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Toward reactant encapsulation for substrate-selectivity

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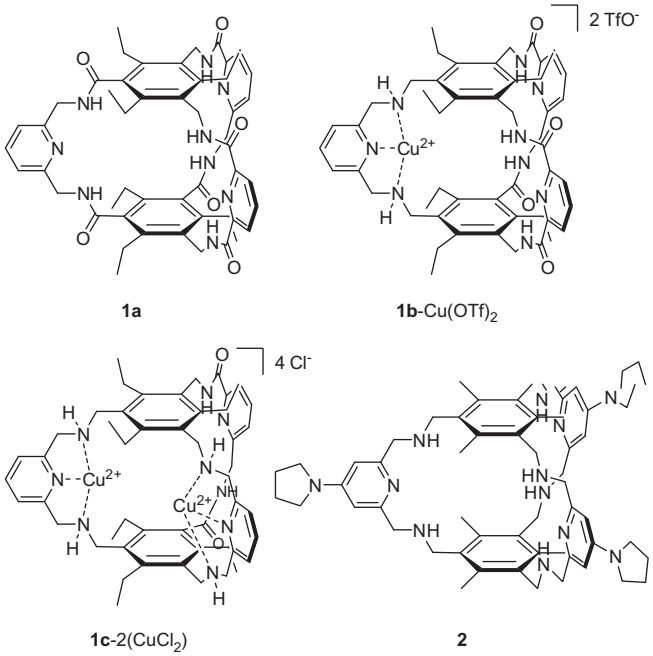
ABSTRACT

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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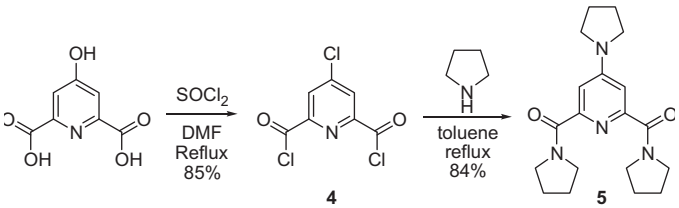
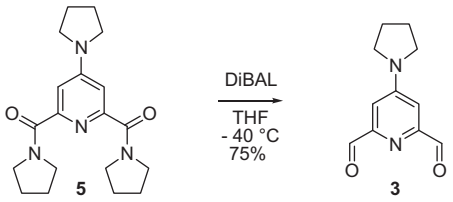


Scheme 1. Preparation of diamide **5**.



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

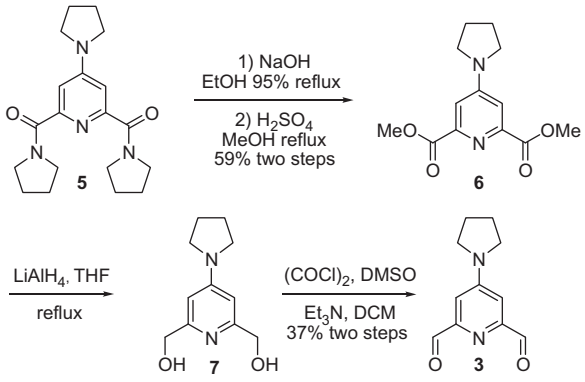
and this work aims to explore such possibility. However, a simple synthetic access to similar aza-cryptands is first needed since non C_3-symmetrical **1b**,**c** require multistep sequences for their preparation. Therefore, we took the advantage of the recently described efficient preparations of C_3-symmetrical 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