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Methods for Preparing Metal Ion Photocages: Application to the Synthesis of CrownCast

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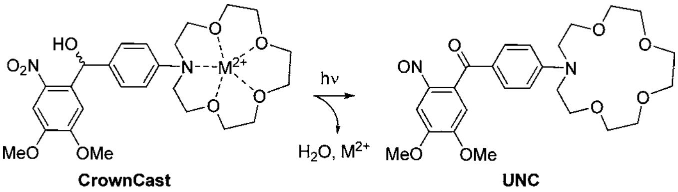
ABSTRACT



Three different synthetic strategies were utilized in the construction of a novel class of macrocyclic containing *o*-nitrobenzhydrol group II cation cages. The synthetic methodology presented herein is unparalleled in scope toward the preparation of caged complexes for various main group and transition block cations.

Caged molecules have been used to study the cellular signaling pathways of different molecular or ionic species.[1] In caged molecules, the biological activity of the analyte is masked by a photochemically labile bond.[2] Upon irradiation, the caged molecule or metal ion is released. Only a few cages for divalent metal ions including Ca,[3−5] Mg,[6] and Cu[7] have been reported to date.

To facilitate the development of caged metal complexes, we have developed two new synthetic approaches for accessing nitrobenzhydrol derived cages. We have demonstrated the utility of each method by preparing CrownCast, a cage that utilizes a macrocyclic NO_4 ligand as the cation receptor. The name CrownCast is derived from the *crown* ether receptor and the ability of the compound to *cast* off a bound cation after photolysis. Upon irradiation, CrownCast undergoes a Norrish-type II photochemical reaction to afford the corresponding nitrosobenzophenone.[8] The resulting photoproduct possesses a reduced binding affinity for the cation because of delocalization of the anilino lone pair onto the benzophenone carbonyl oxygen atom.

Initially, the CrownCast analogue **3** was prepared by the strategy that was utilized by Tsien et al. in the construction of Ca cages (Scheme 1, Method A).[3] The macrocycle *N*-phenyl-1-aza-15-crown-5 (**1**) was prepared as reported[9] and reacted with trimethylsilyl triflate (TMSOTf) and **2** affording the desired benzhydrol as the trimethylsilyl (TMS) ether. The TMS ether was subsequently reacted in situ with tetrabutylammonium fluoride (TBAF) to afford **3** in 33% yield. Since the isolated yields of the desired compound **3** was poor and TMSOTf has potential incompatibility with other functional groups, alternative methods for the construction of CrownCast ligands were explored to facilitate future syntheses.

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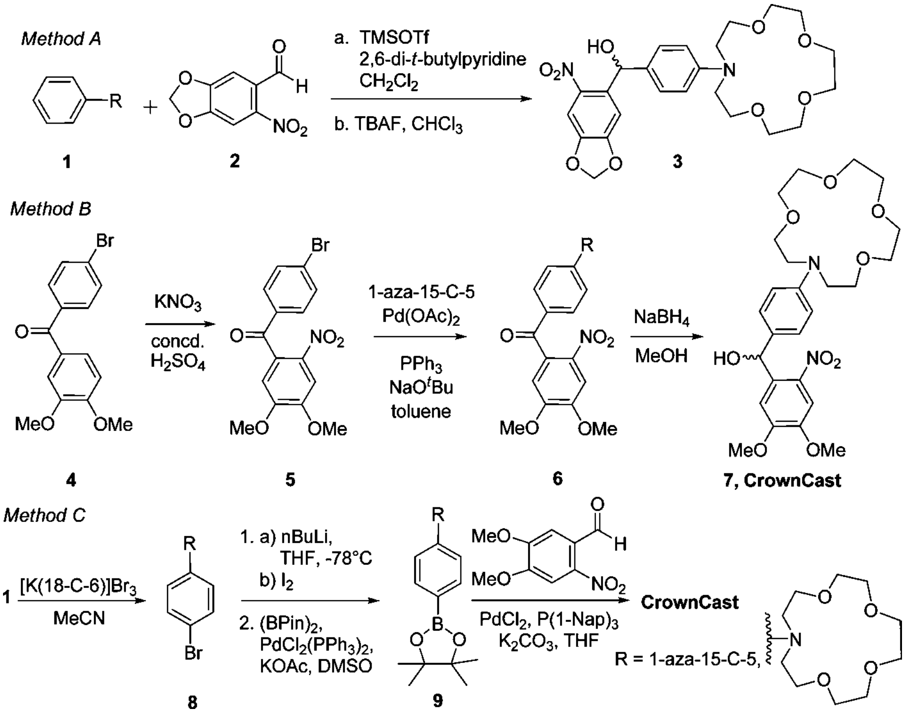
Scheme 1. Synthesis of CrownCast



In the first alternative route, a Pd-catalyzed cross coupling between **5** and 1-aza-15-crown-5 was utilized to assemble the aryl macrocycle (Scheme 1, method B). Compound **4**, which was prepared by reported methods,[10] underwent a regioselective nitration to afford **5** in 61% yield. The macrocycle 1-aza-15-crown-5 was incorporated utilizing a Buchwald−Hartwig coupling using catalytic $Pd(OAc)_2$ and triphenylphosphine (PPh_3).[11,12] The resulting benzophenone **6** was reduced with $NaBH_4$ to afford CrownCast (**7**) in 12% yield. Alternative methods for the reduction of compound **6** to CrownCast resulted in the formation of several byproducts as evidenced by TLC analysis. While borohydride reduction is not ideal for CrownCast, we have successfully applied this method to other targets.

The highest isolated yields of CrownCast were obtained using method C (Scheme 1). Macrocycle **1** was brominated with the unique reagent $\{[K(18\text{-crown-6})]Br_3\}_n$,[13] which afforded **8** in nearly quantitative yield. Compound **8** was converted into the corresponding aryl iodide, which is a better substrate in the subsequent palladium-mediated borylation chemistry.[14] Palladium-catalyzed borylation with bis(pinacolato)diboron provided **9** in 72% yield. The subsequent palladium-catalyzed reaction between **9** and 6-nitroveratraldehyde afforded CrownCast in 71% yield. Rigorous exclusion of O_2 and H_2O from the reaction mixture was not necessary. Generally, palladium-catalyzed 1,2-additions of arylboronic acids into aldehydes results in poor isolated yields;[15] however, tris(1-naphthyl)phosphine ($P(1\text{-NAP})_3$) facilitates the $PdCl_2$-catalyzed 1,2-addition of phenylboronic acid to aldehyde substrates.[16] Although the original report focused on boronic acids as the reactive substrates, the reaction proceeds cleanly with the borate ester. This appears to be the first example where a pinacolato borate is used as the substrate instead of the boronic acid, which is noteworthy since the steric bulk of the reactive components does not inhibit the formation of the desired product. This step not only eliminates the pinacolato borate cleavage step that requires harsh conditions[17] but also provides a reagent that is easier to handle and purify than boronic acids.

The 1:1 binding of CrownCast to several alkaline earth metals Zn^{2+} and Cd^{2+} was evaluated in MeCN using absorbance spectroscopy.[18,19] Upon metal binding, the intensity of the charge-transfer transition of apo-CrownCast

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Table 1. Binding Properties of CrownCast and UNC in MeCN[a]

cation	ionic radius (Å)	K_d' CrownCast/μM	$\Delta\lambda_{max}$ CrownCast (nm)	K_d' UNC/mM	$\Delta\lambda_{max}$ UNC (nm)	$\Delta\log K_f'$
Mg^{2+}	0.86	64 ± 7	−40	13.1 ± 0.7	−75	−2.35
Ca^{2+}	1.14	14 ± 2	−32	0.6 ± 0.1	−61	−1.64
Sr^{2+}	1.32	48 ± 1	−28	2.2 ± 0.2	−56	−1.66
Ba^{2+}	1.49	79 ± 3	−25	3.1 ± 0.1	−50	−1.60
Zn^{2+}	0.88	161 ± 8	−42	NA[b]		
Cd^{2+}	1.09	68 ± 1	−42	NA[b]		

[a] Binding assays were carried out between the respective metal perchlorate and CrownCast (25 μM) or UNC (20 μM) in MeCN. [b] Minimal changes were observed in the absorbance spectra (<5% at 347 nm) when UNC was saturated with >5000 equivs of Zn^{2+} or Cd^{2+}. The $\Delta\log K_f'$ value represents the change in binding affinity in going from CrownCast to UNC.

that occurs at 269 nm was attenuated with the concomitant development of a blue-shifted band at ~220−245 nm (Table 1, Figure 1). CrownCast has a slight binding preference for Ca^{2+} over the other divalent cations tested, which is consistent with log K_f' values measured for other 15-crown-5 derivatives.[20] The strength of the binding of each metal ion appears to be determined by a combination of three factors: the strength of the aniline−metal bond, the fit between the macrocyclic cavity and the cation, and hard−soft acid−base (HSAB) interactions.

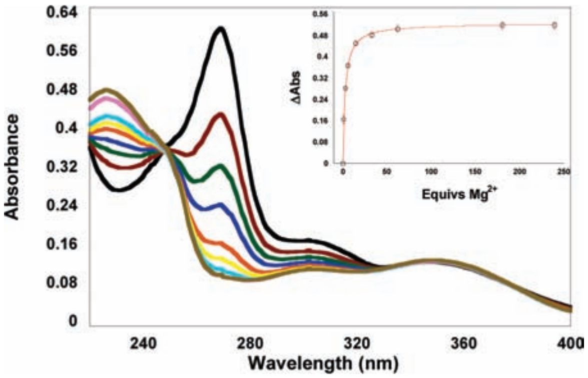
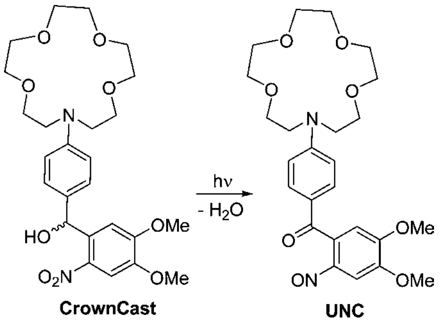


Figure 1. Titration of 25 μM CrownCast with $Mg(ClO_4)_2$ in MeCN. The inset describes the 1:1 binding isotherm with error bars calculated from three trials.

The strength of the resulting N−M bond is proportional to the energy of the blue-shifted CT band that occurs upon metal binding. Mg^{2+}, Zn^{2+}, and Cd^{2+} cause the greatest shifting in the CT band (Table 1). Since Zn^{2+} and Cd^{2+} are moderate Lewis acids, interactions with the borderline aniline base is predicted to be stronger than with alkali earth metals. Despite being a hard Lewis acid, Mg^{2+} induces a large blue shift in the CT transition, which suggests that electrostatic interactions factor into its binding. The ionic potential of Mg^{2+} is the highest of the alkaline earth metals tested since the charge to radius ratio (q/r) decreases down the group in the periodic table. In addition to HSAB factors, metal ion binding with CrownCast becomes weaker as the size of the cation increases. Poor size match between the macrocycle and Mg^{2+} likely accounts for the slight destabilization of the metal complex as compared to Ca^{2+}. Overall, the weakest binding was observed with Zn^{2+}, where a combination of poor size match and employment of nonideal oxygen donors likely accounts for the weaker binding.

After 4 h of irradiation with a high intensity source (1000 W Xe lamp), the photoproduct UNC was produced on a preparative scale (Scheme 2). The binding constants of UNC were determined without interference from CrownCast. The trend in binding selectivity was maintained, but the overall strength of cation binding was attenuated ~40−200 times. The largest changes in log K_f' were seen for Mg^{2+}, Zn^{2+}, and Cd^{2+}, where conjugation of the aniline lone pair into the resulting benzophenone fragment substantially weakens the N−M interaction in the metal complex. The binding of UNC to Zn^{2+} and Cd^{2+} is too weak to accurately determine the K_d'.

Scheme 2. Uncaging of Apo-CrownCast



The quantum yield of photolysis was measured by photolyzing MeCN solutions of CrownCast and its Ca^{2+} and Zn^{2+} complexes at 350 nm with a 150 W source (Figure 2, Table 2). The measured quantum yields (ca. 1%) were in accord with literature values for other nitrobenzhydrol Ca^{2+} cages.[5] A slight increase in the quantum yield was observed for the Ca^{2+} and Zn^{2+} complexes, likewise in agreement with literature reports of the Ca^{2+} cage Nitr-5.[3] Photolysis was carried out using concentrations of M^{2+} where binding to the photoproduct UNC was known from the titration data to be negligible. This allowed for direct spectrophotometric measurements of UNC concentrations over the course of the photolysis.

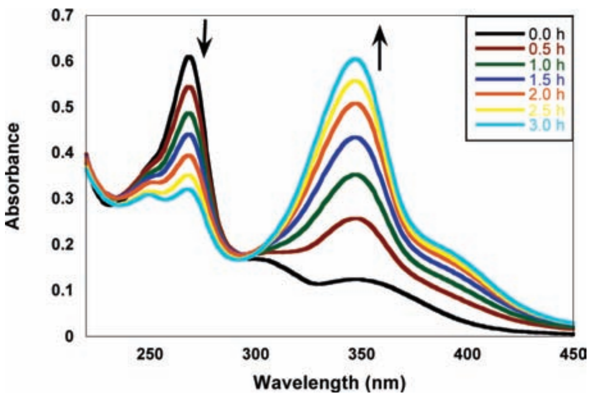


Figure 2. Photolysis of 25 μM CrownCast in MeCN at 350 nm using 150 W source.

In conclusion, we have demonstrated a modular approach toward the construction of nitrobenzhydrol derived cages that utilize a NO_4 macrocyclic receptor. In particular, the Pd coupling between the pinacolato borate and a nitroaldehyde provided CrownCast in yields that were in excess of twice the traditional TMSOTf methods. We also have developed a third route based on Pd-catalyzed aryl amination. Although CrownCast does not interact strongly with metal ions in aqueous solution, our new synthetic methodology provides a roadmap for the future construction of metal ion photocages that will be employed in biological studies. In addition to preparative strategy, the observed trends in metal ion affinity between the caged and uncaged forms of CrownCast will facilitate the selection and rational design of appropriate ligands for caging specific metal analytes.

Table 2. Photophysical Data for Ligands and Complexes[a]

species	λ_{max}/nm (ε cm^{-1} M^{-1})	$\Phi_{photolysis}$
CrownCast	269 (26300), 347 (5300)	0.005 ± 0.002
UNC	347 (46000)	
$[Ca(CrownCast)]^{2+}$	244 (17100), 347 (5300)	0.007 ± 0.002
$[Zn(CrownCast)]^{2+}$	245 (14500), 347 (5300)	0.016 ± 0.006

[a] CrownCast (25 μM) was photolyzed in MeCN with a 150 W Xe source at 350 nm as the apo-cage and in the presence of $Ca(ClO_4)_2$ (125 μM, 5.0 equiv) and $Zn(ClO_4)_2$ (1.25 mM, 50 equiv), where CrownCast was saturated but binding to UNC is negligible.

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Supporting Information Available: Detailed synthetic procedures and ^{1}H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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