Organic Reactions with Self-Assembly Supramolecules

Literature Seminar #2 2024/7/18 M2 Arii

Outline

- 1. Introduction
 - 1-1. Supramolecular Chemistry
 - 1-2. Metal-Ligand Self-Assembling Supramolecule
- 2. Unimolecular Reaction with Supramolecule
 - 2-1. Aza-Cope Rearrangement
 - 2-2. Nazarov Cyclization
 - 2-3. Aza-Prins Cyclization
- 3. Reaction with Metal Encapsulated within Supramolecules
 - 3-1. Development of C(sp³)-C(sp³) Coupling Reaction with Supramolecules
 - 3-2. Development of Coupling Reaction with Cu / Pd in Water
 - 3-3. Selective Catalytic Hydrogenation Independent of Chain Length
- 4. Stereoselective Reaction by Host Size and Flexibility
 - 4-1. Stereoisomer of Self-Assembly Complex
 - 4-2. Stereoselectivity by Host Size (Prins Reaction)
 - 4-3. Stereoselectivity by Host Flexibility (Aza-Darzens Reaction)
- 5. Summary

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Host-Guest Chemistry



Paul J. Lusby, et al., J. Am. Chem. Soc. 2018, 140, 2862.

Joost N. H. Reek, et al., J. Am. Chem. Soc. 2015, 137, 2680.

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1-1

Classical Supramolecular Chemistry



Ronald Breslow and Peter Campbell, J. Am. Chem. Soc. 1969, 91, 3085.

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Classical Supramolecular Chemistry

Introduction ▶ 2 Reactions using cyclodextrin derivativies OAc .OH α-cyclodextrin-PCA-Ni²⁺ 0.10 M acetate buffer (pH 5.17) O_2N O_2N 4 times faster than with PCA-Ni²⁺ OH **103** times faster than under no catalyst HO OHO HO HO [⊖]0-№ OH HO . N−0⊖ N-0[⊖] Host OĤ HO OH PCA-Ni²⁺ reaction center ЮH (pyridine-<u>c</u>arbox<u>a</u>ldoxime) OH HO ÔΗ α-cyclodextrin-PCA-Ni²⁺ HO Encapsulate phenyl groups Extremely close to the reaction center

Breslow, R. and Overman, L. E., J. Am. Chem. Soc. 1970, 92, 1075.

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Richard J. Hooley and Julius Rebek Jr., Org. Biomol. Chem. 2007, 5, 3631.

Development of Supramolecular Chemistry 1-2

Introductior



Advantage

Conformational control over the Guest

Different environments from bulk solutions

- Shifts in equilibria to generate reactive species
- Dramatic **increase** in effective **concentration**

Existing Problems



1-2 Metal-Ligand Self-Assembling Supramolecule Introduction Metallosupramolecular Host : the use of metal-ligand bonding ✓ Self-assembles into the most stable structure because of reversible bonding ✓ Organizing force for the construction of symmetric coordination cages ✓ Easy to synthesize derivatives ✓ More flexible structure than a host consisting only of covalent bonds

First reported metal-ligand self-assembling supramolecule



Hans Georg von Schnering, et al., Angew. Chem., Int. Ed. Engl. 1988, 27, 851.

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Metal-Ligand Self-Assembling Supramolecule



<u>Solubility</u>

Dodecaanionic anion



1-2

Soluble in water and polar organic solvents

<u>Guests</u>



Cationic/neutral molecules with hydrophobic groups

<u>Cavity</u>

Hydrophobic microenvironment of sufficient size

- Can be used as Host
 - Excludes the bulk solution

Flexibility

Movable arene walls via rotation of amide bonds

Encapsulated guests of various shapes.

Kenneth N. Raymond, et al., Inorg. Chem. 2009, 48, 111.

1-2 The Properties of Metallosupramolecular Hosts



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Aza-Cope Rearrangement



Nazarov Cyclization



Kenneth N. Raymond and F. Dean Toste, et al., J. Am. Chem. Soc. 2018, 140, 6591.

Aza-Prins Cyclization



David M. Kaphan, F. Dean Toste, Robert G. Bergman, and Kenneth N. Raymond, J. Am. Chem. Soc. 2015, 137, 9202.

Unimolecular Reaction with Supramolecule



David M. Kaphan, F. Dean Toste, Robert G. Bergman, and Kenneth N. Raymond, J. Am. Chem. Soc. 2015, 137, 9202.

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3-1 Approach to Coupling Reactions with Supramolecule

Reaction with Metal Encapsulated within Supramolecules



Ligands always bind to metal

Supramolecules bind in only one step.

Selectively accelerate only the slowest step and not affect the others



Supramolecular approaches

C(sp³)-C(sp³) Reductive Elimination



18 Kenneth N. Raymond, and F. Dean Toste, et al., J. Am. Chem. Soc. **2016**, 138, 9682. 3-1

C(sp³)-C(sp³) Reductive Elimination



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Development of Coupling Reaction in Water

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3-2 Development of Coupling Reaction in Water

Reaction with Metal Encapsulated within Supramolecules

C(sp²)-C(sp³) coupling reaction product



Candidate for coupling reactions in water.

Possibility of Pd(IV) complex that can also undergo C(sp²)-C(sp³) reductive elimination

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Selective Catalytic Hydrogenation



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Selective Catalytic Hydrogenation



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 Δ -[M(A-A)₃]

 Λ -[M(A-A)₃]



Stereos lectivity by Host Size

t.Downloaded o Attri Commons Diastereoselectivity ,.OH ,OH 2-10 mol% 1-4 Me Me ember 2014. conditions Creativ 6 (±)-5 'OH •OH 5a: R = H Me vol 28 Nov sed under 5b; R = *n*Pr 8 8 8 8 % 7 8 host substrate mol% temp/°C time/h %conv % **9** %6 entry Article. Publish Thus article i<u>s</u> li 60 28 71 2 (±)-1 (±)-5a 54 1a^a 10 33 (S)-**5a** 39 Δ_4 -2 10 40 23 70 51 ∆**₄-2** 3a° (R)-5a 5 40 23 60 30 61 24 <1 71 2 60 (±)-**3** (±)-5a 48 45 60 20 Access 30 50 Λ**4-4** (±)-5a 2 48 68 <1 34 8 (S)-**5a** 5 60 48 56 <1 58 ∆**⊿-4** ∆**⊿-4** (R)-**5**a 5 60 48 80 12 <1 30 58 Open ____ >95^f (±)-1 (±)-5b 10 50 30 20 <1^e >95^f 9a^d Λ₄-2 (±)-5b 2 40 24 60 <1^e <1^e

Smaller cavity

4-2

Trans conformation destabilized

Diasteroselectivity : Large Host

Stereoselective Reaction by Host Size and Flexibility

Enantioselectivity



1b ^a	(±)- 1	10	60	28	91	14	86	-	
2b ^c	Δ_4 -2	2.5	25	50	92	12	88	61	
3b ^c	Δ_4 -2	1	40	16	22	11	89	_	
4b ^c	Λ_4 - 4	2	40	16	93	2	98	33	

Smaller cavity



- Larger steric hindrance
- One enantiomer is more favorable than the other.

Enantioselectivity : Small Host

	Smaller	Larger	
Racemic	1	3	
Enantiopure	2	4	
			27

Kenneth N. Raymond, et al., Chem. Sci. 2015, 6, 1383.

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Aza-Darzens Reaction with Supramolecule

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Kenneth N. Raymond and F. Dean Toste, et al., J. Am. Chem. Soc. 2020, 142, 733.

New Ga(III)-Containing Enantiopure Hosts



Divergent Selectivity in Enantiopure Hosts



Kenneth N. Raymond and F. Dean Toste, et al., J. Am. Chem. Soc. 2020, 142, 733.

4-3 Relationship between Flexibility and Enantioselectivity



Kenneth N. Raymond and F. Dean Toste, et al., J. Am. Chem. Soc. 2020, 142, 733.

4-3 Relationship between Metal lons and Host Flexibility

Relationship between metal ions and host flexibility



Kenneth N. Raymond and F. Dean Toste, et al., J. Am. Chem. Soc. 2020, 142, 733.

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Stereoselective Reaction by Host Size and Flexibility

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Appendix

C(sp³)-C(sp³) Reductive Elimination

Phosphine ligand effects



Kenneth N. Raymond, and F. Dean Toste, J. Am. Chem. Soc. 2016, 138, 9682.

3-1

Application of Dual Catalysis Cycle



3-2 Development of Coupling Reaction in Water

Appendix

Confirmation of product generation (Pd complex)



F. Dean Toste, et al., J. Am. Chem. Soc. 2019, 141, 1701.

Selective Catalytic Hydrogenation

Appendix

~60

conv



10 mol% 1

pH 8 H₂O, H₂ 8 h, rt

Stereoselectivity by Host Size

View Article Online Appendix



⁴¹ Kenneth N. Raymond, *et al.*, *Chem. Sci.* **2015**, *6*, 1383.

Aza-Darzens Reaction with Supramolecule

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Kenneth N. Raymond and F. Dean Toste, et al., J. Am. Chem. Soc. 2020, 142, 733.

Synthesis of [Ga₄L₆]¹²⁻



Ligand **S4a** (0.075 mmol, 6 equiv.) and $Ga(acac)_3$ (18.4 mg, 0.05 mmol, 4 equiv.) were dissolved/suspended in degassed wet ethanol (4 mL, 200 uL added H₂O) and heated to 72 °C. After 15 minutes, KOH (12.6 mg, 0.225 mmol, 18 equiv.) as a solution in wet ethanol (2 mL, 100 uL added H₂O) was added slowly at 0.015 mL/min via syringe pump to the heterogeneous reaction. Upon complete addition of KOH, the yellow reaction mixture became a homogeneous solution, and the reaction was allowed to cool to rt. The host was then precipitated via addition of diethyl ether (15 mL) to the stirring solution. The yellow solid was then collected by filtration and washed with diethyl ether (15 mL) to give the desired supramolecular complex.

Aza-Darzens Reaction with α -diazoesters

Ph (S)-61 or (S)-62/BH3-THF (10 mol%) CO₂Et CH2Cl2 22 °C 63 59 60 with 61: 54-91% yield $R = Ph, p-BrC_6H_4 o-MeC_6H_4 p-NO_2-C_6H_4 3,4-$ 91-98% ee (OAc)₂C₆H₃, 2-furyl, 1-naphthyl, ⁿPr, ^tBu, c-C₆H₁₁ with 62: 55-85% yield 90-98% ee Ph¹ ́ОН Ph Ph/ OН Ph/ •OH (S)-(61) (S)-(62) Scheme 20. Catalytic asymmetric aziridination mediated by chiral boron acid with biaryl VAPOL and VANOL ligands. 64 (10 mol%)





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Appendix



45 Kenneth N. Raymond and F. Dean Toste, *et al.*, *J. Am. Chem. Soc.* **2020**, *142*, 733.

Appendix

4-3 Relationship between Flexibility and Enantioselectivity

5 不斉合成と反応温度

前節までの解説では、鏡像異性体のそれぞれを L-型 もしくは D-型と表現した。この立体化学の表記法は、 基準となる糖質化合物から仮想的な化学変換に基づい て命名されるもので、一般性に乏しいため、現在では3 次元的な分子構造から一定の規則に基づいて機械的に 命名する R/S 表記法が IUPAC (国際純正および応用化 学連合)によって定められている。不斉合成の選択性は、 (S)体と(R)体の分子数から鏡像体過剰率(Enantiomeric Excess, %ee)で評価される(式1)。

%
$$ee = \frac{|(S) - (R)|}{(S) + (R)}$$
 (式1)

全く選択性がない場合(図3)では,0%eeであり, 完全な選択性が実現された場合には,100%eeである。 一方,1884年に提唱された Arrhenius の式によれば,鏡 像体過剰率(%ee)は反応速度定数 k を介して関係付け られる。すなわち,鏡像体過剰率は反応温度(T)の関数 として表現される(式2)。

$$\ln k = -\frac{\Delta \Delta H}{R} \frac{1}{T} + \frac{\Delta \Delta S}{R} = \ln \frac{100 + \% ee}{100 - \% ee} \quad (\pm 2)$$

Appendix

不斉触媒



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Tohru Yamada, JEMEA Bulletin 2021, 6, 10