office of Basic Energy Sciences, and the Division of Chemical Sciences, Geosciences, and Biosciences of the U.S. Department of Energy at LBNL (DE-AC02-05CH11231. The authors thank Amela Drljevic, Kristen Burford, and Rebecca Triano for helpful discussions.

REFERENCES

(1) (a) Breslow, R.; Dong, S. D. *Chem. Rev.* **1998**, *98*, 1997-2011. (b) Pluth, M. D.; Bergman, R. G.; Raymond, K. N. *Acc. Chem. Res.* **2009**, *42*, 1650-1659. (c) Yoshizawa, M.; Klosterman, J. K.; Fujita, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 3418-3438. (d) Meeuwissen, J.; Reek, J. N. H. *Nature Chemistry* **2010**, *2*, 615-621. (e) Wiester, M. J.; Ulmann, P. A.; Mirkin, C. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 114-137. (f) Avram, L.; Cohen, Y.; Rebek, J., Jr. *Chem. Commun.* **2011**, *47*, 5368-5375.

(2) Oshovsky, G. V.; Reinhoudt, D. N.; Verboom, W. *Angew. Chem., Int. Ed.* **2007**, *46*, 2366-2393.

(3) (a) Smit, B.; Maesen, T. L. M. *Nature* **2008**, *451*, 671-678. (b) Seneque, O.; Rager, M. N.; Giorgi, M.; Reinaud, O. *J. Am. Chem. Soc.* **2000**, *122*, 6183-6189. (c) Takezawa, H.; Murase, T.; Fujita, M. *J. Am. Chem. Soc.* **2012**, *134*, 17420-17423.

(4) (a) Dong, V. M.; Fiedler, D.; Carl, B.; Bergman, R. G.; Raymond, K. N. *J. Am. Chem. Soc.* **2006**, *128*, 14464-14465. (b) Sato, S.; Iida, J.; Suzuki, K.; Kawano, M.; Ozeki, T.; Fujita, M. *Science* **2006**, *313*, 1273-1276.

(5) (a) Kuil, M.; Soltner, T.; van Leeuwen, P. W. N. M.; Reek, J. N. H. *J. Am. Chem. Soc.* **2006**, *128*, 11344-11345. (b) Yoshizawa, M.; Tamura, M.; Fujita, M. *Science* **2006**, *312*, 251-254. (c) Hou, J.-L.; Ajami, D.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2008**, *130*, 7810-7811. (d) Iwasawa, T.; Hooley, R. J.; Rebek, J., Jr. *Science* **2007**, *317*, 493-496. (e) Murase, T.; Nishijima, Y.; Fujita, M. *J. Am. Chem. Soc.* **2012**, *134*, 162-164. (f) Wang, Z. J.; Clary, K. N.; Bergman, R. G.; Raymond, K. N.; Toste, F. D. *Nature Chemistry* **2013**, *5*, 100-103.

(6) Caulder, D. L.; Powers, R. E.; Parac, T. N.; Raymond, K. N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1840-1843.

(7) Biros, S. M.; Bergman, R. G.; Raymond, K. N. *J. Am. Chem. Soc.* **2007**, *129*, 12094-12095.

(8) Brown, C. J.; Bergman, R. G.; Raymond, K. N. *J. Am. Chem. Soc.* **2009**, *131*, 17530-17531.

(9) Nishioka, Y.; Yamaguchi, T.; Kawano, M.; Fujita, M. *J. Am. Chem. Soc.* **2008**, *130*, 8160-8161.

(10) (a) Liu, T.; Liu, Y.; Xuan, W.; Cui, Y. *Angew. Chem., Int. Ed.* **2010**, *49*, 4121-4124. (b) Chepelin, O.; Ujma, J.; Wu, X.; Slawin, A. M. Z.; Pitak, M. B.; Coles, S. J.; Michel, J.; Jones, A. C.; Barran, P. E.; Lusby, P. J. *J. Am. Chem. Soc.* **2012**, *134*, 19334-19337. (c) Bolliger, J. L.; Belenguer, A. M.; Nitschke, J. R. *Angew. Chem., Int. Ed.* **2013**, *52*, 7958-7962. (d) Kleij, A. W.; Kuil, M.; Tooke, D. M.; Spek, A. L.; Reek, J. N. H. *Inorg. Chem.* **2005**, *44*, 7696-7698. (e) Otte, M.; Kuijpers, P. F.; Troeppner, O.; Ivanović-Burmazović, I.; Reek, J. N. H.; de Bruin, B. *Chem. Eur. J.* **2013**, *19*, 10170-10178.

(11) Ziegler, M.; Davis, A. V.; Johnson, D. W.; Raymond, K. N. *Angew. Chem., Int. Ed.* **2003**, *42*, 665-668.

(12) Davis, A. V.; Fiedler, D.; Ziegler, M.; Terpin, A.; Raymond, K. N. *J. Am. Chem. Soc.* **2007**, *129*, 15354-15363.

(13) Garrett, T. M.; Miller, P. W.; Raymond, K. N. *Inorg. Chem.* **1989**, *28*, 128-133.

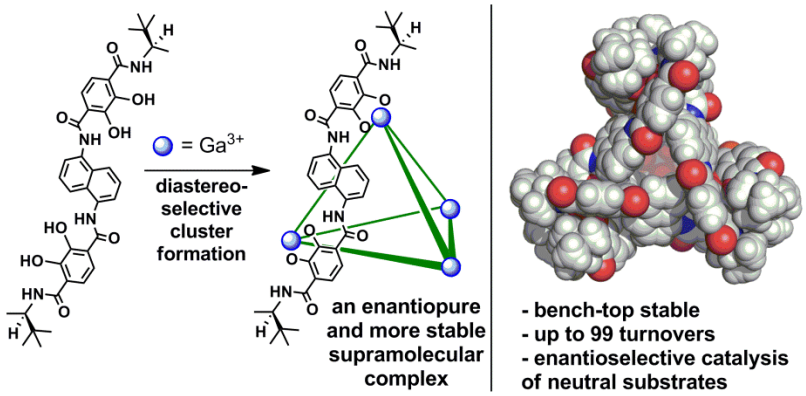
(14) Ziegler, M.; von Zelewsky, A. *Coord. Chem. Rev.* **1998**, *177*, 257-300.

(15) Molecular mechanics calculations of ΔΔΔΔ-[Ga_4(***R***)-**5**$_6$] and ΛΛΛΛ-[Ga_4(***R***)-**5**$_6$] reveal that the ground-state energy difference between the two diastereomers is approximately 19 kcal/mol, favoring the experimentally observed isomer ΔΔΔΔ-[Ga_4(***R***)-**5**$_6$] (see Supporting Information for details).

(16) Hart-Cooper, W. M.; Clary, K. N.; Toste, F. D.; Bergman, R. G.; Raymond, K. N. *J. Am. Chem. Soc.* **2012**, *134*, 17873-17876.

(17) The observed chemoselectivity, yield and enantiomeric excess of **15b** are improved as compared to Lewis-acid catalyzed transformation of the same substrate reported in literature: (a) Mikami, K.; Sawa, E.; Terada, M. *Tetrahedron: Asymmetry*, **1991**, *12*, 1403-1412. (b) Mikami, K.; Terada, M.; Sawa, E.; Nakai, T. *Tetrahedron Lett.* **1991**, *45*, 6571-6574.

(18) For an additional example of an enantioselective transformation of neutral substrate catalyzed by complex **6**, see Supporting Information.


= Ga3+
diastereo-
selective
cluster
formation
an enantiopure
and more stable
supramolecular
complex
- bench-top stable
- up to 99 turnovers
- enantioselective catalysis
of neutral substrates