JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

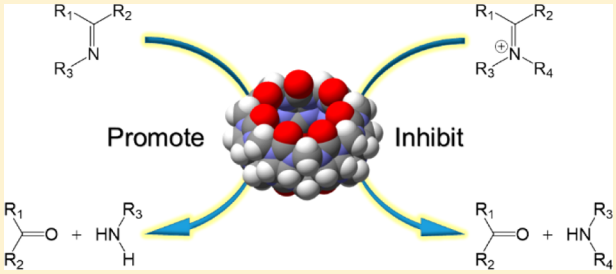
Inhibition and Stabilization: Cucurbituril Induced Distinct Effects on the Schiff Base Reaction

Wanjun Gong, Jun Ma, Zhiyong Zhao, Fang Gao, Feng Liang, Haijun Zhang, and Simin Liu*

The State Key Laboratory of Refractories and Metallurgy, School of Chemistry and Chemical Engineering, Wuhan University of Science and Technology, Wuhan 430081, China

Supporting Information

ABSTRACT: The different effects of cucurbit[7]uril (CB[7]) on the Schiff base reactions in aqueous solution were explored by ^{1}H NMR spectroscopy and single X-ray crystallography. With CB[7], the condensation reaction of aldehyde and primary amine is dramatically inhibited. In contrast, the presence of CB[7] does tremendously stabilize iminium cation in water through ion−dipole interactions. A single crystal structure of the complex of iminium ion 7 with CB[7] grown in water is reported.



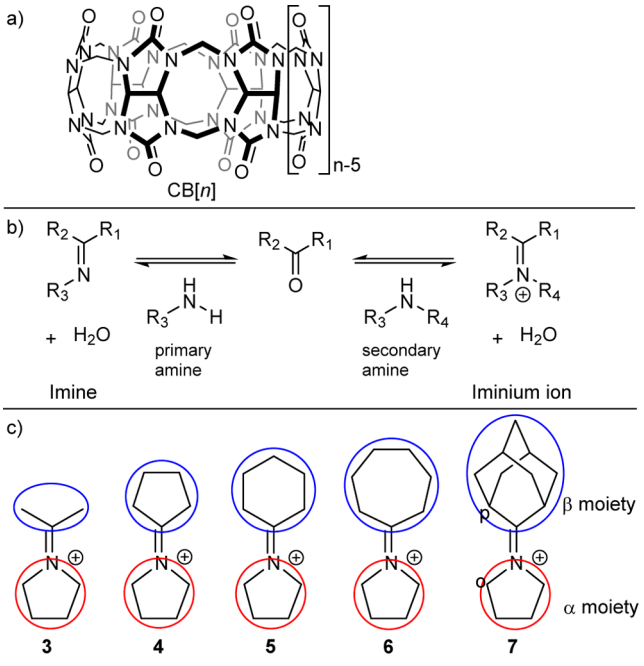
Developing novel, cleaner, more efficient, and selective reactions is always at the heart of synthetic chemistry. To this end, there has been a recent explosion of interest in the use of microenvironments to simulate the catalytic prowess of enzymes.[1−3] Appearing in the late 1990s, nanoreactors (NRs) have attracted considerable attention because of their ability to control reaction processes. Moreover, within supramolecular chemistry, numerous successes in this area have been achieved using different kinds of hosts. For example, self-assemblies such as cages and "soft ball" have been found to catalyze organic reactions.[4−7] In addition, other cyclic hosts such as crown ethers, cyclodextrins, and calixarenes have also been used in different kinds of reactions.[8−10]

Among the macrocyclic hosts, cucurbit[*n*]uril [CB[*n*], where *n* = 5−8 or 10 (Scheme 1a)] possesses a hydrophobic cavity and two identically open portals with 2*n* carbonyl oxygens. These structural features lead to outstanding molecular recognition properties with respect to cationic and neutral guests.[11−13] CB[*n*] have shown exquisite ability as nanoreactors, as catalysts, and in the stabilization of highly reactive species.[14−17] Several groups have focused on the use of CB[*n*] as a protective agent in different reactions.[18,19]

The Schiff base reaction (Scheme 1b), discovered by German chemist Hugo Schiff,[20] is a well-known and widely utilized reaction in numerous domains.[21−23] Furthermore, imines are also important enzymatic intermediates *in vivo* such as the reaction of a common enzyme cofactor PLP and a lysine residue.[24] In this work, we investigate the effects of CB[*n*] on the reversible Schiff base reaction and the stability of iminium cations using ^{1}H NMR spectroscopy and single X-ray crystallography.

The condensation reaction of benzaldehyde (**1**) and benzylamine (**2**) with or without CB[7] was first explored by ^{1}H NMR. In the absence of CB[7], a new peak at ∼8.4 ppm corresponding to the imine product emerged after the addition

Scheme 1. Structure of CB[*n*] (a), Schiff Base Reaction (b), and Structure of Iminium Cation Compounds (c)



of **1** to the solution of **2**, indicating the occurrence of the reaction (Figure 1a,b). Within 20 min, the imine content increased to 35% (Figure 1c). Separately, when CB[7] was added to the solution of **2**, the signals for the aromatic protons of **2** underwent significant upfield shifts ($\Delta\delta$ = 0.5−0.7 ppm), whereas those from the methylene signal underwent a less

Received: January 3, 2017
Published: February 23, 2017

DOI: 10.1021/acs.joc.6b02971
J. Org. Chem. 2017, 82, 3298−3301

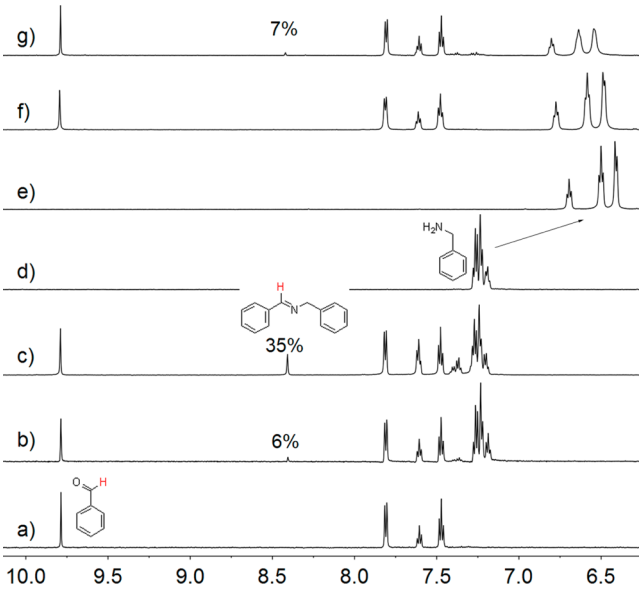
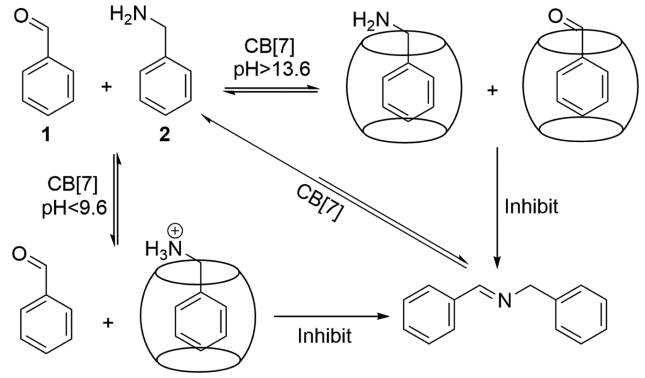


Figure 1. Partial ^{1}H NMR spectra (600 MHz, D_2O) of (a) **1** (2.0 mM), (b) 5 min after the addition of **1** (2.0 mM) to **2** (2.0 mM), (c) 20 min after the addition of **1** (2.0 mM) to **2** (2.0 mM), (d) **2** (2.0 mM), (e) a 1:1.1 mixture of **2** (2.0 mM) and CB[7], (f) 1 day after the addition of **1** (2.0 mM) to a 1:1.1 mixture of **2** (2.0 mM) and CB[7] (pD 9.6), and (g) 1 h after the addition of **1** (2.0 mM) to a 1:1.1 mixture of **2** (2.0 mM) and CB[7] at pD 11.5.

significant upfield shift ($\Delta\delta$ = 0.15 ppm) (Figure 1d,e). These shifts are suggestive of the encapsulation of **2** within CB[7] (fast exchange on the ^{1}H NMR time scale). After addition of **1** to the solution of this complex, the signals of **2** shifted slightly downfield because of the weak competitive binding of **1** (pD 9.6) (K_a values for both **1** and **2** with CB[7] can be found in Table S1). Importantly, no peak at ∼8.4 ppm was observed even after the mixture was left for 1 day, indicating the reaction between **1** and **2** is fully inhibited by the presence of CB[7] at pD 9.6 (Figure 1f). To obtain a comprehensive understanding of the role of CB[7], the reaction was performed at different pD values. Although a small peak at ∼8.4 ppm emerged after 1 h at pD 11.5, the content of imine (7%, according to eq 1) did not increase even after 1 day (Figure 1g). When a strong basic solution (pD 13.6) was used, all signals of protons on both **1** and **2** shifted upfield as a consequence of the encapsulation of two substrates within CB[7] (Figure S1 and Table S1). Despite the relatively larger peaks (11%) reflecting more substrates being converted to imine, the percentage of imine is still smaller than the percentage of those without CB[7] (47%) (Figures S1 and S2). Although CB[7] can bind the guests under both weaker and stronger basic conditions, obviously it prefers to bind the protonated amine **2**, which is why more imine formed with the increase in pD in the presence of CB[7].

Because protonation of **2** is unfavorable to reaction, we sought to probe this inhibition by determining the pK_a values of **2** in the absence and presence of CB[7] (UV/vis titration). As excepted, encapsulation within CB[n] led to an increase in the pK_a of the amino guest,[25] a shift in the pK_a of **2** from 9.7 to 12.1 (Figure S3). The mechanism of inhibition is therefore quite clear. Under a relatively weaker basic condition (pD 9.6), the reaction of free **2** proceeds because it is only partially protonated. However, in the presence of CB[7], the amino group of **2** is almost fully protonated because of the increase in its pK_a. Hence, **2** cannot act as a nucleophile and attack the

Scheme 2. Plausible Mechanism of the CB[7]-Mediated Schiff Base Reaction



carbonyl carbon atom of **1**, so that the reaction is fully inhibited (Scheme 2). In contrast, under strongly basic conditions (pD 13.6), both neutral **1** and **2** competitively bind with CB[7], which reduces the chance of their encounter because of the encapsulation inside CB[7]. Moreover, the electronegative oxygen on the carbonyl groups of CB[7] could stabilize the electropositive carbon on the aldehyde group of **1** by electrostatic interactions and thereby reduce the reactivity of substrate **1** (Scheme 2).[26]

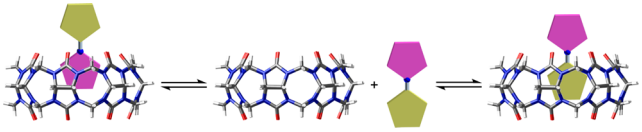
To gather more information about the influence of CB[7] on the reaction, the hydrolysis of imine at various pD values was also explored. We found that in the absence of CB[7] the percentages of imine at pD 13.6, 12.5, and 11.5 were 47, 43, and 36%, respectively, whereas in the presence of CB[7], the values were 22, 16, and 9%, respectively (compare panels a and b of Figure S4, panels c and d of Figure S4, and panels e and f of Figure S4). Apparently, the presence of CB[7] promoted the hydrolysis of imine at all pD values examined. Along with the previous inhibition effect, this promotion of hydrolysis could be attributed to the higher binding affinity between CB[7] and hydrolysis products **1** and **2**.

The inhibition of the Schiff base reaction by CB[7] led us to speculate about reactions involving secondary amine that form iminium cations.[27−30] The Raymond group has developed a route to generate and stabilize these species in aqueous solution by trapping the product in an assembled cage host,[31] which suggested that CB[n] could play the same role because of its high binding affinity for organic cations. Unfortunately, we did not observe that CB[7] can generate these species in aqueous solution. However, CB[7] does promote the stabilization of iminium cations. Several iminium cations of different sizes and shapes were synthesized by the condensation of ketones and secondary amine (Scheme 1c).[32]

The binding of iminium cations with CB[7] was investigated by ^{1}H NMR (Figures 2 and S5−S8), and the complexation-induced chemical shift changes (CIS; $\Delta\delta = \delta_{bound} - \delta_{free}$) exhibited by guest protons were calculated to understand the binding behavior.[12,15,33] CIS values (Table S2) reveal that all iminium cation compounds can be encapsulated within the cavity of CB[7]. Because the positively charged nitrogen is located in the middle of the guest, the α and β moieties (Scheme 1c) on the guest could conceivably bind to CB[7]. According to the CIS values, it is evident that for iminium cation **4**, both similarly sized moieties have equal affinity for the binding site of CB[7]. A binding model of iminium cation **4** within CB[7] is shown in Scheme 3. This model explains why

DOI: 10.1021/acs.joc.6b02971
J. Org. Chem. 2017, 82, 3298−3301

Scheme 3. Kinetic Binding Model of Iminium Cation 4 with CB[7]



the signals for all protons on both five-membered rings of **4** underwent significant upfield shifts.[34] To explain the CIS data for all guests, the packing coefficient (PC)[35] of each moiety (Table S3) was calculated. For example, for iminium cation **3**, the CIS and PC values for protons on the α moiety are much larger than those on the β moiety. Correspondingly, for those having β moieties with larger PC values, their CIS values on the β moiety are obviously larger than those on the α moiety, especially for **7**, which has a β moiety with a nearly perfect PC value (52.68).[35]

The binding ^{1}H NMR of iminium cation **7** with CB[7] is shown in Figure 2. Like those of the other iminium cations, hydrolysis of **7** can be observed in a few minutes by ^{1}H NMR (Figure 2a). According to the split of the NMR signals on CB[7] in Figure 2c, the 1:1 CB[7]·**7** inclusion complex exhibits slow exchange on the ^{1}H NMR time scale.

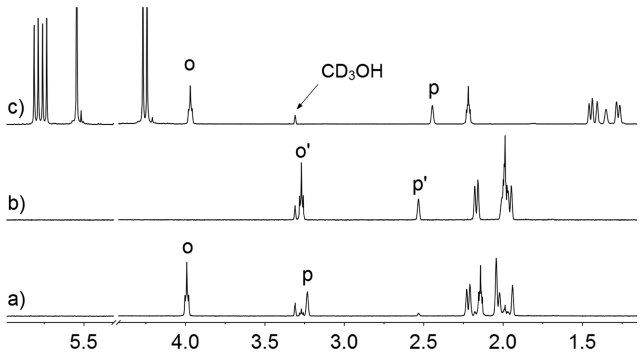


Figure 2. Partial ^{1}H NMR spectra (600 MHz, D_2O) of (a) **7** (1.0 mM) (partially hydrolyzed), (b) fully hydrolyzed **7** (1.0 mM), and (c) CB[7]·**7** (1.0 mM) for 1 day.

Given the encapsulation of iminium cations inside CB[7], we then focus on the stabilization of these high-activity species upon encapsulation. The hydrolysis of **3**–**7** was monitored by ^{1}H NMR spectroscopy in deuterium oxide. All ^{1}H NMR spectra demonstrate that without CB[7], iminium cations hydrolyzed quickly to their corresponding ketone and amine (Figures 2a,b and S5–S8). However, in the presence of CB[7], either no peaks correlating to ketone and amine could be observed or only very small peaks that did not change over time were evident. Apparently, in some cases, hydrolysis was observed before the iminium cation was encapsulated by CB[7]. The lifetimes of **3**–**7** were calculated by NMR signal integration (Figure S9, according to eq 2). In all cases with CB[7], there was no evidence of hydrolysis after 1 day, and for the CB[7]·**7** complex, no obvious hydrolysis was observed even after 2 weeks.

The single crystal of CB[7]·**7** was successfully obtained by adding a small amount of KI to the aqueous solution of the host and guest. This provided direct evidence of the encapsulation and stabilization of iminium ion **7** (Figure 3).[36] The nature of the bound guest was confirmed by (1) the short N=C bond

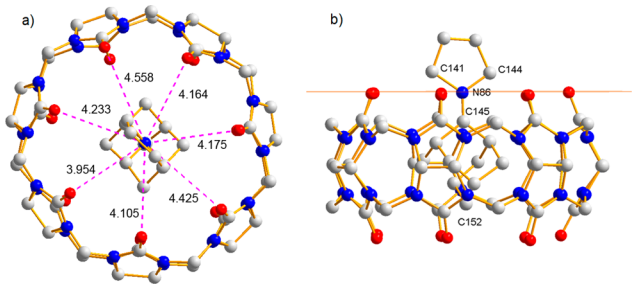


Figure 3. Representation of the X-ray crystal structures of the CB[7]·**7** inclusion complex: (a) top view and (b) side view.

length (1.298 Å for N_{86}=C_{145} vs 1.506 and 1.540 Å for N_{86}–C_{141} and N_{86}–C_{144}, respectively) and (2) the planar array of the four atoms covalently linked to N_{86} and C_{145}. Also apparent from the structure was the fact that all seven oxygens on one ureidyl carbonyl portal of CB[7] are involved in forming C=O···N^+ ion–dipole interactions with the positively charged nitrogen atom on guest **7**. The average distance from oxygen on the ureidyl carbonyl portal to nitrogen on guest **7** was ~4.23(7) Å, which is slightly shorter than the distance of ~4.38(7) Å found in a complex of CB[7] with an attomolar dissociation constant reported by Isaacs.[37] Furthermore, the positively charged nitrogen atom is exactly located on the plane composed of seven oxygens on the portal of CB[7], which maximizes the ion–dipole interactions between CB[7] and the guest. Further inspection reveals that the average distance from oxygen on the ureidyl carbonyl portal to C_{145} (carbon at position 2 in 2-adamantanone) on guest **7** [~4.39(7) Å] is very close to that from C_{152} (carbon at position 6 in 2-adamantanone) to the adjacent oxygens on CB[7] [~4.43(7) Å] (Figure S10). The results imply in this case that the 2-adamantyl "perfectly" fits in the cavity of CB[7].

The binding and stabilization of iminium cations were further extended to smaller CB[6] (Figures S11–S16). To our surprise, although CB[6] has the capacity to hold an aromatic group, no obvious chemical shift changes from the protons of the iminium cations could be observed from the ^{1}H NMR spectra. Nevertheless, by monitoring the progress of the hydrolysis of iminium cations, we found that even though it is inferior to CB[7], CB[6] indeed provided protection to iminium ions from hydrolysis in aqueous solution. We assume that once they are mixed, iminium cations stay at the portals of CB[6] because of the strong ion–dipole interactions, which slows the hydrolysis.

In summary, we have demonstrated that CB[7] can play an important role in Schiff base reactions, inhibiting the condensation reaction of the aldehyde and primary amine. Although CB[7] could not help to generate the iminium cation under aqueous conditions, it does stabilize them by host–guest interaction. Also, for the first time, we report on the crystal structure of an encapsulated iminium ion grown in water. This preliminary finding further points out that CB[*n*] compounds can control the reaction process, via either an obverse effect or a reverse effect. Stabilization of highly unstable iminium ions in water with CB[*n*] could lead to a new way to switch some reactions involving highly active intermediates from the organic condition to the aqueous condition.

EXPERIMENTAL SECTION

General Information. CB[6] and CB[7] were synthesized and separated using procedures found in the literature.[38] Other

DOI: 10.1021/acs.joc.6b02971
J. Org. Chem. 2017, 82, 3298–3301

compounds used in this study were purchased from commercial suppliers and were used without further purification. ^{1}H NMR spectra were recorded on Agilent 600 MHz DD2 spectrometers, and chemical shifts were recorded in parts per million. UV/vis measurement was performed on a SHIMADZU UV-3600 instrument with 1 cm path length cells at 298 K. The X-ray intensity data were measured on a Bruker APEX-II CCD system (collection temperature of 203 K).

General Procedure for Iminium Cation Compound Synthesis. All the iminium cations (as perchlorate salt) were prepared using a method described in the literature.[32] To a solution of ketone (10 mmol) and pyrrolidine (10 mmol) in toluene (25 mL) was added ammonium perchlorate (10 mmol). The solution was heated to reflux while the water being formed was continuously removed. After being cooled in an ice−water bath, the precipitated product was collected by filtration, washed with ether (3 × 10 mL), and dried under vacuum.

Hydrolysis of Imine. 1 (2.0 mM) and **2** (2.0 mM) were mixed in a D_2O/NaOD solvent (pD >13.6) and left overnight. Then the solution was divided into two parts, and to one was added 1.1 equiv of CB[7]. To the solutions described above was added DCl to adjust the pD, and all samples were monitored by ^{1}H NMR until there was no any change in the ^{1}H NMR spectra.

Calculation of the Lifetime of Iminium Cations. Because of the high reactivity of iminium cations to H_2O, the concentrated solution of iminium cations was prepared in CD_3OH. However, upon addition of cations to the aqueous solution of CB[7], quick hydrolysis of the iminium cation was observed before it was stabilized by the encapsulation inside CB[7]. To simplify the calculation, the first percentage for the complex is set to 100% and the subsequent values are calculated on the basis of this value.

$$\text{imine\%} = \frac{[\text{imine}]}{[\text{imine}] + [\text{aldehyde}]} \quad (1)$$

$$\text{iminium cation\%} = \frac{[\text{iminium caiton}]}{[\text{iminium caiton}] + [\text{amine}]} \quad (2)$$

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02971.

Experimental and characterization details and additional figures (PDF)

Crystallographic data for the CB[7]·7 complex (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: liusimin@wust.edu.cn.

ORCID

Wanjun Gong: 0000-0002-3099-032X

Simin Liu: 0000-0002-8696-4833

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was financially supported by the National Natural Science Foundation of China (21472143 and 21604066), the Thousand Youth Talents Program of China (D1118031), and the Program for Innovative Teams of Outstanding Young and Middle-aged Researchers in the Higher Education Institutions of Hubei Province (T201602).

■ REFERENCES

(1) Cram, D. J.; Cram, J. M. In *Container molecules and their guests*; Stoddart, J. F., Ed.; The Royal Society of Chemistry: Cambridge, U.K., 1997.

(2) Garcia, H.; Ferrer, B. Photocatalysis by MOFs. In *Metal Organic Frameworks as Heterogeneous Catalysts*; The Royal Society of Chemistry: Cambridge, U.K., 2013; Chapter 12, pp 365−383.

(3) Zarra, S.; Wood, D. M.; Roberts, D. A.; Nitschke, J. R. *Chem. Soc. Rev.* **2015**, *44*, 419−432.

(4) Yoshizawa, M.; Klosterman, J. K.; Fujita, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 3418−3438.

(5) Conn, M. M.; Rebek, J., Jr. *Chem. Rev.* **1997**, *97*, 1647−1668.

(6) Brown, C. J.; Toste, F. D.; Bergman, R. G.; Raymond, K. N. *Chem. Rev.* **2015**, *115*, 3012−3035.

(7) Kaphan, D. M.; Levin, M. D.; Bergman, R. G.; Raymond, K. N.; Toste, F. D. *Science* **2015**, *350*, 1235−1238.

(8) Shirakawa, S.; Maruoka, K. *Angew. Chem., Int. Ed.* **2013**, *52*, 4312−4348.

(9) Breslow, R.; Dong, S. D. *Chem. Rev.* **1998**, *98*, 1997−2011.

(10) Homden, D. M.; Redshaw, C. *Chem. Rev.* **2008**, *108*, 5086−5130.

(11) Lagona, J.; Mukhopadhyay, P.; Chakrabarti, S.; Isaacs, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 4844−4870.

(12) Masson, E.; Ling, X.; Joseph, R.; Kyeremeh-Mensah, L.; Lu, X. *RSC Adv.* **2012**, *2*, 1213−1247.

(13) Barrow, S. J.; Kasera, S.; Rowland, M. J.; del Barrio, J.; Scherman, O. A. *Chem. Rev.* **2015**, *115*, 12320−12406.

(14) Pemberton, B. C.; Raghunathan, R.; Volla, S.; Sivaguru, J. *Chem. - Eur. J.* **2012**, *18*, 12178−12190.

(15) Assaf, K. I.; Nau, W. M. *Chem. Soc. Rev.* **2015**, *44*, 394−418.

(16) Zheng, L.; Sonzini, S.; Ambarwati, M.; Rosta, E.; Scherman, O. A.; Herrmann, A. *Angew. Chem., Int. Ed.* **2015**, *54*, 13007−13011.

(17) Jiao, Y.; Li, W.-L.; Xu, J.-F.; Wang, G.; Li, J.; Wang, Z.; Zhang, X. *Angew. Chem., Int. Ed.* **2016**, *55*, 8933−8937.

(18) Ren, H.; Huang, Z.; Yang, H.; Xu, H.; Zhang, X. *ChemPhysChem* **2015**, *16*, 523−527.

(19) Berbeci, L. S.; Wang, W.; Kaifer, A. E. *Org. Lett.* **2008**, *10*, 3721−3724.

(20) Schiff, H. *Justus Liebigs Ann. Chem.* **1864**, *131*, 118−119.

(21) Das, P.; Linert, W. *Coord. Chem. Rev.* **2016**, *311*, 1−23.

(22) Jia, Y.; Li, J. *Chem. Rev.* **2015**, *115*, 1597−1621.

(23) Gupta, K. C.; Kumar Sutar, A.; Lin, C.-C. *Coord. Chem. Rev.* **2009**, *253*, 1926−1946.

(24) Eliot, A. C.; Kirsch, J. F. *Annu. Rev. Biochem.* **2004**, *73*, 383−415.

(25) Ghosh, I.; Nau, W. M. *Adv. Drug Delivery Rev.* **2012**, *64*, 764−783.

(26) Basilio, N.; García-Río, L.; Moreira, J. A.; Pessêgo, M. *J. Org. Chem.* **2010**, *75*, 848−855.

(27) Erkkilä, A.; Majander, I.; Pihko, P. M. *Chem. Rev.* **2007**, *107*, 5416−5470.

(28) Appel, R.; Chelli, S.; Tokuyasu, T.; Troshin, K.; Mayr, H. *J. Am. Chem. Soc.* **2013**, *135*, 6579−6587.

(29) Mupparapu, N.; Battini, N.; Battula, S.; Khan, S.; Vishwakarma, R. A.; Ahmed, Q. N. *Chem. - Eur. J.* **2015**, *21*, 2954−2960.

(30) Murphy, J. J.; Bastida, D.; Paria, S.; Fagnoni, M.; Melchiorre, P. *Nature* **2016**, *532*, 218−222.

(31) Dong, V. M.; Fiedler, D.; Carl, B.; Bergman, R. G.; Raymond, K. N. *J. Am. Chem. Soc.* **2006**, *128*, 14464−14465.

(32) Saba, S.; Vrkic, D.; Cascella, C.; DaSilva, I.; Carta, K.; Kojtari, A. *J. Chem. Res.* **2008**, *2008*, 301−304.

(33) Li, S.; Yin, H.; Wyman, I. W.; Zhang, Q.; Macartney, D. H.; Wang, R. *J. Org. Chem.* **2016**, *81*, 1300−1303.

(34) Tootoonchi, M. H.; Yi, S.; Kaifer, A. E. *J. Am. Chem. Soc.* **2013**, *135*, 10804−10809.

(35) Mecozzi, S.; Rebek, J., Jr. *Chem. - Eur. J.* **1998**, *4*, 1016−1022.

(36) CCDC entry 1477092 for the CB[7]·7 complex contains supplementary crystallographic data. These data can be obtained free of change from The Cambridge Crystallographic Data Centre.

(37) Cao, L.; Šekutor, M.; Zavalij, P. Y.; Mlinarić-Majerski, K.; Glaser, R.; Isaacs, L. *Angew. Chem., Int. Ed.* **2014**, *53*, 988−993.

(38) Day, A.; Arnold, A. P.; Blanch, R. J.; Snushall, B. *J. Org. Chem.* **2001**, *66*, 8094−8100.

DOI: 10.1021/acs.joc.6b02971
J. Org. Chem. 2017, 82, 3298−3301