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Toward reactant encapsulation for substrate-selectivity

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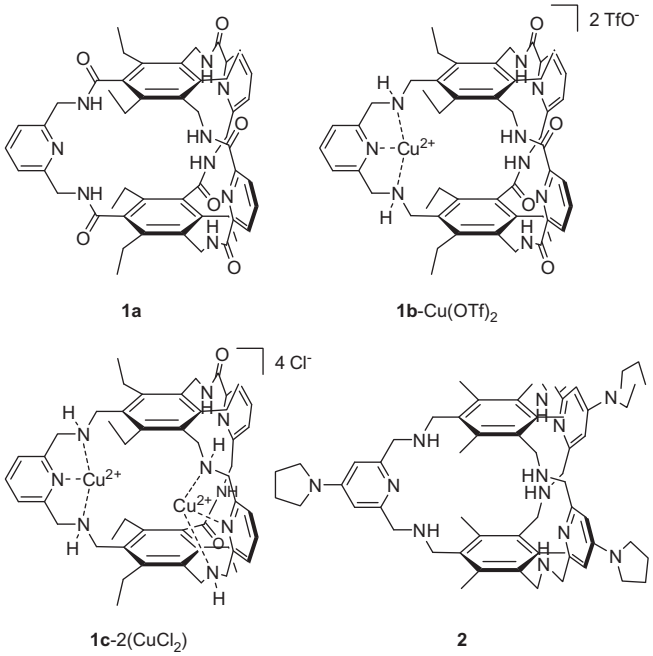
ABSTRACT

A synthetic tris-(bis-(aminomethyl)pyridine) receptor was prepared in excellent yields via reversible imine condensation strategy. Catalytic activity in Henry reactions of the corresponding copper(II) complex was studied. Capitalizing on previous works by Anslyn with related receptors, the dramatic increase in basicity induced by this type of complex on diketo-derivatives was used to perform a nucleophilic addition of a deprotonated substrate onto an electrophile within the cavity. Hence, a Lewis acid stabilized nitronate was reacted with various aldehydes. A notable preference for small reactants easily accommodated in the cavity over encumbered ones was observed, thus representing an example of substrate-selectivity.

Since their discovery, the fascinating reactivity of enzymes has been idealized as perfect models for chemists aiming to promote organic reactions with high levels of selectivity. These natural catalysts are able to selectively encapsulate substrates through molecular recognition and to considerably modify their reactivity.[1] This temporary enzyme–substrate association matches the perfect conditions to catalyze an impressive number of reactions leading to a wide variety of structural patterns with high efficiency and selectivity.[2] In this context,[3] inspired by enzymes' reactivity, Diederich first reported an example of organocatalysis within a macrocyclic host.[4] The macrocyclic compound behaved as a pseudo-enzymatic catalyst allowing the efficient conversion of an aldehyde substrate, followed by the release of the benzoin product. Later, the groups of Fujita,[5] Raymond[6], and Rebek[7] designed macropolycyclic compounds with a tridimensional internal cavity able to promote transformations of encapsulated substrates.[8] In this context, Rebek first described the synthesis and evaluation of a purely organic cage containing an acid functionality directed inside the cavity which was shown to promote the ring closure of an epoxyalcohol with very high levels of regioselectively. In this field, Anslyn[9,10] introduced aza-cryptand **1a** and copper(II) complexes **1b,c** and demonstrated their ability to increase the acidity of carbon-acids complexed within their cavity. Hexa-amide receptor **1a** could induce a pK_a lowering of nearly three units uniquely relying on H-bonding with the diketo-substrate. More strikingly, aza-cryptand **1b**-Cu(OTf)$_2$ induced a lowering of the pK_a value of 2-acetylcyclopentanone of not less than 12 units upon complexation in acetonitrile (Fig. 1). This dramatic effect was explained as the result of an electrostatic/coordination interactions between the copper(II) center and the anionic π system of the diketo-system. If the cage is able to tolerate an additional electrophile, one can thus expect to promote a reaction between two complexed reactants,



1a **1b**-Cu(OTf)$_2$ **1c**-2(CuCl$_2$) **2**

Figure 1. Synthetic receptors **1** and **2**.

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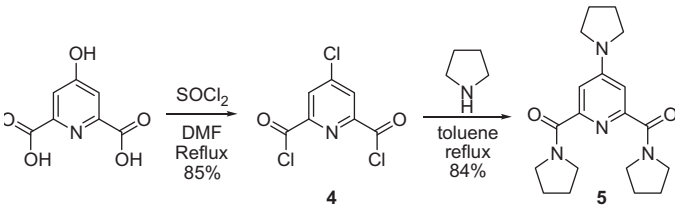
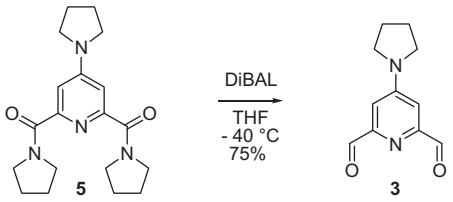


Scheme 1. Preparation of diamide **5**.



Scheme 3. Direct reduction to dialdehyde **3**.

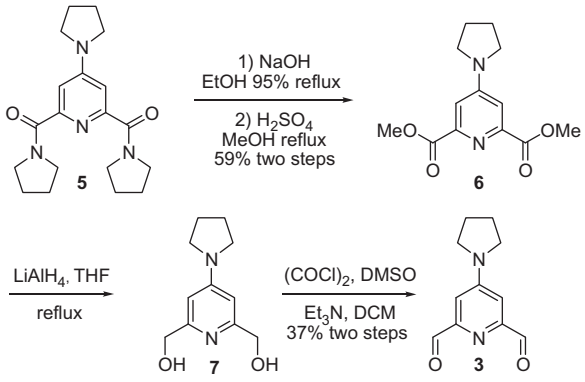
and this work aims to explore such possibility. However, a simple synthetic access to similar aza-cryptands is first needed since non C_3-symmetrical **1b**,**c** require multistep sequences for their preparation. Therefore, we took the advantage of the recently described efficient preparations of C_3-symmetrical aza-cyclophanes[11] described by Roelens,[12] Delgado,[13] Ghosh,[14] and our group.[15]

These syntheses rely on thermodynamically driven imine condensation allowing nearly quantitative formation of polyamine of type **2** after reduction of the imine functions. Therefore, our investigation began with the synthesis of a new aza-cryptand **2** containing three 2,6-bis-(aminomethyl)pyridine moieties able to bind copper(II) salts (Fig. 1). Use of the corresponding copper(II) complex for copper(II)-catalyzed Henry (nitroaldol) reaction[16–18] was next considered. Indeed, due to the modest size of the involved nucleophilic nitronate that can therefore easily enter within aza-cryptand's cavity, we hoped to demonstrate that such catalyst could display some selectivity as regard to the size of the reacting aldehyde partner.

Preparation of aza-cryptand **2** began with the synthesis of dialdehyde **3** which contains the 4-pyrrolidino-pyridine pattern. We chose to include this electron-rich pyridine moiety in the structure of cage **2** aiming to maximize the copper(II) chelation by the tridentate 2,6-bis-(aminomethyl)pyridine moiety. Intermediate diamide **5** was prepared from the commercially available chelidamic acid by chlorination to give **4**, followed by reaction with pyrrolidine leading to diamide **5** in good yields (Scheme 1).

A first approach to the targeted dialdehyde was explored following previously described route reported for the 4-dimethylamino analog.[19] Diamide **5** was thus hydrolyzed by a solution of sodium hydroxide in ethanol and was then bis-esterified with methanol in acidic medium, leading to diester **6** in 59% over two steps. Reduction of the ester with $LiAlH_4$ gave crude diol **7**, which was then oxidized using Swern conditions to give dialdehyde **3** in moderate yield over two steps. This sequence allowed the preparation of small amounts of dialdehyde **3** in four steps in a global yield of 22%, Scheme 2.

This lengthy preparation could be optimized through a direct reduction of diamide **5** into dialdehyde **3**. Various conditions were



Scheme 2. First preparation of dialdehyde **3**.

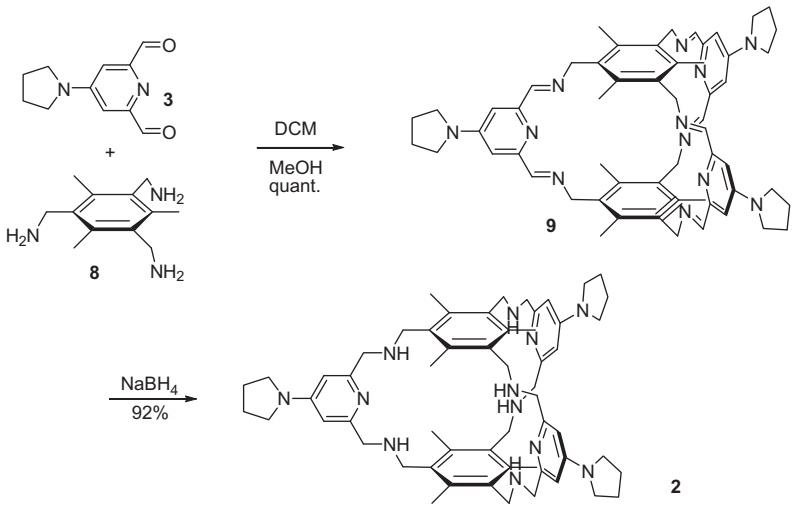
investigated to achieve this delicate twofold selective reduction and, after some experimentation following reported amide-aldehyde interconversion methodologies,[20] optimal conditions were spotted with DIBAL.

The double reduction was thus best effected in THF, at −40 °C, using a DIBAL solution with a fourfold excess. This allowed the preparation of dialdehyde **3** in a yield of 75% in only one step (Scheme 3). Remarkably this protocol was repeated with the Weinreb diamide but did not allow us to produce any quantity of dialdehyde **3**. As shown in the previous studies,[15] this compound is a good candidate for imine condensation reactions with an aromatic triamine to elaborate hexa-azacryptands. Dialdehyde **3** was therefore reacted with triamine **8** in a mixture of DCM/MeOH to furnish hexa-imine cage **9**, containing a C_3-symmetry axis, in quantitative yield. The six imine moieties of macrocycle **9** were easily reduced with an excess of $NaBH_4$ to give hexa-amine cage **2**, in a 92% yield, without need for any purification (Scheme 4). This aza-cryptand constitutes an electron-rich version of the cage prepared and studied by the group of Delgado.[13]

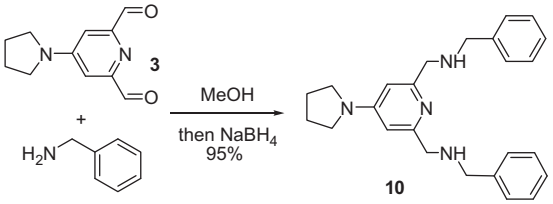
For comparative experiments, we also prepared the simple ligand **10** by reaction of aldehyde **3** with benzylamine and subsequent reduction, see Scheme 5.

Once the synthesis of cage **2** had been secured, we explored its use, as a copper(II) complex, for its potential catalytic activity in nitro-aldol reactions with aldehydes. Anslyn and co-workers examined the binding stoichiometry of receptors **1b** and **1c** with copper(II) salts in acetonitrile, an aprotic solvent. These two receptors are fitted with, respectively, one and two diaminopyridine moieties, it was hence shown that cage **1b** formed a 1:1 complex with copper(II), while cage **1c** formed the 1:2 complex. Titration studies indicated high association constants.[9] Due to the virtually insoluble nature of cage **2** in acetonitrile, we could not perform a comparable study. The group of Delgado recently undertook the careful study of the complexing properties of a similar C_3-symmetrical cage in an aqueous medium (H_2O/MeOH: 1/1) taking into account the different protonated forms of the receptor. This study demonstrated that cage **2**, fitted with three complexing units, was able to accommodate three copper(II) ions. For our catalysis experiments only one copper(II) center is necessary inside the reaction cavity, we thus assumed that upon addition of slightly less than one equivalent of copper(II) salt, the predominant species in organic solution would be the 1:1 complex.

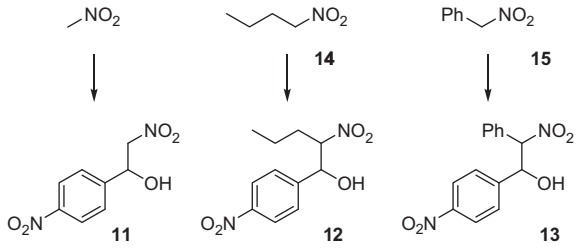
The first set of experiment was devised in order to demonstrate the feasibility of a Henry reaction within cage **2**. We chose 4-nitrobenzaldehyde as the test substrate for its good electrophilicity and nitromethane as the nucleophile. We also adopted copper(II) acetate as the copper source as being the most commonly employed in the literature. Different solvents and mixtures of solvents were tested. As mentioned above, cage-ligand **2** is poorly soluble in polar solvents such as acetone, acetonitrile, DMF, DMSO or dioxane and is totally insoluble in protic solvents like methanol, ethanol. Although freely dissolved by THF, ethyl acetate or toluene, the best results were obtained with a DCM/MeOH 1:1 mixture. All further experiments were thus performed in this mixture. The successful Henry condensation was observed using the protocol as follows



Scheme 4. Preparation of azacryptand **2**.



Scheme 5. Preparation of 'open'-ligand 10.



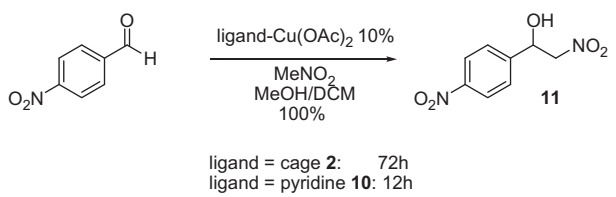
Scheme 7. Henry condensations with various nitroalcanes.

with a catalyst loading of 10% in a 1:1 complex. The latter was preformed by mixing 12% of ligand **2** with 10% of copper acetate for 12 h, resulting in a deep-blue clear solution (λ_{max} = 500 nm). Reactants were thus added and progression of the reaction was monitored by TLC and proton NMR. At ambient temperature, 72 h were necessary to observe the complete disappearance of the starting aldehyde. After this period of time, nitroaldol derivative **11** was isolated in quantitative yield (Scheme 6). Interestingly, the reaction using the same conditions with pyridine derivative **10** as the ligand gave **11** after only one night of reaction, showing the shielding effect exerted by the cage around the reactive center.

Under similar conditions, hexa-imine cage **9** displayed much lower catalytic activity, since after 6 days, aldehyde conversion into nitroaldol was limited to 29%. This result can unveil a critical role of the secondary amines inside the cryptand, may be acting as Brönsted bases to deprotonate the complexed nitromethane. We then checked the role of each constituent of the catalytic system by performing blank experiments. Thus, $Cu(OAc)_2$ or ligand **2** or ligand **10** alone was not able to promote the Henry reaction. Hence, the occurrence of a background reaction promoted by remaining free copper(II) ions can be ruled out. In the same way, the native bis-(aminomethyl)pyridine moiety is not catalytically active either. This proves that the only active species is indeed the liganded copper center. Additionally, it should be noted that complexes prepared by mixing cage **2** with either two or three equivalents of copper salt were not effective in promoting the Henry reaction, suggesting that only the mononuclear complex is active.

In the following set of experiments, various nitro-containing substrates were engaged in the test reaction. Using open ligand **10**, the Henry reaction was performed separately with nitrobutane and phenylnitromethane[21] to give both nitroaldol products as mixtures of diastereomers (*syn*/*anti*), see Scheme 7. We then ran competition experiments in order to evaluate the different ligands toward a potential substrate-selectivity, see Table 1. 'Open' ligand **10** was used in order to determine the relative chemical reactivity of nitromethane/nitrobutane and nitromethane/phenylnitromethane mixtures.

From this, we conclude to the intrinsic superior reactivity of nitromethane over other nitro compounds. Nitrobutane seems to inhibit cage-catalyst **2** since its introduction stops any Henry reaction. We can hypothesize that nitronate derived from nitrobutane is strongly bounded within the cage but is unreactive toward the aldehyde. With nitromethane/phenylnitromethane mixtures



Scheme 6. Henry reaction.

Table 1
Competition experiments with nitro-compounds[a]

Ligand	$MeNO_2$/*n*$BuNO_2$	$MeNO_2$/$BnNO_2$
10	11/12:85/15 (95%,[b] 6 d)	11/13:80/20 (85%,[b] 5 d)
Cage **2**	nr[c]	11/13:100/0 (65%,[d] 14 d)

[a] Reactions and conditions: DCM/MeOH 9:1, $Cu(OAc)_2$ 10%, ligand 12%, $MeNO_2$/RNO_2/ArCHO, 40/40/1. Time in days for disappearance of the aldehydic proton in NMR. Product ratios according to proton NMR integrations.
[b] Based on mass-recovery after filtration over silica.
[c] No reaction after 15 days.
[d] Isolated yield.

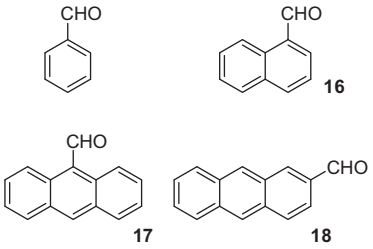


Figure 2. Various aldehydes tested in the Henry condensation.

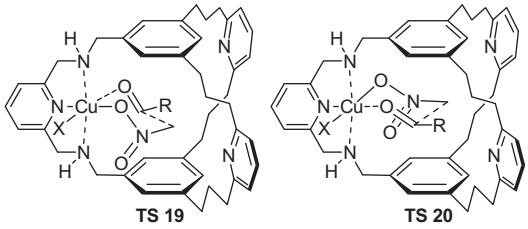


Figure 3. Two plausible transition states for the Henry reaction. (Substituents are omitted for clarity reasons, X = OAc).

cage-ligand **2** succeeds in discriminating the smaller nitroalkane since only nitroaldol **11** is observed in the crude reaction mixture.

Different aldehyde partners with contrasted steric hindrance around the carbonyl group were then tested as substrates. We first tested separately: benzaldehyde, 1-naphthaldehyde **16** and two aldehydes with much contrasted environments anthracene-9-carbaldehyde **17** and anthracene-2-carbaldehyde **18** following the disappearance of the aldehydic protons in NMR on aliquots, see Figure 2. The experiments were done employing either the open ligand **10** or cage **2**. We determined the time necessary to reach 50% and 90% conversion; the results are gathered in Table 2.

From this, we conclude that benzaldehyde and **16** behave in very similar ways with the complex of **10** or with the cage **2** complex, the latter showing no sign of discrimination between these substrates. In contrast, upon examination results with aldehydes **17** and **18** with very dissimilar environment we can observe a partial discrimination exerted by the cage ligand. Interestingly, with the open ligand **10** the more encumbered aldehyde **17** is still the most reactive, this can be explained by a more electrophilic 9-aldehyde function compared to the 2-substituted isomer **18**. Then switching to cage catalyst the observed reactivity is reversed. Henry reaction is faster with the less hindered isomer **18** than with **17**. Thus, these two substrates are partially discriminated by the encapsulated catalytic center, although reaction rates are only moderately differentiated. In fact, if we examine the plausible mechanism[22] of this Henry reaction in the cage cavity, one is to wonder if reactants are truly entering the empty space of cage **2**. As reported by Anslyn with an open-ligand complexing copper(II) triflate, X-ray diffraction analysis shows that metallic center is adopting a pseudo-octahedral geometry. We can thus infer that Henry reaction transition state with this catalyst also possesses a copper ion with a nearly octahedral environment, see Figure 3. With this hypothesis three arrangements are possible according to the respective placement of the three oxygenated ligands: nitronate, aldehyde, and acetate counterion. If the acetate is coordinating in the plan defined by the three nitrogen atoms, nitronate, and aldehyde partners are in *trans* disposition and cannot thus react. There is only two reactive coordination isomers; either the nitronate is in the trisamine plan and thus inside the cavity, the aldehyde occupying the *cis*-position 'at the door' of the cavity, see TS **19**. Alternatively, it is the aldehyde coordinated inside and the nitronate that occupies the lateral position, just at the entrance of the cavity, see TS **20**.

Table 2
Time for conversion of various aldehydes

Aldehyde	50% Conv	90% Conv
PhCHO	6 h with **10**	18 h with **10**
	24 h with **2**	72 h with **2**
1-Naph-CHO **16**	8 h with **10**	24 h with **10**
	26 h with **2**	72 h with **2**
9-Anthr-CHO **17**	6 h with **10**	24 h with **10**
	72 h with **2**	360 h with **2**
2-Anthr-CHO **18**	9 h with **10**	30 h with **10**
	48 h with **2**	168 h with **2**

In any cases, one of the reactant is not formally captured within the cavity in order to reach the reactive center and is not in fact fully subjected to the cage discriminating features. Therefore, in order to insure more efficient substrate selection, larger cavities are desirable mimicking an enzymatic pocket that could accommodate both reactants and let them interact with an inwardly directed active functionality playing the role of an active site.

We prepared in good yields hexa-amine cage compound **2**, using a reversible imine-condensation strategy with readily prepared building blocks. This architecture displays three electron-rich tris-dentate moieties able to coordinate a copper(II) ion center which then shows catalytic activity in Henry reactions between nitro alkanes and aldehydes. Premises of substrate selectivity were observed by partial discrimination of small substrates. Relevant selectivities are probably hampered by intrinsic inability of cage **2** to encapsulate both reacting partners. We are currently preparing larger cage-compounds with more spacious cavities that would hopefully accommodate a truly incarcerated bimolecular reaction triggered by an inwardly directed functional group.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.11.078.

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